Complete Response Obtained and Maintained by Combination of S-1 and CPT-11 in Hepatic Metastases of Colon Cancer: A Case Report

YUKIHIKO TOKUNAGA, HIROKAZU SASAKI and TOHRU SAITO

Department of Surgery, Osaka North Japan Post Hospital, Osaka, Japan

Abstract. *Background: An oral combined fluoropyrimidine, S-1 (tegafur, gimeracil and oteracil) has recently been used alone or in combination for colorectal cancer (CRC). Case and Methods: A 67-year-old man underwent left hemicolectomy for the descending colon cancer with multiple hepatic metastases. A combined chemotherapy with S-1 and irinotecan (CPT-11) was started after surgery. After three courses of the chemotherapy, no metastasis was observed in contrast computed tomography with decline of tumor markers. The patient was judged to have achieved a complete response (CR). The chemotherapy, continued on an outpatient basis, has maintained the CR for 15 months so far, though adverse reactions such as neutropenia, thrombocytopenia, and hypolacrimia have occurred. Conclusion: This case indicates that the combination of S-1 and CPT-11 is feasible on an outpatient basis and has potential as one of the treatment choices for hepatic metastasis from CRC.*

In this decade, a combination of irinotecan (CPT-11) with continuous intravenous infusion of 5-fluorouracil (5-FU) and leucovorin has been considered one of the standard regimens for advanced colorectal cancer (CRC). However, the regimens need central venous access, which sometimes cause complications such as line trouble and thrombosis. Moreover, a duration of 48-hour continuous infusion every two weeks gives inconvenience not only to the patients but also to the medical workers. Recently, concerns about the safety and inconvenience of continuous infusion have encouraged the development of combination therapies with new oral fluoropyrimidine derivatives and more effective regimens. Among several potential oral agents recently developed, an oral combined fluoropyrimidine, S-1 (tegafur, gimeracil, and oteracil), has recently been used alone or in combination with other agents for CRC (1, 2).

Several cases have been reported to have achieved partial response by a combination chemotherapy with S-1 and CPT-11 (3, 4). To date, however, few case has reported complete response (CR) to this combination chemotherapy in advanced CRC (5) with respect to uridine diphosphate glucuronosyltransferase (UGT) 1A1 (6, 7). Here a case of multiple hepatic metastases from CRC in which CR has been maintained for 15 months by chemotherapy with S-1 and CPT-11 is presented.

Correspondence to: Yukihiko Tokunaga, MD, Ph.D., Department of Surgery, Osaka North Japan Post Hospital, 1-1-6 Nakazaki, Kita-ku, Osaka 530-8798, Japan. Tel: +81 6 6361 2071, Fax: +81 6 6361 8324, e-mail: tokunagay@usay6.com

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Case Report

A 67-year-old man presented with constipation and malaise. The patients' complete blood count showed anemia. The white blood cells and platelet levels were normal. Laboratory studies showed a normal bilirubin, liver enzymes, alkaline phosphatase, serum creatinine, and C-reactive protein. Barium enema and colon fiber showed an advanced cancer in the descending colon, and biopsy revealed adenocarcinoma. Computed tomography (CT) showed multiple hepatic metastases. The patient underwent left hemicolectomy for the colon cancer and radio-frequency ablation of a hepatic tumor as he requested. Multiple hepatic metastases remained in the lobes after surgery (Figure 1). According to TNM classification and Duke's classification, this case was classified as T2N1M1 (stage IV) and Duke's D respectively. Pathological findings were type 2, 30×20 mm, moderately differentiated adenocarcinoma, ss, ly2, v2, n1, according to the general rules for clinical and pathological studies on cancer of the colon, rectum and anus in Japan. DNA analysis of UGT polymorphism showed 1A1*6 G/G (wild-type), 1A1*27 C/C (wild-type), and 1A1*28 6/6 (wild-type) respectively. At the initiation of chemotherapy, height was 168 cm; body weight 61 kg and body surface area 1.64 m^2. A combined chemotherapy with

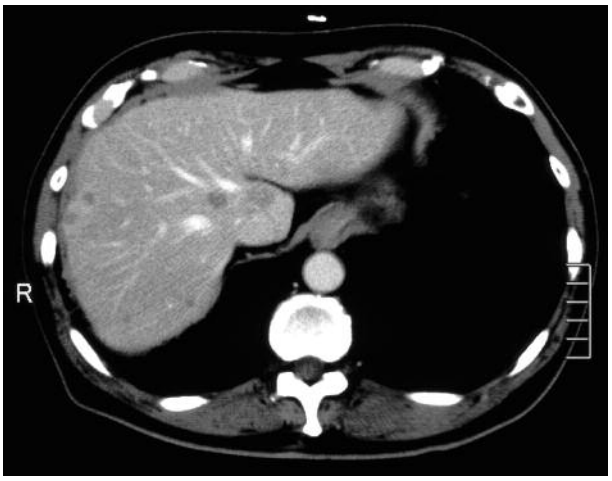

Figure 1. *Computed tomography (CT) showed multiple hepatic metastases in the hepatic lobes before the chemotherapy with S-1 and CPT-11.*

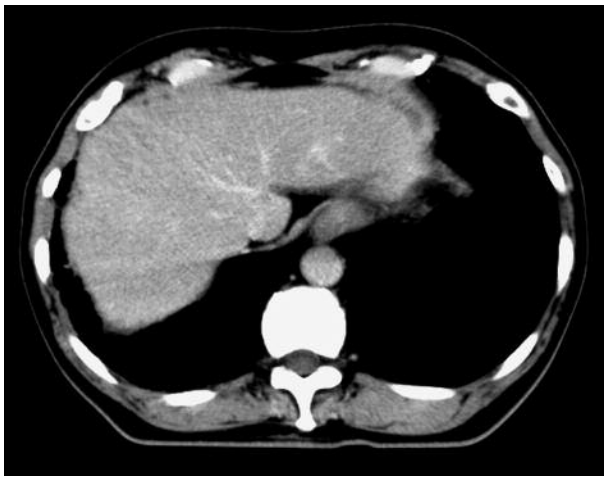

Figure 2. *After two courses of chemotherapy, contrast CT showed that most of the low density area had resolved, and the patient was judged to have achieved a partial response.*

S-1 (120 mg/day on days 1-21 with 14 days off) and CPT-11 (130 mg/day on days 1 and 15) was started three weeks after surgery. After two courses of the chemotherapy, abdominal contrast CT showed that most of the low density areas (LDA) in the hepatic lobes had resolved (Figure 2). After three courses, no LDA was observed in contrast CT, and the patient was judged to have achieved a CR (Figure 3). Tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 had declined markedly from 17.4 ng/mL and 428 IU/mL to normal levels respectively (Figure 4). Most of the courses were performed regularly on an outpatient basis except for a one week delay in some courses due to adverse reactions. There were no severe complications, though adverse reactions such as neutropenia (grade 2), thrombocytopenia (grade 2) and hypolacrimia (grade 2), according to the National Cancer Institute Common Toxicity Criteria occurred. In the contrast CT evaluations after each course of chemotherapy, there has been no relapse of the disease in the liver nor the lung and no increase in tumor markers for 15 months up to the present.

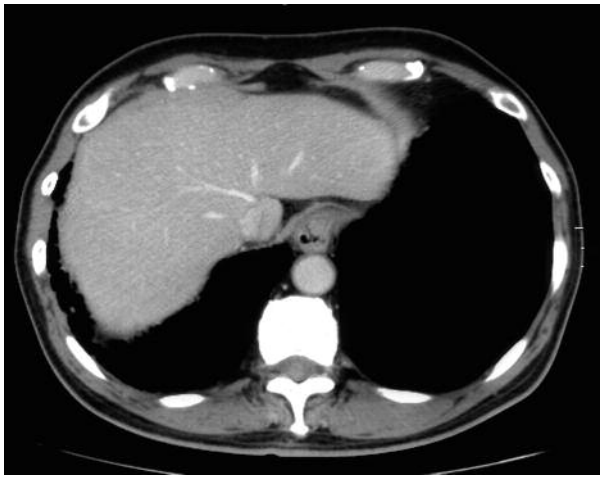

Figure 3. *After three courses, no low density area was observed in contrast CT, and the patient was judged to have achieved a complete response.*

Discussion

S-1 consists of tegafur and two modulators, 5-choloro-2, 4-dihydroxypyrimidine (CDHP) and potassium oxonate (OXO). CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is an enzyme for 5-FU degradation. OXO ameliorates the gastrointestinal toxicity of tegafur by a competitive inhibition of orotate phosphoribosyltransferase in the gastrointestinal mucosa (1). As a single agent in a phase II study for metastatic CRC, the response rate of S-1 was 39.5 % , with a low incidence of grade 3 or 4 toxicity (2).

One of the concerns about oral drugs is the maintenance of 5-FU concentration in the serum. The serum concentration of 5-FU with S-1 administration has been reported to be as high as that by continuous 5-FU infusion (8). Another concern is the interaction between CPT-11 and S-1, since previous reports indicated that 5-FU might affect the conversion of CPT-11 to SN-38, which is the active form (9). A pharmacokinitic (PK) study of S-1 combined with CPT-11 showed similar results to those with S-1 as a single agent (10). Additionally, it was reported that the PK analysis of CPT-11 in this combination showed no change

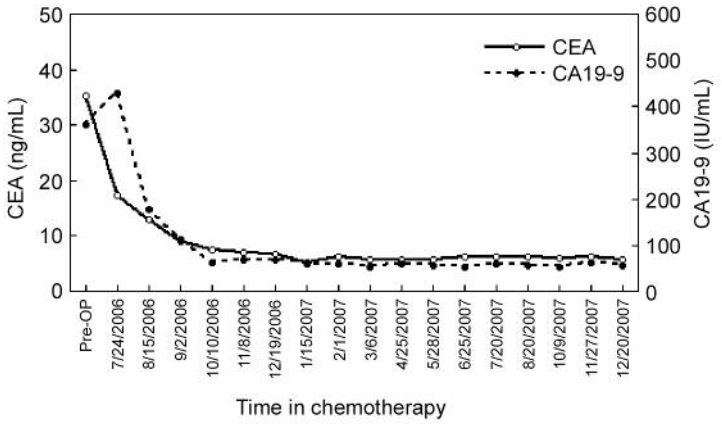

Figure 4. *Time course changes in tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, which declined to normal levels.*

in any PK parameter as compared with the expected values for CPT-11 as a single agent (11). Taking these data together, it appears there is no interaction between these agents. Furthermore, CPT-11 was shown to lack cross resistance with 5-FU in both experimental and clinical settings, and studies using cell lines and xenografts have suggested that the combination has additive-to-synergistic antitumor effects (12).

At first, in a phase I study with metastatic gastric cancer, the feasibility and safety of a combination of S-1 (80 mg/m^2) on days 1-14 of a 21-day cycle and CPT-11 (150 mg/m^2) on day 1 was evaluated (11). Another phase I study assessed the feasibility and safety of the regimen in advanced gastric cancer (10). In the latter study, S-1 was given at 80 mg/m^2 for 21 consecutive days followed by a 2-week rest. CPT-11 was given on day 1 and 15. Based on the results, the recommended dose of CPT-11 was 80 mg/m^2. The overall response rate was 58.3% for gastric cancer.

Based on the results of these phase I studies in gastric cancer, a recent phase II study evaluated the efficacy and safety of the combination of S-1 (80 mg/m^2) on days 1-14 of a 21-day cycle and CPT-11 (150 mg/m^2) on day 1 in patients with advanced or recurrent CRC. Five out of 40 patients had a CR, and 20 had a partial response (PR) (13). The overall response rate was 62.5% . Median progression-free survival was 8.0 months. The rate of grade 3 or 4 toxicity was neutropenia 15% , anemia 7.5% , anorexia 12.5% and diarrhea 7.5% . The study concluded that combined treatment with S-1 and CPT-11 was effective, well-tolerated, and convenient for patients with advanced CRC.

Another phase II study evaluated the combination of S-1 (40 mg/m^2) on days 1-14 of a 28-day cycle and CPT-11 (100 mg/m^2) on day 1 and 15 (14). The results showed an overall response rate of 50 % without any serious adverse reactions in hematological and non-hematological parameters.

These phase I/II studies indicated that the combination of S-1 and CPT-11 was very effective in the treatment of patients with advanced CRC. Toxicity was generally mild and manageable. Furthermore, the regimen might be more convenient not only for the patients but also for the medical workers than a combination of CPT-11 plus continuous infusional 5-FU and leucovorin.

Grade 2 ocular toxicity occurred in our case, perhaps due to the S-1 rather than the CPT-11, since our case was a favorable genotype with respect to UGT 1A1. Although the safety database of the manufacturer of S-1 indicates that the incidence of ocular toxicity is less than 5% , systemic therapy with 5-FU has been reported to cause epiphora due to stenosis and fibrosis of tear ducts (15). Prolonged mild ocular toxicity, including epiphora and blurred vision, was relatively frequent, especially in patients who received long-term treatment with 5-FU. Since epiphora was often reversible on stopping chemotherapy (16), subsequent courses of chemotherapy were delayed with appropriate local therapy.

Some metastatic lesions evaluated as CR by CT alone have been found to grow again within a year (17), and intensive follow-up with a combination of tumor markers and CT was recommended (18). Our case has maintained a CR, evaluated by tumor markers and CT, for 15 months so far. This case indicates that the combination of S-1 and CPT-11 may be one of the treatment choices for multiple hepatic metastases from CRC.

References

1 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi H, Kato T, Yonekura K and Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective toxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs *7*: 548-557, 1996.

2 Shirao K, Ohtsu A, Takada H, Mitachi Y, Hirakawa K, Horikoshi N, Okamura T, Hirata K, Saitoh S, Isomoto H and Satoh A: Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. Cancer *100*: 2355-2361, 2004.

3 Mado K, Ishii Y, Mazaki T, Ushi M, Masuda H and Takayama T: A case of bone metastasis of colon cancer that markedly responded to S-1/CPT-11 combination chemotherapy and became curable by resection. World J Surg Oncol *18(4)*: 3-6, 2006.

4 Nakao K, Tsunoda A, Amagasa H, Suzuki N, Yamazaki K and Kusano M: A case of poorly-differentiated adenocarcinoma in sigmoid colon cancer with liver and pulmonary metastasis responding to TS-1 and CPT-11. Gan To Kagaku Ryoho (Jpn J Cancer Chemother) *33*: 109-112, 2006.

5 Katsumata K, Mori Y, Hisada M, Ishizaki T, Suzuki S, Wada T, Tsuchida A and Aoki T: CR of rectal cancer and synchronous liver and lung metastases obtained with TS-1 plus CPT-11 combination therapy – case report. Gan To Kagaku Ryoho (Jpn J Cancer Chemother) *34*: 113-115, 2007.

6 Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K and Hasegawa Y: Polymorphism of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmagogenetic analysis. Cancer Res *60*: 6921-6926, 2000.

7 Innocenti F, Undevia SD, Iyer L, Chen PX, Das D, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE and Ratain MJ: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol *22*: 1382-1388, 2004.

8 Hirata K, Horikoshi N, Aiba K, Ozaki M, Denno R, Sasaki K, Nakao Y, Ishizuka H, Yamada Y, Uno S, Taguchi T and Shirasaka T: Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res *5*: 2000-2005, 1995.

9 Sasaki Y, Ohtsu A, Shimada Y, Ono K and Saijo N: Simultaneous administration of CPT-11 and fluorouracil: alteration of the pharmacokinitics of CPT-11 and SN-38 in patients with advanced colorectal cancer. J Natl Cancer Inst *86*: 1096-1098, 2004.

10 Takiuchi H, Narahara H, Tsujinaka T, Goto M, Kawabe S, Katsu K, Ishi H, Tatsuta M, Fujitani K, Furukawa H and Taguchi T: Phase I study of S-1 combined with irinotecan (CPT-11) in patients with advanced gastric cancer (OGSG 0002). Jpn J Clin Oncol *35*: 520-525, 2005.

11 Yamada Y, Yasui H, Goto A, Arai T, Ura T, Hamaguchi T, Muro K, Shimada Y and Shirao K: Phase I study of irinotecan and S-1 combination therapy in patients with metastatic gastric cancer. Int J Clin Oncol *8*: 374-380, 2003.

12 Vanhoefer U, Harstock A, Achterrath W, Cao S, Seeber S and Rustum YM: Inrinotecan in the treatment of colorectal cancer; clinical overview. J Clin Oncol *19*: 1501-1518, 2001.

13 Goto A, Yamada Y, Yasui H, Kato K, Hamaguchi T, Muro Y, Shimada K and Shirao K: Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol *17*: 968-973, 2006.

14 Komatsu Y, Yuki S, Tateyama M, Kudo M and Asaka M: Irinotecan plus oral S-1 in patients with advanced colorectal cancer – biweekly IRIS regimen. Gan To Kagaku Ryoho (Jpn J Cancer Chemother) *33*: 131-134, 2006.

15 Brink HM and Beex LV: Punctal and canalicular stenosis associated with systemic fluorouracil therapy. Doc Ophthalmol *90*: 1-6, 1995.

16 Hassan A, Hurwitz JJ and Burkes RL: Epiphora in patients receiving systemic 5-fluorouracil therapy. Can J Ophthalmol *33*: 14-19, 1998.

17 Benoist S, Brouquet A, Penna C, Julie C, EL Hajjam M, Chagnon S, Mitry E, Rougier P and Nordlinger B: Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol *24*: 3939-3945, 2006.

18 Bhattacharjya S, Aggarwal R and Davidson BR: Intensive follow-up after liver resection for colorectal liver metastases: results of combined serial tumour marker estimations and computed tomography of the chest and abdomen – a prospective study. Br J Cancer *95*: 21-26, 2006.

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