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A Case of Gastric Cancer with Peritoneal Metastasis Effectively Treated by a Prolonged Period of S-1 Therapy, Combined with Paclitaxel as Second-line Chemotherapy

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We describe a patient with peritoneal metastasis from gastric cancer treated with S-1 (TS-1®) in whom survival was further prolonged by concomitant treatment with paclitaxel (Taxol®), given as second-line chemotherapy. S-1 (80 mg/day) was given orally for 21 days, and paclitaxel (40 mg/m^2) was given by intravenous infusion on days 1, 8, and 15 of a 5-week cycle, administered primarily on an outpatient basis. A 61-year-old man presented with body weight loss. Type 4 gastric cancer was diagnosed on endoscopic examination. The patient underwent total gastrectomy for gastric cancer with peritoneal metastasis. Twelve cycles of S-1 were given postoperatively. A computed tomographic scan revealed increased peritoneal metastasis and disease recurrence. Paclitaxel was therefore given concomitantly with S-1. After 11 cycles of combination chemotherapy, peritoneal metastasis remained unchanged. The patient died 3 years 7 months after the diagnosis of peritoneal metastasis. In the patient with gastric cancer and peritoneal metastasis relatively refractory to S-1 therapy, the combination of a low weekly dose of paclitaxel and S-1 prolonged survival further without severe toxicity. We conclude that this regimen can be given for many cycles on an outpatient basis and prolong survival.

Key words: S-1, paclitaxel, gastric cancer, peritoneal metastasis

Introduction

Peritoneal metastasis is the most frequent type of recurrence associated with advanced gastric cancer, accounting for 40% to 50% of all recurrence[1)2)]. Combination regimens of chemotherapy including 5-fluorouracil (5-FU) are often used to treat gastric cancer and have a response rate between 20% and 40%[3)4)]. S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, has a response of 44% to 49% in advanced gastric cancer[5)6)]. We therefore use S-1 as first-line chemotherapy in outpatients with advanced gastric cancer. Patients who do not respond to first-line treatment are candidates for second-line chemotherapy with topoisomerase I inhibitors or taxane derivatives such as paclitaxel[7)]. We describe a patient with gastric cancer and peritoneal metastasis who responded to a combination of S-1 and a low weekly dose of paclitaxel, used as second-line chemotherapy.

Case Report

A 61-year-old man consulted a local physician in March 1999 because of body weight loss. Endoscopic examination of the stomach revealed a type 4 gastric cancer between the angulus and antrum. The patient was introduced to our hospital for further evaluation and treatment. A computed tomographic (CT) scan showed abdominal aortic aneurysm 5 cm in diameter and no metastatic lesions in abdominal cavity (Fig. 1a). Surgery was performed for gastric cancer. The omentum had clumped together, and many nodules were sporadically found at the splenic hilum and the right sub-

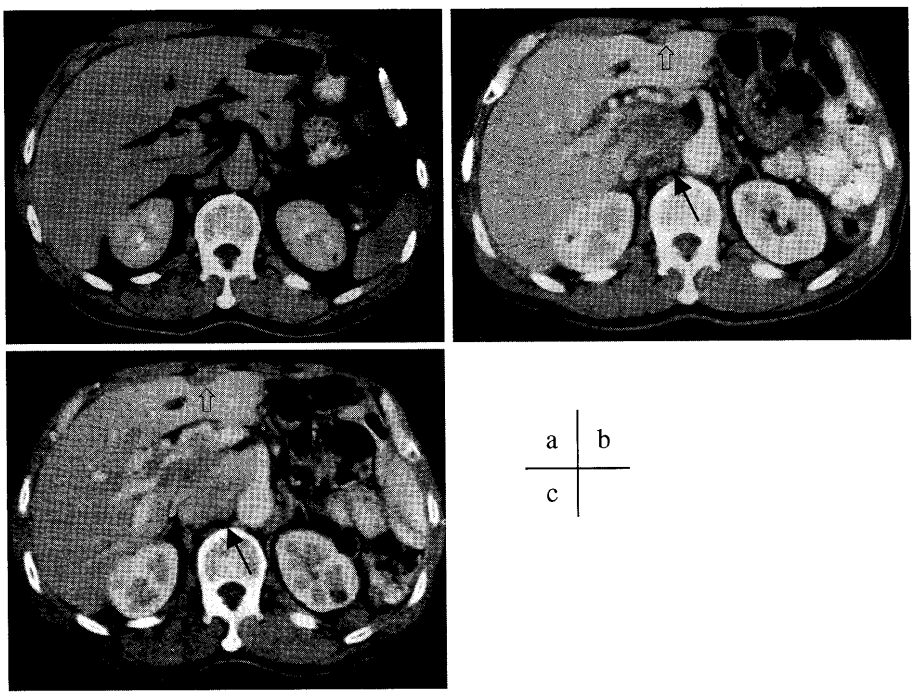

Fig. 1 Computed tomographic (CT) scans obtained in patient
a: CT scan showed no metastatic lesions in abdominal cavity preoperatively. However, many nodules were sporadically noticed at omentum, splenic hilum and right subdiaphragmatic region during surgery.
b: After 12 courses of chemotherapy with S-1 (24 months), recurrence was found from the porta hepatis to the head of the pancreas (→). Peritoneal metastasis had increased at the right subdiaphragmatic region (⇨).
c: After 11 courses of S-1 plus paclitaxel (14 months), recurrence from the porta hepatitis to the head of the pancreas had increased (→). The peritoneal metastasis in the right subdiaphragmatic region was unchanged (⇨).

diaphragmatic region. Peritoneal metastasis was diagnosed. Cytological examination of peritoneal cells showed adenocarcinoma (CY1). Total gastrectomy with splenectomy and dissection of the D2 lymph nodes was performed. Histopathological examination revealed a stage IV mucinous adenocarcinoma (T3, N2, M0) with peritoneal metastasis (P1). The postoperative course was good. After discharge, treatment with S-1 was begun. Each course of treatment consisted of 120 mg/day of S-1 for 4 weeks followed by no treatment for 2 weeks. CT scan obtained in July 2001, after the patient had received 12 courses of treatment with S-1 (24 months), showed increased peritoneal metastasis in the right subdiaphragmatic region and tumor recurrence from the porta hepatis to the pancreatic head (Fig. 1b). Antitumor effect of S-1 regimen was progressive disease. However, in consideraton of peritoneal metastasis from gastric mucinous adenocarcinoma confirmed intraoperatively, the growth of cancer was slow and considered to be inhibited by S-1. Therefore, S-1 was continued in second-line chemotherapy.

The time courses of tumor markers are shown in Fig. 2. Tumor marker levels increased with time. However, CT scanning showed a gradual increase in metastasis after 2 years of oral treatment with S-1. Furthermore, the patient had no signs or symptoms of peritoneal metastasis or of toxicity. S-1 was considered to be effective. Therefore, the drug was continued at a dose of 80 mg/day for 3 weeks followed by 2 weeks of no treatment. The patient additionally received 40 mg/m^2 of paclitaxel, given as a 90-min intravenous infusion on an outpatient basis, on days 1, 8, and 15. To prevent hypersensitivity reactions, 20 mg of dexamethasone and 50 mg of ranitidine were infused intravenously 45 min before paclitaxel administration, and 50 mg of diphenhy-

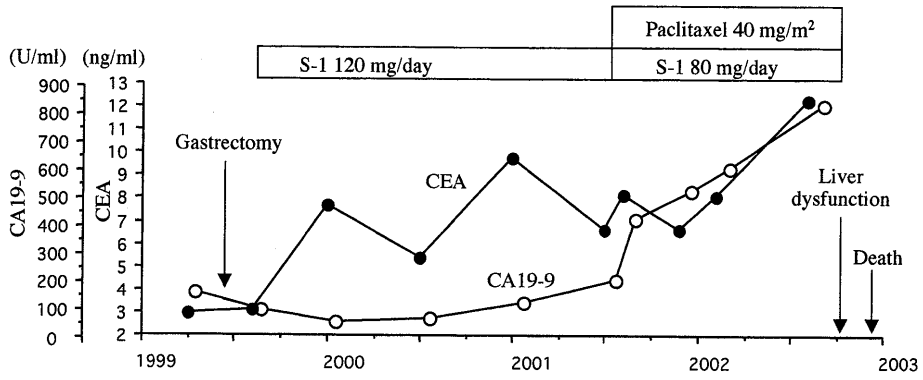

Fig. 2 The time courses of tumor markers
Tumor marker levels increased with time. However, the patient had no signs or symptoms of peritoneal metastasis until liver dysfunction was presented. CA 19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen

dramine was simultaneously given orally.

In September 2002, after the patient had received 11 courses of treatment with S-1 and paclitaxel (14 months), there was a gradual moderate increase in recurrence from the porta hepatis to the pancreatic head, but the peritoneal metastasis at the right subdiaphragmatic region was unchanged (Fig. 1c). Antitumor effect of S-1 plus paclitaxel regimen was no change. The patient was free of signs and symptoms. Except for mild alopecia, the combination of S-1 and paclitaxel had no toxic effects and could be continuously given on an outpatient basis. Subsequently, the patient was temporarily admitted to the hospital because of mild obstructive jaundice cause by recurrence at the porta hepatis, and chemotherapy was discontinued because of liver dysfunction. The patient died 3 years 7 months after the diagnosis of peritoneal metastasis.

Discussion

Most cases of gastric cancer with peritoneal metastasis cannot be cured by surgical resection, chemotherapy and radiation therapy. However, multidisciplinary therapy can have an important role. At our department, palliative gastrectomy is performed in patients with peritoneal metastasis who satisfy three conditions. First, primary gastric cancer is expected to cause gastric obstruction, perforation, or bleeding before the development of ileus due to peritoneal seeding. Resection of the primary lesion is necessary to relieve gastric symptoms. Second, palliative gastrectomy with removal of a large portion of tumor is likely to increase the potential benefits of chemotherapy. Third, palliative gastrectomy is expected to prolong survival. Several reports have strongly recommended palliative gastrectomy as the treatment of choice for gastric cancer with peritoneal seeding[8)9)]. We therefore performed total gastrectomy with splenectomy and D2 lymph node dissection in our patient since the lesions appeared to have been completely resected on macroscopic examination.

A standard regimen for the postoperative chemotherapy of gastric cancer has not to be established yet, but 5-FU-based regimens with methotrexate, leucovorin and cisplatin were often used as first-line chemotherapy in the 1990s. However, several phase II studies of S-1 have reported high response rates as described above[5)6)]. S-1 produces a sustained, stable plasma concentration of 5-FU, similar to that obtained with continuous intravenous infusion of 5-FU[10)]. In addition to a good response, S-1 can be given on an outpatient basis and is less toxic than conventional chemotherapy. In view of therapeutic effectiveness and the quality of life, we use S-1 as first-line chemotherapy in patients with peritoneal seeding at our department.

Patients who do not respond to first-line treatment are candidates for second-line chemotherapy with cisplatin, CPT-11 or paclitaxel[7)11)12)]. Cisplatin has some severe side effects such as nephrotoxicity and myelosuppression. Diarrhea and myelosuppression occasionally occur during CPT-11 therapy[13)]. In

consideration of the side effects, cisplatin and CPT-11 are difficult to be administered in outpatients for a long time. Paclitaxel is a novel agent with a unique cytotoxic mechanism of action that involves tubulin stabilization and polymerization, resulting in non-functional microtubules[14]. In human carcinoma cell lines in vitro, a combination of paclitaxel and 5-FU has demonstrated additive or subadditive enhancement of activity[15]. Clinically, chemotherapeutic agents including 5-FU and paclitaxel provided a response rates between 32% and 51% with modest side effects[16)17)]. Because the activity of paclitaxel is enhanced by concomitant therapy, we often combined S-1 with paclitaxel for second-line therapy in peritoneal metastasis of gastric cancer at our department.

The median survival time of patients who have gastric cancer with peritoneal metastasis is less than 12 months[1)2)]. During the past 13 years at our department, the median survival time after gastrectomy in patients with peritoneal seeding was 6 months, with 1-year and 5-year survival rates of 27% and 6%, respectively. In our patient with gastric cancer and peritoneal metastasis relatively refractory to S-1 therapy, a combination of paclitaxel and S-1 as second-line chemotherapy produced a long-term stable response and prolonged survival to 3 years 7 months after surgery.

In consideraton of peritoneal metastasis due to gastric mucinous adenocarcinoma, the tumor growth was slow and considered to be inhibited by S-1 in first-line therapy. Therefore, we added paclitaxel to S-1 as second-line therapy. This second-line therapy was well tolerated: the patient received 11 cycles of the combined regimen. We attributed the prolonged survival in our patient primarily to the therapeutic effects of paclitaxel plus S-1. Macroscopic evidence of complete tumor resection is also considered an important factor related to prolonged survival.

The recommended dosage of paclitaxel for gastric cancer is 210 mg/m^2 once every 3 weeks. However, low-dose paclitaxel once weekly is as effective as 210 mg/m^2 of paclitaxel once every 3 weeks and can be given on an outpatient basis[18]. In recent phase II studies, Honecker and Kollmannsberger combined weekly paclitaxel with 5-FU, folinic acid, and cisplatin and reported a response rate of 48% in patients with gastric cancer[16]. This response is similar to that with paclitaxel once every 3 weeks, with a lower frequency of leukopenia[19)20)]. The recommended dose for weekly treatment with paclitaxel is generally 60 to 90 mg/m^2. Because he is the first patient combined with paclitaxel in our hospital and had severe abdominal aortic aneurysm, we administered a low weekly dose of paclitaxel (40 mg/m^2). The dose of paclitaxel was not increased thereafter, since tumor growth was very slow and he had great performance status during long-term treatment (long stable disease). Paclitaxel continued at a dose of 40 mg/m^2 on an outpatient basis, and there were no toxic effects during long-term treatment except for alopecia.

It remains unclear whether 40 mg/m^2 of paclitaxel weekly is the optimal dose for combination with S-1. However, Ohchi et al have reported a good response to a combination of 100 mg/day of S-1 and low-dose (60 mg/time) weekly paclitaxel in a patient who had advanced gastric cancer with pancreatic involvement[21]. This dosage is similar to that given to our patient and may be sufficient for combined chemotherapy. Further studies should be performed to establish the optimal dosage of paclitaxel for combined chemotherapy.

The levels of tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 increased gradually over time. However, our experience suggests that a combination of paclitaxel and S-1 inhibited tumor growth for a prolonged period, as confirmed by radiographic examination. Combined chemotherapy with S-1 and paclitaxel was associated with great performance status and prolonged survival, without severe side effects. Our results indicate that S-1 plus a low weekly dose of paclitaxel can be given for many cycles on an outpatient basis and has clear-cut benefits in terms of survival and patients' quality of life.

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Second-line に paclitaxel の併用で長期の S-1 投与が有用であった胃癌腹膜転移の1例

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われわれはS-1の反応が悪くなった胃癌腹膜転移の1例に2nd-line chemotherapyとしてpaclitaxelを併用して有効であったことを報告する．投与方法はS-1 80mg/日 3週連日経口投与＋paclitaxel 40mg/m^{2}をday 1, 8, 15に点滴静脈注射し，2週休薬する5週間1コースの併用である．主に外来化学療法として行った．症例の腹膜転移を有する4型胃癌に対し，胃全摘＋脾合併切除術，D2郭清を施行した．術後S-1を12コース投与した．CTで右横隔膜下に腹膜転移の増強と肝門部に再発の増大を認めたため，paclitaxelを併用した．併用11コース後，肝門部再発が徐々に軽度増大したが，腹膜転移は不変で，長期間にわたって全身状態は良好であった．腹膜転移診断後3年7ヵ月でご永眠された．S-1の反応が悪くなった胃癌腹膜転移例に2nd-line chemotherapyとしてpaclitaxelを併用して生存期間をさらに延長したと考えられる．この化学療法は重症な副作用がなく，外来で頻用できる有効な治療である．