COMPLETE REMISSION AFTER COMBINATION CHEMOTHERAPY FOR STAGE IV GASTRIC CANCER WITH PERITONEAL DISSEMINATION AND LIVER METASTASES: CASE REPORT

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Abbreviations: 5-fluorouracil; 5-FU, leucovorin; LV, tegafur/gimeracil/oteracil potassium; TS-1, tegafur/uracil; UFT, cisplatin; CDDP

Abstract

A 64-year-old man underwent gastroscopy to investigate epigastric discomfort and marked weight loss. An 8-cm Borrmann type II lesion was detected in the body of the stomach on the greater curvature, so total gastrectomy was performed on December 15,
2000. Histopathological examination revealed mucinous adenocarcinoma of the stomach with metastases to the omentum and the paragastric lymph nodes (P1H0N1SE; stage IV). Postoperative chemotherapy was scheduled, but abdominal adhesiolysis had to be performed instead (January 12, 2001) because of repeated episodes of postoperative ileus. After the patient was discharged, two metastases in the right lobe of the liver were detected in April 2001 and systemic chemotherapy was started. The liver metastases disappeared after three courses of low-dose cisplatin plus 5-fluorouracil. After three more courses, his chemotherapy was changed to oral TS-1 plus leucovorin. At 2 years and 10 months after surgical resection, the patient is disease-free and receiving oral chemotherapy on an outpatient basis.

Introduction

Stage IV advanced gastric cancer with peritoneal dissemination and multiple liver metastases has a grave prognosis. Most patients with such tumors undergo palliative surgery to relieve gastrointestinal obstruction and receive systemic chemotherapy in an attempt to prolong survival (Kondo, Murase et al., 1996; Ogawa, Maki et al., 1999; Mori, Masaki et al., 1999; Shinkai, Kida et al., 1999). As chemotherapy for advanced gastric cancer, regimens based on 5-fluorouracil (5-FU) are often used, such as 5-FU + cisplatin (CDDP), 5-FU + methotrexate, and 5-FU + leucovorin (LV) (Konishi, Hirishi et al., 1994; Hsu, Yeh et al., 1997; Iwamoto, Kimoto et al., 1998; Pérez, Lacava et al., 1998; Kim, Murakami et al., 1999; Chen, Liu et al., 1999; Enjoji and the Nagasaki Digestive Organ Cancer Chemotherapy Study Group, 2002). In Japan, postoperative adjuvant therapy with 5-FU and low-dose CDDP as the modulator is often performed as first-line chemotherapy (Kondo, Murase et al., 1996; Ogawa, Maki et al., 1999; Mori, Masaki et al., 1999; Shinkai, Kida et al., 1999). Recently, to improve the response to oral fluoropyrimidines that are widely used after intravenous consolidation therapy in Japan and to allow ambulatory follow-up of elderly patients, several new-generation oral fluoropyrimidine preparations such as TS-1 and Orzel have been developed for use in combination with oral modulators. TS-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) was developed for the treatment of gastric cancer by combining tegafur with gimeracil (CDHP), which is a dihydropyrimidine dehydrogenase (DPD)-inhibiting fluoropyrimidine, and oteracil potassium (Oxo) to control the gastrointestinal toxicity of 5-FU. Orzel (Taiho
Pharmaceutical Co., Ltd., Tokyo, Japan) is a combination of tegafur/uracil (UFT) with LV, which is indicated for the treatment of colorectal cancer. Several reports on the efficacy of these newer preparations have been published (Sakata, Ohtsu et al., 1998; Sugimachi, Maehara et al., 1999; Koizumi, Kurihara et al., 2000; Mukai, Moriya et al., 2001).

We encountered a patient with stage IV advanced gastric cancer, who had peritoneal dissemination and lymph node involvement, and who developed two new liver metastases at 4 months after surgery. The patient received first-line treatment with low-dose CDDP + 5FU, followed by oral outpatient maintenance therapy with TS-1 + LV as a modulator. At 2 years and 10 months after surgery, this patient is currently disease-free, without ascites or any signs of recurrent liver metastasis. Here we report the details of this case in which stage IV gastric cancer responded to intravenous consolidation therapy plus outpatient maintenance therapy using a next-generation oral fluoropyrimidine preparation.

**Case Report**

**Onset and course:** In November 2000, a 64-year-old man presented to our hospital with epigastric discomfort and weight loss of about 8 kg since September 2000. Gastroscopy revealed an 8-cm Borrmann type II tumor in the body of the stomach on the greater curvature. With a diagnosis of advanced gastric cancer, the patient was admitted to hospital for surgery on December 6, 2000.

**Past history:** He had suffered from diabetes mellitus for 15 years and was managed on insulin.

**Findings on admission:** The patient was 163.7 cm tall and weighed 68.4 kg. He had no evidence of anemia or jaundice. Although hepatosplenomegaly was not detected, there was a slight bulge in the epigastrium where a rubbery, but firm, fist-sized mass was palpable. Digital rectal examination did not detect marked induration in the pouch of Douglas.

**Admission laboratory tests:** Laboratory tests showed the following: leukocyte count, 8200 µl; red blood cell count, 428 x 10^6/µl; hemoglobin, 12.4 g/dl; hematocrit, 38.5 %; platelet count, 22.3 x 10^9/µl; total protein, 7.2 g/dl; albumin, 3.6 g/dl; glucose 112 mg/dl; blood urea nitrogen, 10.2 mg/dl; serum creatinine, 0.9 mg/dl; GOT, 23 IU/L; GPT, 33 IU/L;
total bilirubin, 0.9 mg/dl; LDH, 157 IU/L; ALP, 223 IU/L; CEA, 2.3 (<5) ng/ml; and CA 19-9, 14.6 (<37) ng/ml. There were no significant abnormalities of these findings, including the tumor markers.

**Barium contrast radiography:** A protruding Borrmann type II lesion with a diameter of 8 cm was observed to arise from the posterior wall of the greater curvature in the gastric body. The tumor seemed to involve the greater omentum and the transverse mesocolon, but the duodenum and transverse colon were apparently unaffected (Figure 1).

**Gastroscopy:** A protruding and ulcerated mass was located on the posterior wall of the greater curvature in the gastric body. Biopsy of this lesion gave a diagnosis of poorly differentiated adenocarcinoma.

**Colonoscopy:** No mucosal abnormalities of the transverse colon were observed, and there were no macroscopic lesions in the large intestine.

**Abdominal ultrasonography:** There was a fist-sized tumor in the gastric body on the greater curvature, as well as a small volume of ascites in the peritoneal cavity. The boundaries of the tumor with the transverse mesocolon and the pancreas were relatively well defined, suggesting that other organs were not involved by direct invasion.

**Abdominal magnetic resonance imaging:** A fist-sized tumor was observed on the greater curvature of the stomach in the gastric body. Although involvement of the greater omentum was strongly suspected, the boundaries between the tumor and the transverse mesocolon or the pancreas were relatively clear, suggesting that there was no direct invasion of these organs.

**Preoperative surgical diagnosis:** Based on these results, the patient was diagnosed as having stage III advanced gastric cancer with ascites and metastasis to Group 1 lymph nodes around the stomach. The patient and his family were provided with an explanation of the disease, after which he gave informed consent to surgical resection and subsequent chemotherapy. Accordingly, total gastrectomy with D2 lymph node resection and splenectomy were performed on December 15, 2000 (Figure 2).

**Findings at laparotomy:** There was a fist-sized tumor on the greater curvature in the body of the stomach and the greater omentum was involved by the lesion. There was a hard, white nodule (10 mm in diameter) in the greater omentum that was separate from the
Figure 1. (TOP) Barium contrast radiograph showing an ulcerated protruding lesion in the body of the stomach on the greater curvature (white arrows). Involvement of the greater omentum is suggested, with tumor invasion beyond the serosa.

Figure 2. (BOTTOM) The primary tumor is located on the greater curvature, extending from the body of the stomach to the posterior wall of the antrum. It is an ulcerated mass about 8 cm along its major axis. The paragastric lymph nodes and the lesser omentum are also involved.
gastric tumor, and it was diagnosed as a metastasis by intraoperative frozen section examination (P1; p+) (Figure 3-A). No masses were palpable in the liver (H0), but the Group 1 lymph nodes around the stomach were markedly enlarged (N1). There was a small amount of ascites, but the transverse mesocolon and the pancreas were intact and no other organs were directly involved. Therefore, the patient had surgical stage IV disease [P1 (p1+) H0N1SE].

**Histological findings:** The primary tumor in the stomach was histopathologically a mucinous adenocarcinoma with subserosal invasion of the gastric wall (Figure 3-B). Among the lymph nodes resected during D2 dissection, only one of the Group 1 paragastric nodes (1/54 nodes) was involved by metastasis (Figure 3-C).

**Postoperative course:** The early postoperative course was uncomplicated, and the patient started to eat on the 7th hospital day. Although chemotherapy was scheduled to start from the 14th hospital day, it was delayed because his oral intake did not increase smoothly. On the 20th hospital day, vomiting developed and plain abdominal radiography revealed ileus due to small bowel obstruction. Conservative treatment using a long tube achieved temporary relief, but ileus recurred several times as his oral intake was increased, so adhesiolysis was performed on January 12, 2001. After this operation, there were no further problems with feeding and the patient was discharged with his wound completely healed on February 8, 2001. During outpatient follow-up in April 2001, abdominal ultrasonography, computed tomography, and magnetic resonance imaging detected at least two metastases each measuring 2 cm in diameter in segments 7 and 8 of the liver just under the right hemidiaphragm (Figure 4).

The patient was readmitted and received systemic chemotherapy with the low-dose CDDP + 5-FU regimen [1-4]. CDDP (5 mg/m² as a 1-hr intravenous infusion) and 5-FU (500 mg/m² as a 24-hr continuous intravenous infusion) were given on 5 consecutive days per week for 2 weeks per month followed by a 2-week drug holiday as one course (Figure 5). In July 2001, after three courses of this treatment had been completed, the metastases in segments 7 and 8 of the liver were almost eliminated along with the ascites on CT and MRI (Figure 6). A total of six courses were given over about 6 months. There were no significant adverse reactions, such as alopecia, anorexia, or laboratory abnormalities.
Figure 3. (TOP) A 1-cm metastatic nodule that was detected in the greater omentum separate from the main lesion: evidence of peritoneal seeding (A; left upper, H.E. stain, x 200). The primary tumor is a mucinous adenocarcinoma and the depth of tumor invasion is subserosal (B; lower, H.E. stain, x 40). A metastasis detected among the paragastric lymph nodes near the primary tumor on the posterior wall of the body of the stomach (C; right upper, H.E. stain, x100).

Figure 4. (BOTTOM) Abdominal ultrasound (left) and abdominal MR imaging (right) at 4 months after surgery. At least, two metastases can be seen in the right lobe of the liver (segments 7 and 8) just beneath the right hemidiaphragm.
5 consecutive days per week / x 2 weeks / x 6 courses

Day 1—— 5 —— 8 —— 12 —— 28 / 1 course

CDDP 5 mg/m² (1-hr intravenous infusion)
5-FU 500 mg/m² (24-hr continuous intravenous infusion)

Figure 5. (TOP) Schedule for consolidation chemotherapy with 2 weeks of low-dose cisplatin (CDDP) plus 5-fluorouracil (5-FU) and a 2-week drug holiday (4 weeks per course).

Figure 6. (BOTTOM) Abdominal MR image obtained after three courses of chemotherapy with low-dose CDDP + 5-FU (left). The metastases in segments 7 and 8 of the liver have almost disappeared. Abdominal MR image obtained after six courses of treatment (right). The liver metastases have been completely eliminated.
(leukopenia, thrombocytopenia, or renal dysfunction). However, prominent skin pigmentation was noted. Before the 7th course of chemotherapy, the patient stated that he wanted to cease inpatient therapy and take oral anticancer drugs on an outpatient basis instead. Therefore, maintenance therapy was started with oral TS-1 (80 mg/day) + LV (30 mg/day). The drugs were administered daily for 4 weeks followed by a 2-week drug holiday, so a total of 6 weeks was required per course. During the 4th week of this treatment, however, severe diarrhea developed. Accordingly, the dose of LV was reduced to 20 mg/day and the schedule was changed to 2 weeks of treatment followed by a 2-week drug holiday (a total of 4 weeks per course) (Figure 7).

14 consecutive days per month x 18 courses

Day 1 ——— 14 ——— 28 / 1 course

TS-1 ; 80 mg / day (orally ³)

Leucovorin ; 20 mg / day (orally ⁰)

Figure 7. Schedule for oral maintenance therapy with 2 weeks of TS-1 plus leucovorin (LV) and a 2-week drug holiday (4 weeks per course).

At about 2 years and 10 months after surgery, the patient is still receiving this treatment on an outpatient basis without any signs of recurrence, including ascites, new liver metastases, or increased levels of tumor markers.

Discussion

The response rate to 5-FU or CDDP alone has been reported to be about 20%, while treatment with 5-FU plus CDDP increases the response rate to 30-40% or more (Ohtsu, Yoshida et al., 1991; Lacave, Barón et al., 1991; Cohn, Tester et al., 1998). The antitumor effect of 5-FU depends on inhibition of DNA synthesis by the formation of a ternary complex between FdUMP (a metabolite of 5-FU), methylenetetrahydrofolate (CH₂FH₄), and thymidylate synthase (TS), leading to the inactivation of TS (Hsu, Yeh et al., 1997; Kim, Murakami et al., 1999; Chen, Liu et al., 1999). On the other hand, CDDP blocks the uptake of methionine by cells in addition to inhibition of DNA synthesis. If intracellular
methionine stores are depleted by administration of CDDP, methionine synthesis is activated and folate metabolism is also accelerated. This increases the level of CH$_2$FH$_4$ and promotes that antitumor effect of 5-FU. Low-dose CDDP is less likely to cause adverse reactions; it promotes apoptotic cell death through a receptor signaling pathway even in the absence of intracellular free platinum, while the increase of folate metabolites due to CDDP and stimulation of a non-receptor signaling pathway by 5-FU are reported to facilitate the apoptotic death of gastric carcinoma cells (Kim, Tanabe et al., 2002). Intermittent administration of 5-FU has been reported to reduce its toxicity (Terashima, Irinoda et al., 2003). Although a higher response rate can be achieved, patients are often hospitalized for long periods because 24-hr infusion must be continued for 4-6 weeks (Kondo, Murase et al., 1996; Ogawa, Maki et al., 1999; Mori, Masaki et al., 1999; Shinkai, Kida et al., 1999). Accordingly, we modified the regimen to give at least six courses in order to compensate for shortening the duration of administration to 2 weeks per month. Despite the relatively sustained duration of administration (2 weeks per month), there were no adverse effects such as myelosuppression, renal dysfunction, or diarrhea throughout the treatment period. However, the patient developed prominent brown pigmentation of the face, fingers, and forearms, which was probably caused by the impact of 5-FU on epidermal keratinocytes and prickle cells.

TS-1 was developed by combining tegafur with gimeracil (CDHP), which is a dihydropyrimidine dehydrogenase (DPD)-inhibiting fluoropyrimidine, and oteracil potassium (Oxo) to minimize the gastrointestinal toxicity of 5-FU. This is a new-generation fluoropyrimidine preparation with double modulation. Our patient was given oral chemotherapy with triple-modulation by adding LV, and this may be the most powerful combination available and seems promising as a next-generation oral fluoropyrimidine regimen that is stronger than Orzel (UFT + LV). However, when the standard 6-week course of this therapy (4 weeks of treatment plus a 2-week drug holiday) was attempted, severe diarrhea developed during the 4th week. After the regimen was modified to 2 weeks of treatment followed by a 2-week drug holiday, few adverse effects were noted and outpatient treatment has since been continued for more than 1.5 years. In Japan, the national health insurance system has only approved this regimen for gastric
cancer and cancer of the head and neck. It is hoped that the indications for next-generation oral fluoropyrimidine preparations, including TS-1, will be expanded in the future as the optimum dose and schedule for employment of these preparations after intravenous consolidation therapy and for oral outpatient maintenance therapy are determined.

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References


