

Successful Treatment with S-1 plus CPT-11 for Lymph Node Metastasis from Colon Cancer: Report of a Case

KAZUHIKO YOSHIMATSU, HAJIME YOKOMIZO, TAKASHI FUJIMOTO, TAISUKE OTANI, ATSUO MATSUMOTO, GAKUJI OSAWA, HIROKO ITAGAKI, ARIHIRI UMEHARA, SHUNICHI SHIOZAWA, TAKAO KATSUBE, YOSHIHIKO NARITAKA and KENJI OGAWA

*Department of Surgery, Tokyo Women's Medical University Medical Center East,
2-1-10 Nishiogu Arakawa-ku, Tokyo, 116-8567, Japan*

Abstract. S-1 is a novel oral anticancer drug, composed of tegafur (FT), gimestat (CDHP) and otastat potassium (Oxo), based on the biochemical modulation of 5-fluorouracil (5-FU). S-1 plus irinotecan (CPT-11) for advanced colorectal cancer as expected showed equally good results as these with CPT-11 plus infusional 5-FU/LV (FOLFIRI regimen). A case of unresectable lymph node metastasis from colon cancer successfully treated with S-1 plus CPT-11 is reported here. A 65-year-old man had metastasis to the lymph nodes in the left supra clavicular region and the superior mesenteric artery. S-1 plus CPT-11 was chosen for the treatment. After 2 courses, since grade 2 toxicity for dysgeusia was observed, S-1 administration was shortened. After 3 courses of the revised regimen, the enlarged lymph nodes disappeared on conventional CT and fluorine-18 fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and the case was assessed as a complete response (CR). Because CR was continued by an additional four courses of treatment, the regimen was changed to a single administration of S-1. Although eighteen months have passed since the induction of CR by S-1 plus CPT-11 therapy, no symptoms or findings of relapse have been observed.

Abbreviations: FT, tegafur; CDHP, gimestat; Oxo, otastat potassium; 5-FU, 5-fluorouracil; CPT-11, irinotecan; DPD, dihydropyrimidine dehydrogenase; MST, median survival time; PFS, progression-free survival; RR, response rate; CR, complete response; FOLFOX, infusional 5-FU/leucovorin (LV) with oxaliplatin; FOLFIRI, infusional 5-FU/LV with irinotecan; FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography with CT.

Correspondence to: Kazuhiko Yoshimatsu, MD, Department of Surgery, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu Arakawa-ku, Tokyo, 116-8567, Japan. Tel: +81 3 3810 1111, Fax: +81 3 3894 5493, e-mail: kyoshsu@dnh.twmu.ac.jp

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S-1 is a novel oral anticancer drug, composed of tegafur (FT), gimestat (CDHP) and otastat potassium (Oxo) at a molar ratio of 1:0.4:1, based on the biochemical modulation of 5-fluorouracil (5-FU) (1). S-1 improves the tumor-selective toxicity of 5-FU by the actions of two modulators, CDHP and Oxo (1-4).

In phase II trials of S-1 as a single agent, response rates ranging from 19% to 39% have been obtained in patients with advanced colorectal cancer (4-6). This regimen produced favorable results compared to treatment with a bimonthly schedule of high-dose leucovorin (LV) and 5-FU bolus plus continuous infusion (de Gramont regimen) (7). Based on this result, clinical phase I and II studies of S-1 plus irinotecan (CPT-11) for advanced colorectal cancer have been conducted as expected, showed equally good results as CPT-11 plus infusional 5-FU/LV (FOLFIRI regimen) (8, 9). Goto *et al.* (10) reported a phase II study with S-1 orally for 14 days and CPT-11 intravenously every 21 days which gave an overall response rate of 62.5% and a progression-free survival (PFS) of 8.0 months, while grade 3 or 4 toxicity was similar to the toxicity found in the FOLFIRI regimen (8, 9). In our experience of treatment with S-1 plus CPT-11, the overall response rate was 45.5%, the median PFS was 9.0 months and the median survival time (MST) was 21.2 months (11). A case of unresectable lymph node metastasis from colon cancer successfully treated with S-1 plus CPT-11 is reported.

Case Report

A 65-year-old man underwent operation for transverse colon cancer in June 2005. In the operative findings, 8 cm-sized tumor was located at the transverse colon and invaded the duodenum. He underwent right hemicolectomy, even though additional pancreatoduodenectomy for R0 operation was needed. Pathologically, tumor cells were exposed to the cutting surface. He was brought to our department for additional

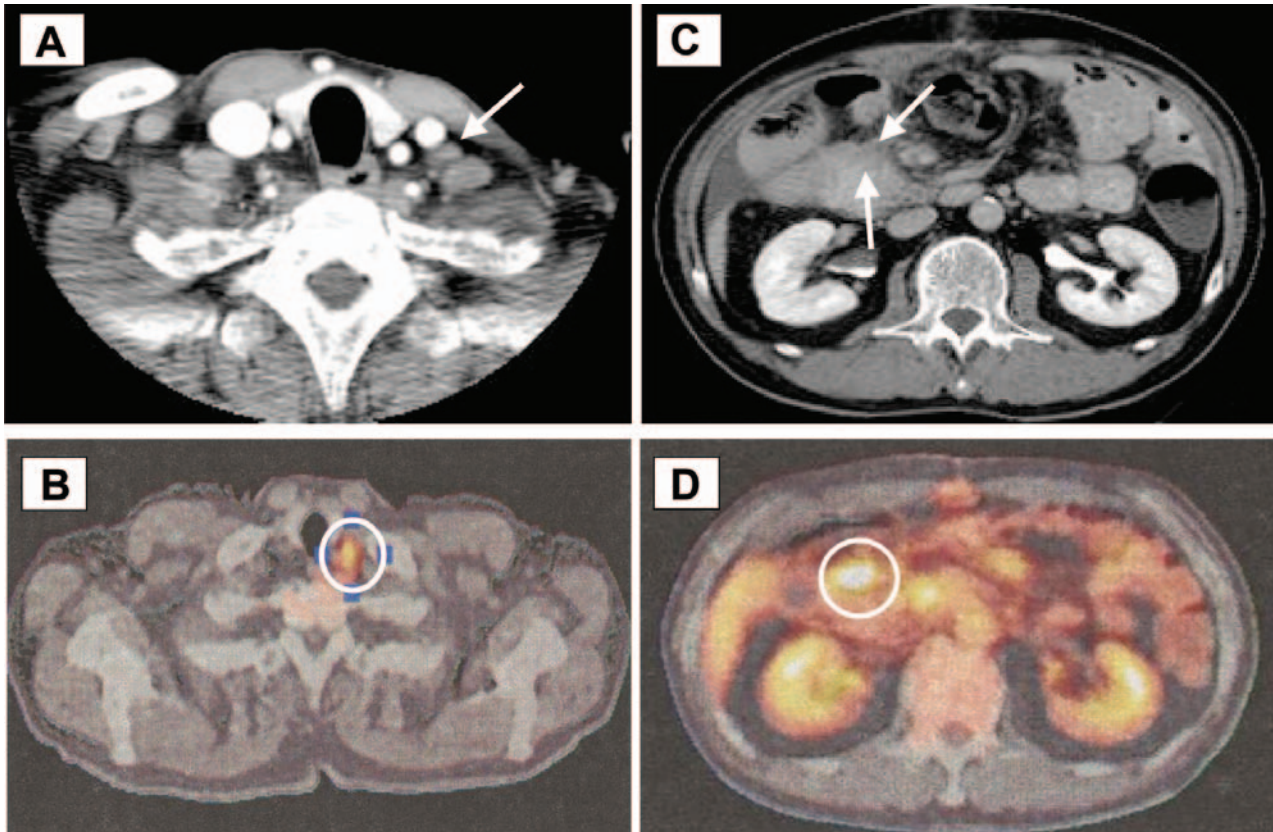


Figure 1. The enlarged lymph node with nonuniform enhancement was observed in the left supra clavicular region (white arrow) by conventional CT (A). An increased amount of FDG was accumulated in the same portion (white circle) (B). An irregularly shaped low density area was observed in the superior mesenteric region (white arrows) by conventional CT (C). Increased amount of FDG was also accumulated there (white circle) (D).

treatment. In our department, because CT scan and fluorine-18 fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) revealed lymph node metastases, including the left supra clavicular (Figure 1A, B) and superior mesenteric (Figure 1C, D) lymph nodes, additional resection was not indicated. Hence, chemotherapy with S-1 plus CPT-11 was chosen for the treatment. S-1 (Taiho Pharmaceutical Co. Ltd, Tokyo Japan) was administered orally at 40 mg *b.i.d.*, within an hour after breakfast. S-1 was given for 21 consecutive days followed by a 14-day rest period. CPT-11 was administered as a 90-minute intravenous infusion at a dose of 80 mg on days 1 and 15, after the initial oral dose of S-1. Courses of treatment were repeated every 35 days. However, after two courses, the administration schedule was changed due to the unacceptable toxicity (grade 2 dysgeusia). The revised regimen was follows: S-1 was given for 7 consecutive days followed by a 7-day rest period. CPT-11 was administered on day 1. Courses of treatment were repeated every 14 days, with 28 days of treatment counted as one course. After 3 courses of the revised regimen, the enlarged lymph

nodes were not apparent by conventional CT and FDG-PET/CT (Figure 2) and the case was assessed as a complete response. Because complete response was continued by an additional four courses of treatment, the regimen was changed to a single administration of S-1. Although eighteen months have passed after complete response with S-1 plus CPT-11 therapy, no symptoms or findings of relapsed disease have been observed on examination.

Discussion

Therapy for non-resectable advanced recurrent colon cancer has rapidly progressed since the report by Saltz *et al.* (12). Prolongation of the MST to about 20 months has been achieved by the use of FOLFORI or FOLFOX regimens (8, 9, 13). It has also been reported that the use of 5-FU/LV, CPT-11, and oxaliplatin (L-OHP) together for primary or secondary therapy and thereafter has prolonged the survival time (14). Although the rate of CR has been increased by the addition of bevacizumab to the above regimens, the aim

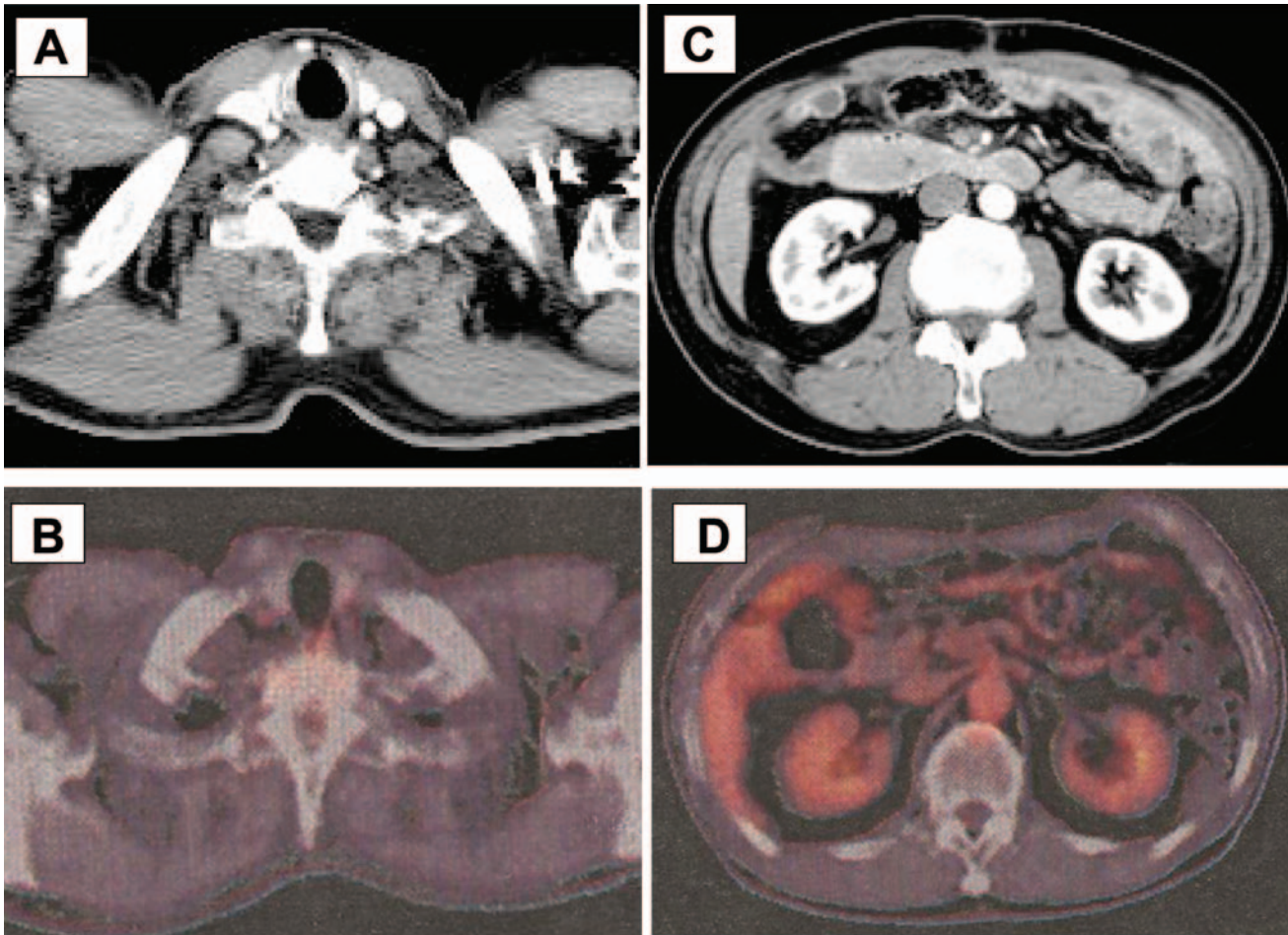


Figure 2. The metastatic lesions disappeared on CT (A, C) and no accumulation of FDG was observed (B, D).

of chemotherapy is still prolongation of survival. Additionally, quite unfavorable toxicities and inconvenience during 48 hours intravenous continuous infusion often cause discontinuation of chemotherapy.

In our department, low-dose chemotherapy were performed under the concept of tumor dormancy and a relative favorable survival had been obtained (15, 16). Our regimen with S-1 plus CPT-11 was settled to the about 60% of dose compared to other phase II trials. However, PFS and MST were approximately equal (11).

For the assessment of chemotherapy, the RECIST criteria are usually used (17), however, the antitumor effect might be obtained without actual shrinkage of tumor size. FDG-PET/CT is a useful tool for monitoring the effect of anti-tumor therapy, including chemoradiotherapy (16). Hence, we use CT and FDG-PET/CT for the assessment of therapy. In this case, the lesions were reduced and disappeared with the chemotherapy and no accumulation of FDG was observed.

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