Unresectable Advanced Gastric Cancer Effectively Treated by Combined Chemo–Immunotherapy: A Report of Two Cases

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Summary: We have experienced two cases of unresectable advanced gastric cancer effectively treated by chemo-immunotherapy. One case was of a 68-year-old male patient diagnosed as having inoperable advanced gastric cancer with liver and lung metastasis. This patient was treated by combined chemo-immunotherapy of MMC 10 mg/M, 5'-DFUR 800 mg/day and OK-432 5 KE/2W. At 6 months later, a computed tomography (CT) scan and upper gastrointestinal (GI) series revealed that the metastatic liver tumors and stomach lesion were remarkably decreased in size, and endoscopic biopsy confirmed no cancer cells in the stomach lesion. Moreover, the metastatic lung tumor had disappeared on chest X-ray. The other case was of a 68-year-old female patient with unresectable advanced gastric cancer treated by combined administration of MMC 10 mg/M, 5-FU 200 mg/day and OK-432 5 KE/2W. At 2 months after commencing the treatment, there was a reduction in the serum carcinoembryonal antigen (CEA) level. At 6 months later, the CEA had decreased to normal, the primary and metastatic sites had completely disappeared on CT, and endoscopic biopsy confirmed no cancer cells in the stomach lesion. This patient has survived to date for 5 years and 6 months after commencing the treatment. These results suggested that combined chemo-immunotherapy of MMC, antimetabolite, and OK-432 was an effective treatment for unresectable advanced gastric cancer.

Key words gastric cancer, chemotherapy, immunotherapy

INTRODUCTION

The prognosis of unresectable advanced gastric cancer has been very poor. The 1-year survival rate of such cases has been only 10% [1]. Moreover, the positive-response rate of chemotherapy has been very low. However, chemotherapy was very effective in a few cases. In this paper, we present two cases of unresectable advanced gastric cancer treated effectively by combined chemo-immunotherapy. One case was an inoperable case with liver and lung metastasis. This case was treated by combined therapy of MMC, 5'-DFUR and OK-432, and the metastatic liver tumors and stomach lesion were remarkably decreased in size and the metastatic lung tumor disappeared. The other case with unresectable advanced gastric cancer was treated by combined therapy of MMC, 5-FU and OK-432, and the primary and metastatic sites completely disappeared. This patient has survived to date for 5 years and 6 months after commencing the treatment.

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CASE REPORT

Case 1

A 68-year-old man visited a private hospital because of diarrhea and weight loss in April 1991. Advanced gastric cancer with metastatic liver tumors was diagnosed based on abdominal ultrasonography (US), computed tomography (CT) and upper gastrointestinal endoscopy. The patient was referred to Kurume University Hospital for further examination and treatment for gastric cancer and metastatic liver tumors on June 17, 1991. Liver, spleen and tumor were not palpable on physical examination on admission. The serum level of carbohydrate antigen 19-9 (CA19-9) was normal, and that of carcinoembryonal antigen (CEA) was elevated at 16.8 ng/ml. Gastrography and upper gastrointestinal endoscopic examination showed gastric cancer type 3, about 10 cm in size, on the posterior wall of the upper body in the stomach (Figs 1a and 2a). The pathological diagnosis based on a biopsy specimen was tubular

Fig. 1. a: Before the treatment, Borrmann type 3 gastric cancer was recognized on the posterior wall of the upper body on the gastrography.

b: At 6 months after commencing the treatment, a conversing fold was recognized, and the surrounding elevated region had disappeared.

Fig. 2. a: Before the treatment, an irregular ulcer with a surrounding elevated region was recognized on the posterior wall of the upper body on endoscopy.

b: Eight months after commencing the treatment, ulcer lesion altered to scar and elevated lesion had disappeared.
adenocarcinoma moderately-differentiated type. CT showed low density masses of 8 cm, 2 cm and 1.5 cm in size at S8, S3 and S4 respectively in the liver suggesting metastatic liver tumors (Fig. 3a). A chest X-ray showed a metastatic tumor in the left lung (Fig. 4a).

This case was concluded to be inoperable. Treatment with combined chemo-immunotherapy of MMC 10 mg/M, 5'-DFUR 800 mg/day and OK-432 5 KE/2W was begun from June 25. The patient showed no side effects due to these drugs. The performance status (PS) of the patient had been 0 during the treatment. At 5 months after commencing chemo-immunotherapy, CT revealed that the metastatic liver tumors at S3, S4 had disappeared, and the tumor at S8 was remarkably decreased in size from 8 cm to 3 cm (Fig. 3b). Moreover, the metastatic lung tumor had disappeared on chest X-ray (Fig. 4b). At 6 months after commencing the therapy, gastrography showed a converging fold on the upper body and the
type 3 tumor had disappeared (Fig. 1b). At 8 months after commencing the treatment, endoscopic examination showed both the ulcer and the elevated region surrounding the tumor had altered to a flat lesion (Fig. 2b). Also, endoscopic biopsy confirmed no cancer cells in the gastric lesion. At 3 months after

Fig. 5. a: Before the treatment, Borrmann 2 type gastric cancer was recognized on the greater curvature of the antrum on gastrography. b: Twelve months after commencing the treatment, conversing fold was recognized, but tumor had disappeared.

Fig. 6. a: Before the treatment, irregular ulcer with surrounding elevated lesion was recognized at the antrum on the endoscopy.

b: Twelve months after commencing the treatment, ulcer scar completely covered with regenerative epithelium was recognized.
Fig. 7. Relationship between serum CEA and month of the treatment.

commencing the treatment, the serum level of CEA was decreased to 3.6 ng/ml. US showed no metastatic liver tumors in the liver, and the serum CEA level was only slightly elevated at 3.5 ng/ml, in April 1992. However, from July, the liver tumor began to metastasize again and the patient eventually died of liver metastasis on January 1, 1993.

Case 2

A 68-year-old woman visited a private hospital because of epigastric pain. The serum level of CEA was elevated at 464 ng/ml, and advanced gastric cancer was diagnosed based on gastrography and endoscopy. The patient was referred to Kurume University Hospital for further examination and treatment for advanced gastric cancer on April 10, 1991. The liver, spleen and tumor were not palpable on physical examination on admission. The serum level of CA 19-9 was normal, and that of CEA was elevated at 464 ng/ml. Gastrography and endoscopic examination showed gastric cancer type 2, 4.5 × 4.0 cm in size on the greater curvature of the antrum in the stomach (Figs 5a and 6a). The pathological diagnosis based on a biopsy specimen was moderately-to-poorly differentiated adenocarcinoma. No metastatic liver tumors were recognized, but swellings in the No.8 and No.9 lymph nodes were recognized on CT.

Surgery was performed through a median laparotomy. Several nodules of peritoneal dissemination were recognized on the greater omentum, and the tumor invaded the pancreas head and the portal vein on intraoperative US. This tumor was concluded to be unresectable, from these intraoperative findings. So, the operative procedure was exploratory laparotomy. Administration of MMC (18 mg iv) was given on the operative day, and administration of OK-432 (1 KE/day sc) was given from the second postoperative day to the fourth postoperative day. Administration of OK-432 (5 KE sc) every two days was begun from the sixth postoperative day. Administration of 5-FU (200 mg/day po) was begun from the 14th postoperative day, and the patient left the hospital on the 17th postoperative day. After that, the patient was treated by combined administration of MMC (10 mg/month), 5-FU (200 mg/day) and OK-432 (5 KE/2 weeks). At 2 months after the operation, there was a decrease in the serum CEA level (175 ng/ml). At 6 months after the operation, the serum CEA level had decreased to normal (2.9 ng/ml). An endoscopic examination showed the tumor decreased in size, and the elevated region changed to a flat lesion. The central ulcer lesion was reduced, and changed to a flat lesion covered with regenerative epithelium. Moreover, endoscopic biopsy confirmed no gastric cancer cells. At 12 months after the operation, an ulcer scar was recognized on gastrography (Fig. 5b), and the tumor completely disappeared with an ulcer scar on endoscopic examination (Fig. 6b). Swellings in the lymph nodes completely disappeared on CT. The side-effect of the treatment was only slight leukopenia, grade 2. The PS of the patient had been 0 during the treatment. The patient had survived for 5 years and 6 months from commencing the treatment (Fig. 7).

DISCUSSION

Generally, various combined chemotherapy of 5-FU, MMC and CDDP have been administered for unresectable gastric cancer, but a positive-response rate has been only about 20-30% [2]. Here, we present two cases with a good response to chemotherapy consisting of MMC (10 mg/month) intravenous administration, and 5'-DFUR (800 mg/day) or 5-FU (200 mg/day) per oral administration, and immunotherapy of OK-432 (5 KE/2 weeks) intrasubcutaneous administration. Kurihara et al. [3] reported the features of cases with good response to chemotherapy were Borrmann 2 macroscopic type, differentiated histological type, without metastatic lesions, and with good PS. The features of macroscopic improvement in gastric cancer by chemotherapy was alteration in the tumor to a flat lesion [3]. Both our two cases were differentiated histological type with good PS, and macroscopic type (case 2) Borrmann 2 type. The tumors were altered to a flat lesion by chemotherapy. Cases that have responded well to chemotherapy were clinically
improved after a short period [4-6], and at about 6 months after commencing treatment, no cancer cells were confirmed by endoscopic biopsy in these cases [6,7]. In our two cases, at 2 or 3 months after commencing treatment, there was a decrease in the serum CEA level, and at 6 or 8 months after commencing the treatment, no cancer cells were confirmed by endoscopic biopsy. Some reports have said that administration of 5'-DFUR was effective for a metastatic lesion from gastroenterological cancer [8-11], and that combined chemotherapy of MMC and 5'-DFUR was effective for both the primary and the metastatic lesion in gastroenterological cancer [12-14]. There have been many cases on the efficacy of combined chemotherapy of MMC and antimetabolite [2]. Arinaga et al. [15] have reported the efficacy of combined chemoinmunotherapy of MMC and OK-432. Both our two cases had no severe side effect, and the PS in these cases was good during the treatment. Combined chemoinmunotherapy of MMC, antimetabolite and OK-432 is thought to be an effective treatment for unresectable gastric cancer and is useful for an improved quality of life of the patient.

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