Unresectable Alpha Fetoprotein-producing Gastric Cancer Successfully Treated with Irinotecan and Mitomycin C after S-1 Failure

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Abstract

Diagnostic imaging of a 70-year-old woman revealed widespread lymph node swelling and pyloric stenosis due to alpha fetoprotein-producing gastric cancer. Second line chemotherapy of irinotecan and mitomycin C was administered after S-1 failure. After 6 courses of 2nd line chemotherapy, pyloric stenosis was improved, and lymph node swelling disappeared. This patient has been alive without disease for more than 3 years since 2nd line chemotherapy began and for more than 4 years since her first admittance to our hospital. Second line chemotherapy may have contributed to the favorable clinical outcome in this patient.

(Key words: gastric cancer, survival time, second line chemotherapy, complete response, anticancer drugs)

Introduction

Alpha fetoprotein (AFP)-producing gastric cancer (AFPGC) accounts for only 2–9% of gastric cancer (1). In such patients, liver metastases are often noted (2), or the tumor has progressed to advanced gastric cancer at the time of diagnosis. Few of these patients survive for a long period if they are treated with chemotherapy. Recently, novel anticancer drugs such as S-1 and irinotecan (CPT-11) are used for the treatment of advanced gastric cancer. S-1, in which tegafur is combined with modulators, showed high response rates for gastric cancer in recent phase II studies (3, 4). Chemotherapy with CPT-11 and mitomycin C (MMC) was introduced for patients with advanced gastric cancer at our institution in 1999. CPT-11 is expected to be a promising antitumor drug against unresectable gastric cancer that is resistant to prior therapy (5). However, this combination therapy has rarely achieved a complete response (CR) in patients with unresectable gastric cancer.

Herein, we report a patient diagnosed as unresectable AFPGC and treated with 1st chemotherapy of S-1, who survived without recurrence for more than 3 years after being treated with 2nd line chemotherapy with CPT-11 and MMC.

Case Report

The patient was a 70-year-old woman, 151 cm tall and weighing 49.0 kg. She visited our hospital for further evaluation of abdominal fullness in June 1999. She had been in good health, and no specific family or past medical history was noted. Her body temperature was 36.6°C with blood pressure at 110/66 mmHg. Her radial pulse rate was 72 beats/min and regular. She had neither anemia nor jaundice. A neurological examination revealed no abnormal findings, and there was no lymphadenopathy.

Laboratory tests showed a red blood cell count of 409×10^4/ml, a white blood cell count of 7,200/μl, and a platelet count of 22.6×10^4/μl. Hemoglobin concentration was 12.7 g/dl. The levels of hepatic and biliary enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), leucin aminopeptidase (LAP), γ-glutamyltranspeptidase (γ-GTP), and lactate dehydrogenase (LDH) were normal. A test for C-reactive protein revealed a level of 0.14 mg/dl (NR <1.0 mg/dl). On renal function tests, blood urea nitrogen and creatinine levels were normal. Serological studies for hepatitis B and C viruses were negative. Regarding tumor markers, carbohydrate antigen 19–9 was negative, however, carcinoembryonic antigen (CEA) and AFP were high at 137.7 ng/ml (normal ʽ5 ng/ml) and 26.1 ng/ml (normal ʽ10 ng/ml), respectively.

Barium meal examination (Fig. 1) and endoscopic examination (Fig. 2) revealed pyloric stenosis due to advanced gastric cancer of type 3. A diagnosis of moderately differentiate-
ed adenocarcinoma was made by the pathological examination of biopsy specimens obtained from the lesion. Immunohistological studies were carried out for biopsy specimens and cancerous lesions represented a positive immunohistochemical reaction for AFP (Fig. 3). Examination by computed tomography (CT) showed a large tumor, about 5 cm in diameter, in the antrum (Fig. 4A) and lymph node swelling at the #3, 4d, 6, 7, 11, and 16 according to the Japanese classification of gastric carcinoma (6), which was suggestive of lymph node metastasis (Fig. 4B). She was diagnosed as having advanced AFPGC. The final diagnosis was T3, N3, M0 and stage IV according to the Japanese classification of gastric carcinoma (6). At that time a curative operation was considered to be impossible. Gastrojejunal bypass surgery was performed to avoid obstruction. Thereafter she received three courses of chemotherapy consisting of S-1 [100 mg/body/day, every day (day1–28), p.o.]. She had grade 1 nausea as an adverse reaction during S-1 chemotherapy (7). Though the primary lesion was reduced in size by 70% and was considered as “No Change” (NC), the metastatic lymph nodes were reduced to 30% of their original size and judged to be “Partial Response” (PR) after 2 courses of treatment. After 2 courses of S-1 therapy, serum level of CEA was decreased to 29.9 ng/ml, however, AFP level was increased to 80.5 ng/ml. She received 3 courses of S-1 therapy in total. However, after 3 courses, the lymph nodes enlarged again. Serum levels of CEA and AFP had reached 196.9 ng/ml and 130.2 ng/ml, respectively in December 1999. The patient underwent 2nd line chemotherapy with a 90-minute infusion of CPT-11 150 mg/m² I.V. day 1, and bolus infusion of MMC 5 mg/m² I.V. day 1, repeated every 2 weeks, followed by 6 courses of chemotherapy. Endoscopic examination after 6 courses of chemotherapy revealed an improvement of pyloric stenosis (Fig. 5), and disappearance of type 3 gastric cancer and lymph node swelling (Fig. 6). After chemotherapy, serum levels of AFP and CEA were decreased to the normal range (AFP: 2.3...
ng/ml, CEA; 2.2 ng/ml). Her clinical course is shown in Fig. 7. She appeared to have CR after 6 courses of chemotherapy. She had grade 3 leukopenia as an adverse reaction during 6 courses of chemotherapy (7). She underwent an additional 5 courses of CPT-11/MMC chemotherapy (MMC 5 mg/body) and a further 5 courses of CPT-11 alone in succession in the outpatient clinic. Second line chemotherapies were completed by January 2001 and additional therapy was not performed. She has been under close periodic observation, and there has been no evidence of disease for more than 3 years since 2nd line chemotherapy commenced. And she has been alive for more than 4 years since her first admittance to our hospital.

Discussion

Generally, the prognosis for AFPGC is poor because in such patients, liver metastases are often noted at the time of diagnosis (2, 8). Even if the tumor is early gastric cancer, AFPGC have a tendency to cause liver metastasis, blood vessel invasion, or lymphatic vessel invasion (9). In the present case, she was diagnosed as unresectable because of widespread lymph node metastases.

Various combination regimens of chemotherapy have been reported for the treatment of gastric cancer and these include 5-fluorouracil (5-FU), doxorubicin, MMC, methotrexate, leucovorin, and cisplatin (10). The combined use of cisplatin, 5-FU and epirubicin had been reported to be effective for AFPGC (8), however, a standardized treatment has not been established. Recently, novel anticancer drugs such as S-1, CPT-11, paclitaxel and docetaxel are used for the treatment of advanced gastric cancer. S-1 is a new oral-agent combining of tegafur, a prodrug of 5-FU; 5-chloro-2, 4-dihydroxypyridine (CDHP), an inhibitor of 5-FU catabolism; and potassium oxonate (Oxo), an inhibitor of 5-FU-induced diarrhea (11). In the 2 independent phase II studies conducted in Japan, S-1 showed high response rates of 49% and 44% (3, 4). Thus, S-1 was reported to be effective in patients with advanced gastric cancer, and it has been approved for use in the treatment of advanced gastric cancer in Japan. In the present case, the patient showed partial remission (PR) after 2 courses of chemotherapy with S-1. However, after 3 courses, the disease progressed. CPT-11 is a derivative of camptothecin, a topoisomerase-I inhibitor with marked cytotoxic activity (12). Futatsuki et al reported that the overall response rate was 23.3% and the response rate was 16.1% for the patients who had received prior chemotherapy in the late phase II study (5). Second line therapy with CPT11/MMC
was chosen in the present case because Yamao et al reported that this therapy was effective against advanced gastric cancer, and there was little cross-resistance with 5-FU based regimens (13). The present patient achieved CR after 6 courses of CPT-11/MMC chemotherapy. Second line therapy with CPT-11/MMC was very effective, and well tolerated in the present case. To our knowledge, there have been no reports describing the effectiveness of CPT-11/MMC chemotherapy for AFPGC. We speculate that one of the reasons why the present case achieved CR was that liver metastasis was not seen at the diagnosis although widespread lymph node metastases were seen. The other reason might be that we tried to treat this patient with MMC. Takahashi showed that a combination of MMC and AFP antibody has an appreciable inhibitory effect on AFPGC tumor growth (14). Moreover, as to CPT-11, Shimada et al recently reported two

Figure 6. An abdominal computed tomography (CT) scan after 6 courses of irinotecan (CPT-11) and mitomycin C (MMC) revealed the disappearance of the tumor in the antrum (black arrows) (A) and lymph node swelling at #16 (black arrow) (B).

Figure 7. Patient’s clinical course after admission to our department. CEA: carcinoembryonic antigen, AFP: alpha fetoprotein, TS-1: S-1 (tegafur · gimeracil · oteracil potassium), CPT-11: irinotecan, MMC: mitomycin C.
cases with AFPGC with liver metastases successfully treated with CPT-11 (100 mg/body) plus low-dose cisplatin (10 mg/body) and described that this combination might be worth trying as 1st line chemotherapy for this disease (15). Thus, both CPT-11 and MMC may have promising antitumor activity against AFPGC. Further studies on the effectiveness of CPT-11/MMC chemotherapy for AFPGC are certainly necessary.

There have been several case reports of advanced gastric cancer in which CR was achieved after first or 2nd line chemotherapy with different regimens; CDDP/5-FU, 5-FU/adriamycin/MMC, MMC/5-FU/OK-432 (16), and S-1/CDDP (17). Recently, Shimada et al (18) described that CPT-11/low-dose CDDP regimen was recommended as a promising 2nd line chemotherapy for patients with metastatic gastric cancer resistant to 5-FU and 2 of their 21 patients achieved CR. However, the number of patients who achieved CR after 2nd line chemotheraphy was too small to make predictive analysis on effectiveness of 2nd line chemotherapy for gastric cancer patients in terms of age, sex, clinical stage, and microscopic and pathological features of gastric cancer. A large-scale control study is necessary in order to address the type of 2nd line chemotherapy and clinical outcome in patients with advanced gastric cancer.

To date, 17 patients with unresectable gastric cancer have received CPT-11/MMC chemotherapy at our institution. A phase II study of CPT-11/MMC chemotherapy is being conducted as the second line chemotherapy by Japan Clinical Oncology Group from which data should be analyzed. As with the present patient, there are some patients with unresectable gastric cancers who live for a long time, although such cases are very rare. Yamao et al (13) noted that 1 of 30 their patients who received 2nd line chemotherapy of CPT-11/MMC achieved CR. Thus, further studies on the combinations, administration method, and efficacy of the chemotherapies with novel drugs for advanced gastric cancer are necessary.

In conclusion, we report a patient with unresectable AFPGC that survived for more than four years after chemotherapy. Even in the 2nd line chemotherapy, CPT-11/MMC may contribute to the improvement in the prognosis of patients with unresectable gastric cancer, and this combination therapy is promising.

References