Irinotecan as Second-Line Treatment for Unresectable Liver Metastases of Colon Cancer

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A 53-year-old woman had shown repeated, partial responses to chemotherapy for large, multiple liver metastases of sigmoid colon cancer. After a partial response to 5-fluorouracil plus leucovorin therapy, an 89.7% reduction of the 5-fluorouracil–resistant metastatic tumor was achieved by giving CPT-11 (irinotecan) at a dose of 100 mg/body per week. We suggest that CPT-11 should be recommended as an effective second-line treatment for unresectable liver metastases of colon cancer, after 5-fluorouracil–based chemotherapy.

Int J Clin Oncol 1998;3:117–120

Key words: CPT-11, irinotecan, colon cancer, liver metastasis

INTRODUCTION

Since the majority of metastatic tumors exhibit cross-resistance to multiple, unrelated anticancer drugs, the development of methods to circumvent this phenomenon is important. The front-line therapy for patients with advanced colorectal cancer is biochemical modulation of fluorouracil, including 5-fluorouracil plus leucovorin therapy.[1–4] The second-line treatment, however, after 5-fluorouracil–based chemotherapy, remains to be established. CPT-11 (irinotecan) is a candidate for salvage therapy, because CPT-11, a selective topoisomerase-I inhibitor, has a different cytotoxic mechanism than 5-fluorouracil.[4–6] This report describes a case with partial response to CPT-11 therapy from a 5-fluorouracil–resistant tumor.

CASE REPORT

A 53-year-old woman was referred to the Cancer Research Institute Hospital for a complete medical examination, after she consulted her family physician. The patient had been well until a month earlier, when she began to notice epigastric mass and poor appetite.

On physical examination, the liver was palpable 7 cm below the costal margin. The diagnosis of advanced sigmoid colon cancer with unresectable, metastatic liver involvement was made after an evaluation consisting of a colonoscopy and CT scan. The patient then underwent a segmented resection of the sigmoid colon, and catheterization into the hepatic artery. Histopathologic findings showed a well-differentiated adenocarcinoma of 2.7 cm in size, with vascular invasion, but the locoregional lymph nodes were intact.

Twelve days after the operation, 5-fluorouracil plus leucovorin therapy was administered at a 5-fluorouracil dose of 250 mg/body per day (179 mg/m^2 per day), with the leucovorin dose at 30 mg/body per day (21 mg/m^2 per day), through an implanted reservoir. This therapy was administered for 4 consecutive days, followed by a 3-day rest period. The patient gave oral informed consent before each chemotherapy treatment. Since the adverse events were limited to anorexia and epigastric discomfort (grade 1), subsequent treatments were continued in an outpatient setting, that is, intra-arterial infusion of 5-fluorouracil plus oral leucovorin at the same dose. After a 4-month administration, the sum of the products of the perpendicular dimensions of her measurable tumor shrank from 1141.0 cm^2 to 82.5 cm^2 (92.8% reduction) (Fig. 1A, B), and her carcinoembryonic antigen level had also decreased logarithmically from 1250 ng/mL to 10 ng/mL, in parallel with her serum carbohydrate antigen19-9 level (Fig. 2). Therapy was continued, and this response lasted for 4 months. After that time, however, the hepatic tumors progressed.

Therapy was continued through the implanted reservoir for 4 days per week, at a 5-fluorouracil dose of 250 mg/body per day and a cisplatin dose of 10 mg/body per day. However, a CT scan and tumor marker analysis showed no response, even after 3 courses of this therapy. This result indicated that the metastatic tumor was resistant to 5-fluorouracil at that time. Next, we chose CPT-11 as a second-line therapy at a dose of 100 mg/body per week (71 mg/m^2 per week). CPT-11 was

Received Dec. 16, 1996; revised Jul. 24, 1997; accepted for publication in revised form Sep. 24, 1997. *Correspondence and requests for reprints to: Department of Surgery, Cancer Research Institute Hospital, Kanazawa University, Kanazawa, Ishikawa 921-8044, Japan.

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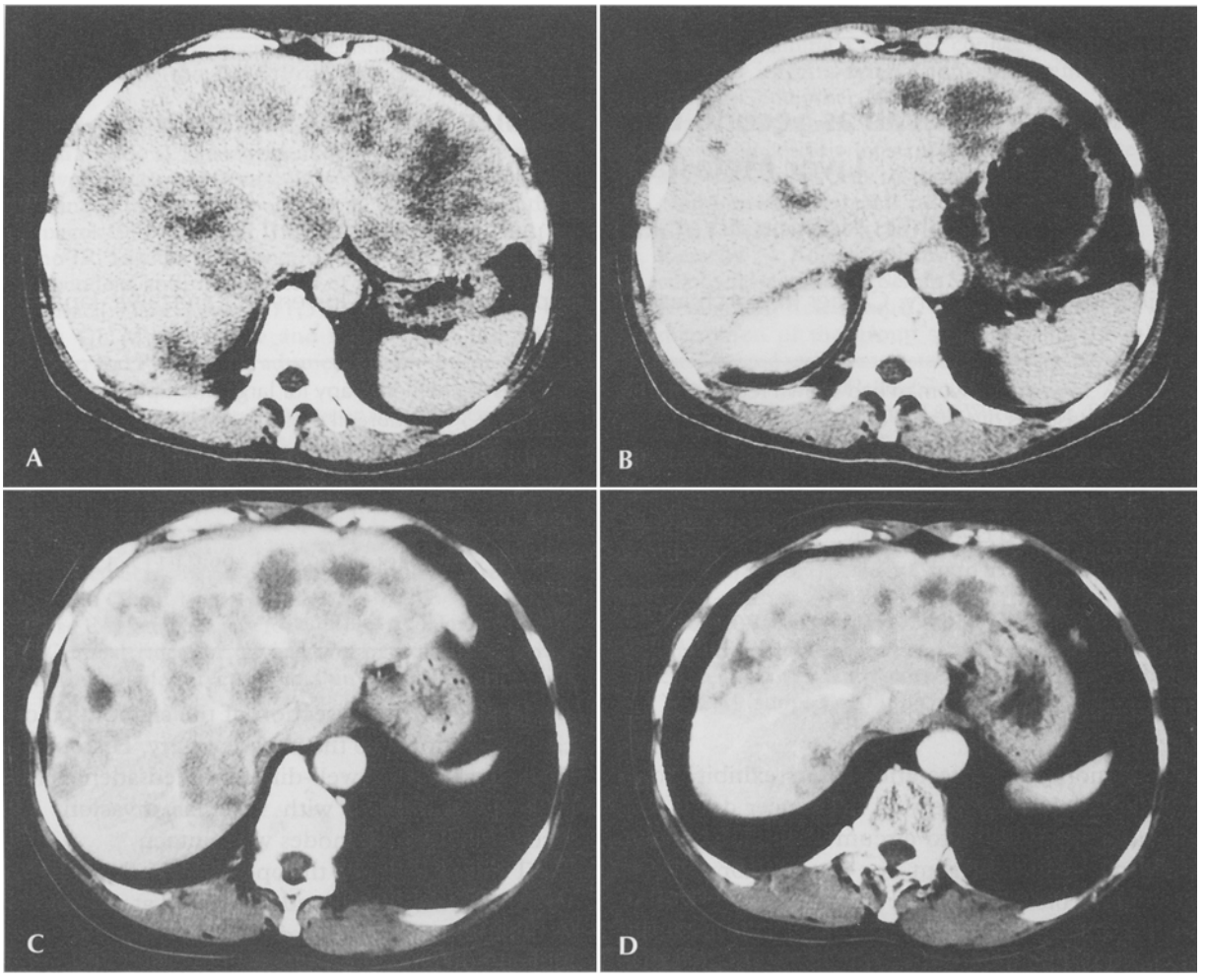

Fig. 1. Abdominal CT scans of a 53-year-old woman showing liver metastases of sigmoid colon cancer, (**A**) before and (**B**) after a 4-month treatment with 5-fluorouracil plus leucovorin, and (**C**) just before and (**D**) after 2 cycles of treatment with CPT-11 (irinotecan).

administered intravenously once per week for 3 consecutive weeks, followed by a 1-week rest period. After 2 cycles of this regimen, the administration of CPT-11 at a dose of 80 mg/kg body weight per week (57 mg/m^2 per week) was continued in an outpatient setting. On the third cycle, the sum of her measurable tumors had shrunk from 628.3 cm^2 to 64.5 cm^2 (89.7% reduction) (Fig. 1C, D), and her carcinoembryonic antigen level had also decreased from 753 ng/mL to 40 ng/mL (Fig. 2). The response duration of CPT-11 was 3 months. No significant adverse effects, other than anorexia and alopecia (grade 1), were observed during the treatment with CPT-11.

DISCUSSION

The patient in this case report showed repeat, partial responses for large, multiple liver metastases of sigmoid colon cancer. After a 92.8% reduction of the hepatic tumor by the administration of 5-fluorouracil and leucovorin, an 89.7% reduction of the 5-fluorouracil–resistant tumor was achieved with CPT-11. Recently, 5-fluorouracil, biomodulated with leucovorin, has been generally accepted by many as the first-line standard regimen for advanced colorectal cancer, with a major response rate of over 30%.[1–3] However, there is no standard salvage therapy for patients with metastatic colorectal cancer who have disease progression after having received 5-fluorouracil–based chemotherapy.

There has been much attention paid recently to CPT-11, which is a new, semisynthetic, water-soluble anticancer agent, derived from the plant alkaloid, camptothecin. In vivo, CPT-11 is enzymatically converted to an active metabolite (SN-38) in the liver. It inhibits the nuclear enzyme DNA topoisomerase I, leading to a lethal accumulation of single-strand DNA breaks in the cell, by interfering with the relaxation and recombination of supercoiled DNA.[4–6] CPT-11 not only presents new cytotoxic mechanisms, but also has a unique clinical efficacy. According to a phase II study of CPT-11 for metastatic colorectal cancer in Japan, the response rate reached 22%, despite the patients having previously received prior 5-fluorouracil–

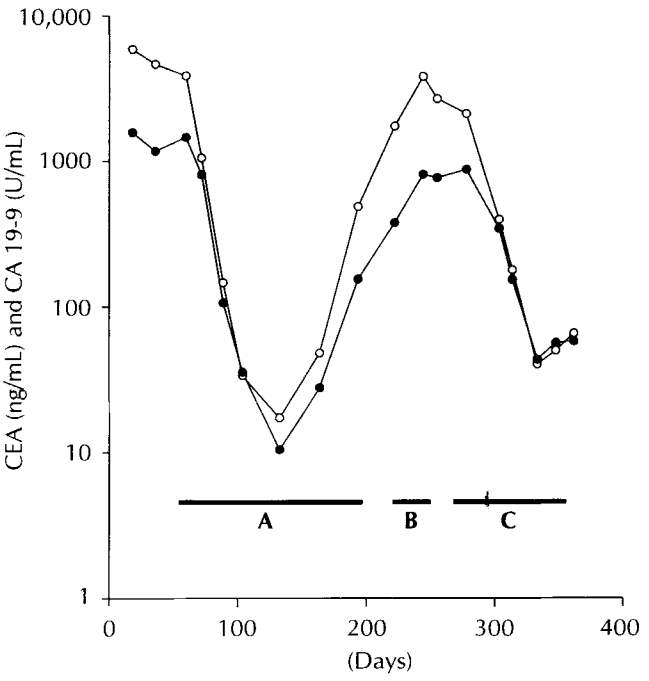

Fig. 2. Effects of chemotherapy in patient described in Fig. 1 are represented by a logarithmic decrease of tumor markers, including serum levels of carcinoembryonic antigen (CEA) (-●-) and carbohydrate antigen (CA) 19-9 (-○-). Bars indicate the periods of treatment with 5-fluorouracil plus leucovorin (**A**), 5-fluorouracil plus cisplatin (**B**), and CPT-11 (**C**). Upper normal limits of CEA and CA 19-9 are 2.5 ng/mL and 37 U/mL, respectively.

containing chemotherapy.[7] This study showed CPT-11 had promising antitumor activity against a metastatic colorectal cancer that was resistant to prior chemotherapy. Other clinical phase II studies have shown consistent response rates from the use of CPT-11 for advanced colorectal cancer, in both pretreated (14% to 23%) and chemotherapy-naive patients (15% to 32%).[8–11] These results suggest that the incidence of cross-resistance between CPT-11 and 5-fluorouracil might be low. Therefore, CPT-11 should be recommended as a second-line treatment for 5-fluorouracil–resistant tumors.

In a phase II study in Japan, Shimada et al. also indicate that the response to CPT-11 differed in metastatic sites of colorectal cancer, reporting that liver metastases show a lower response rate (15%) than lung (39%) or lymph node metastases (36%).[7] They suggest possible explanations for the differences in CPT-II response rate as being differences in the tissue distributions of CPT-11, differences in the efficiency of conversion from CPT-11 to SN-38 (an active metabolite), and the longer mean retention time of SN-38 in pulmonary metastases.[7] Conversely, a phase II trial, conducted by Rothenberg and colleagues, shows that 8 of 10 responders had liver metastases, and that the response rate in patients with liver metastases was 25% (8 of 32 cases). Conversely, no response was observed in patients with lung metastases.[9] Therefore, we must wait for further clinical studies to evaluate the differences in efficiency between metastatic sites. Recently, Goldwasser et al. found that the amount of functional topoisomerase I-cleavable complexes is a good indicator for predicting sensitivity to CPT-11 in vitro.[12] Applying this indicator to clinical investigations may help to explain the reasons for intrapatient and intraorgan variations in sensitivity to this drug, and to predict the clinical response of metastatic tumors to CPT-11.

Severe bone marrow suppression and diarrhea were dose-limiting factors of CPT-11.[4,5] Phase I and pharmacokinetic trials show that severe neutropenia (grade 3 or 4) was observed in 4 of 18 patients (22%), at doses of more than 125 mg/m^2, but in none of the patients at doses of less than 100 mg/m^2. Phase II studies[7,9–11] also report severe leukopenia in 16% to 25% of cases at doses of 100 to 150 mg/m^2. Similarly, severe diarrhea occurred in 13% to 42% of the cases in the phase II trials.[7,9–11] No episodes of severe adverse effects were encountered in our patient, because the dose of CPT-11 was less than 100 mg/m^2. Although the dose in our case was lower than that in previous studies, there is a need to evaluate the antitumor efficacy of CPT-11 when administered at low doses for protracted periods, as Armand pointed out in a recent review.[13]

In this case, repeat responses to the sequential chemotherapy prolonged the disease progression significantly. Rothenberg et al. report that half of responding patients had a longer time to tumor progression on second-line treatment with CPT-11, than on front-line treatment with 5-fluorouracil–based therapy.[9] The sequential strategy of 5-fluorouracil–based chemotherapy and CPT-11 may therefore contribute to a prolongation of disease progression and survival time of patients with advanced colorectal cancer.

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