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Complete Response Obtained with S-1 Plus CDDP Therapy in a Patient with Multiple Liver Metastases from Gastric Cancer

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ABSTRACT

A 58-year-old woman with advanced gastric cancer underwent total gastrectomy in May 2012. The histological diagnosis was poorly differentiated adenocarcinoma, cT4a (SE), pN1, cM0; fStage IIIA. Chemotherapy by S-1 was started after surgery. Six months after the operation, two metastatic nodules were noticed on the liver. Therefore, the chemotherapy was switched to S-1 plus cisplatin (CDDP) in November 2012. TS-1 (80 mg/body) was administrated from day 1 to 21 followed by 14 days rest as one course. CDDP (70 mg/body) was infused on day 1. After 3 courses of this combination chemotherapy, remarkable diminution of the metastatic lesions on CT images was observed. Because of the adverse event of Grade 2 nausea, the patient was forced to discontinue chemotherapy. The patient underwent partial resection of the liver (Hr-0: S8, S7) at 1 year after the first operation. The resected specimens showed no sign of malignancy, although uneven fatty deposition was observed more frequently than in the surroundings, and designated as histologically complete response (CR). The patient has been alive 30 months after the second operation without any recurrent sites. Thus, combined use of peroral S-1 and CDDP should be recommended for multiple liver metastases after gastrectomy.

Key words: *Advanced gastric cancer, Chemotherapy, Liver metastasis, Complete response*

Gastric cancer remains one of the most common malignancies in Japan despite its reduced incidence and mortality. At the time of diagnosis, approximately 50% of patients with gastric cancer have metastatic disease. A number of randomized clinical trials have established the role of chemotherapy in the treatment of these patients. Previous reports demonstrated that patients who received chemotherapy had longer survival, when comparing chemotherapy plus best supportive care with best supportive care alone[4,5,23,25]. However, a standard combination chemotherapy regimen for advanced gastric cancer has not been well established. Recent reports have demonstrated that a response rate of 25.0 - 42.9% has been reported for S-1 applied to liver metastatic foci, and when combined with CDDP its response rate has been reported to be increased to up to 54.0%[17]. Therefore, the standard therapy for advanced gastric cancer with distant metastasis and recurrence is the systemic chemotherapy of S-1 combined with CDDP[3,11]. Herein, we report a case of metachronous liver metastases of gastric cancer, in which a pathological complete response of gastric liver metastases was confirmed after 3 cycles of chemotherapy with S-1 and CDDP.

CASE REPORTS

A 58-year-old woman visited her family doctor due to epigastric pain. She received gastroendoscopic examination and was diagnosed as type 2 advanced gastric cancer located in the upper part. She was transferred to our surgical division on March 1, 2011. There was nothing particular in her family history. She was 151 cm tall and 35.8 kg in weight on admission. No abnormal findings were found on laboratory findings other than a slight elevation of CEA level (CEA: 7.65 ng/ml). Upper gastrointestinal endoscopy showed a type 2 tumor in the upper part of the stomach (Fig. 1-a, b) and endoscopic biopsy revealed signet-ring cell carcinoma and tub1. Abdominal computed tomography (CT) showed thickening of the gastric wall and perigastric lymphadenopathy (Fig. 1-c). Under the preoperative diagnosis of advanced gastric cancer (U, post, type2, 45 × 30 mm, cT4a (SE), cN1, cH0, cP0, cM0, cStageIIIA), the patient underwent total gastrectomy with Roux en Y reconstruction and cholecystectomy in March 11, 2011. The resected surgical specimen showed a type 3 gastric cancer

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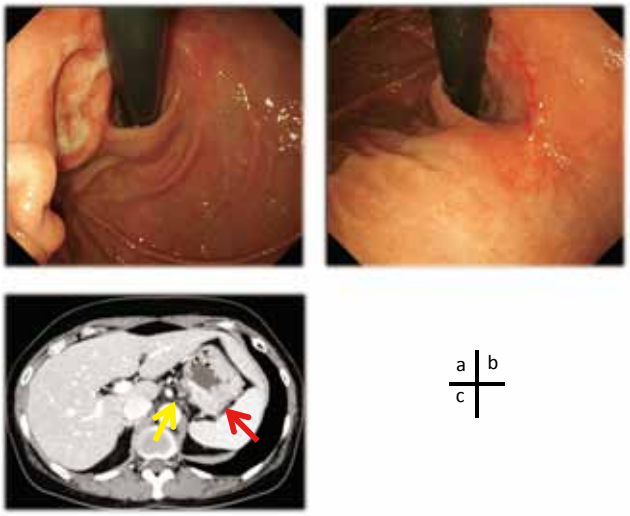

Fig. 1. (a) (b) Endoscopy showed a type 2 tumor in the upper part of the stomach. (c) CT showed gastric wall thickening and perigastric lymphadenopathy.

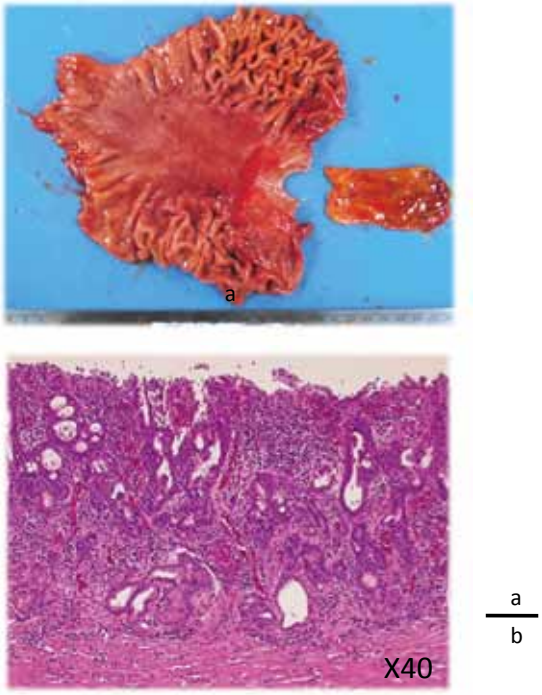

Fig. 2. (a) Gross finding of the surgical specimens showed a type 3 gastric cancer. (b) Microscopic findings revealed the main part was poorly differentiated adenocarcinoma.

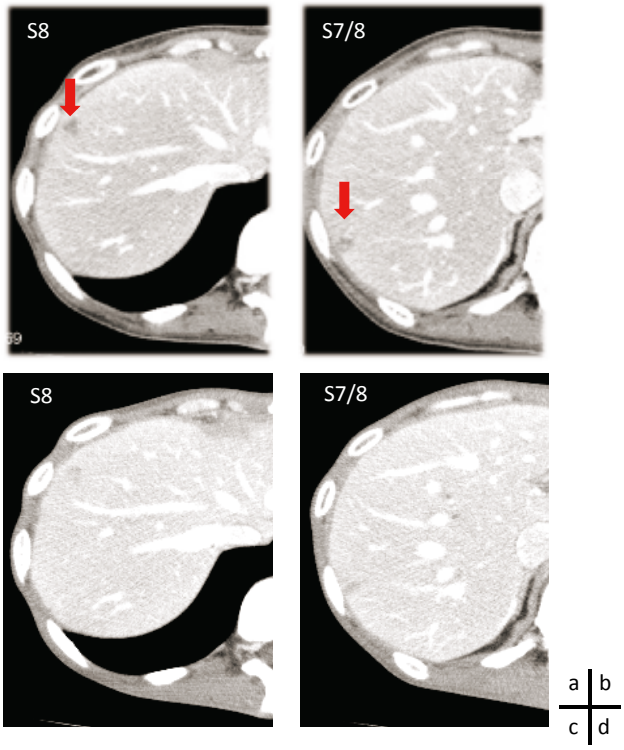

Fig. 3. (a) (b) Abdominal CT before combined S-1/CDDP therapy showed two nodules (S8, S7/8). (c) (d) Both nodules were remarkably diminished after 3 cycles of S-1/CDDP chemotherapy.

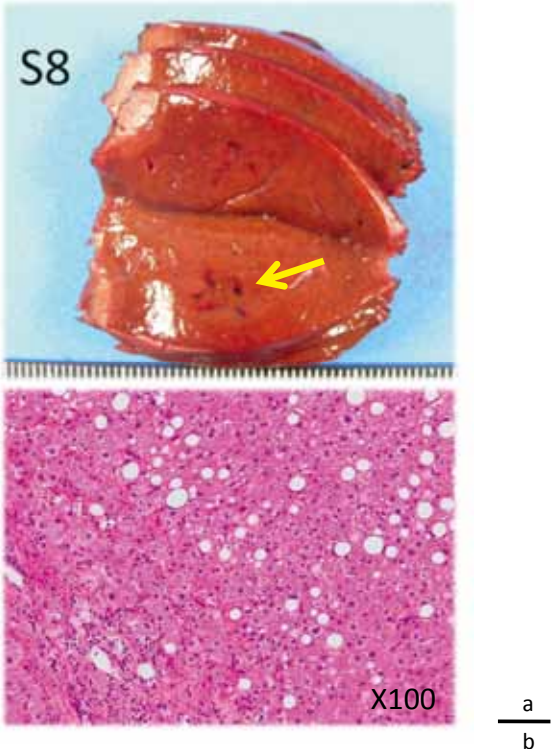

Fig. 4. (a) (b) The surgical specimens revealed no evidence of cancer, indicating pathological CR.

(Fig. 2-a) and the histological findings of gastric cancer revealed poorly differentiated (por1) > moderated differentiated adenocarcinoma (tub2) > signet ring cell carcinoma (sig) (Fig. 2-b). The final diagnosis was as follows: Gastric cancer U post type3 5.5 × 3.8 cm por1 > tub2 > sig se sci INFc ly1 v0 pPM0 pDM0 n (+) 2/61 pT4a pN1 cM0 f-StageIIIA. The CEA value had become normal (3.34 ng/ml) on April 12, 2011. Peroral administration of S-1 was started in conformity with the guideline two months after surgery. However, abdominal CT images showed two nodules (S8, S7/8) on the liver six months after the operation (Fig. 3-a, b) and the CEA levels were also increased to 14.58 ng/ml on September 11. Therefore, we diagnosed two nodules as metachronous metastatic lesions from gastric cancer and the chemotherapy was switched to S-1 (80 mg/body) plus CDDP (70 mg/body) in November 2012. TS-1 (80 mg/body) was administrated from day 1 to 21 followed by 14 days rest as one course. CDDP (70 mg/body) was infused on day 1. After 3 courses of this combination chemotherapy, remarkable diminution of the metastatic lesions was observed (Fig. 3-c, d), and FDG-PET revealed no accumulation. However, because of the adverse event of Grade 2 nausea, chemotherapy was discontinued. Because the general condition of the patient was stable, she underwent S8, S7/8 partial hepatectomy for liver metastasis to enhance the curability on March 26, 2012. The resected specimens showed no apparent evidence of metastatic tumor, although uneven fatty deposition was observed more frequently than in the surrounding tissue (Fig. 4-a, b), and designated as histologically complete response (CR). The patient has been alive 30 months after the second operation without any visible recurrent sites, although the tumor marker had been maintained at relatively high levels (Fig. 5).

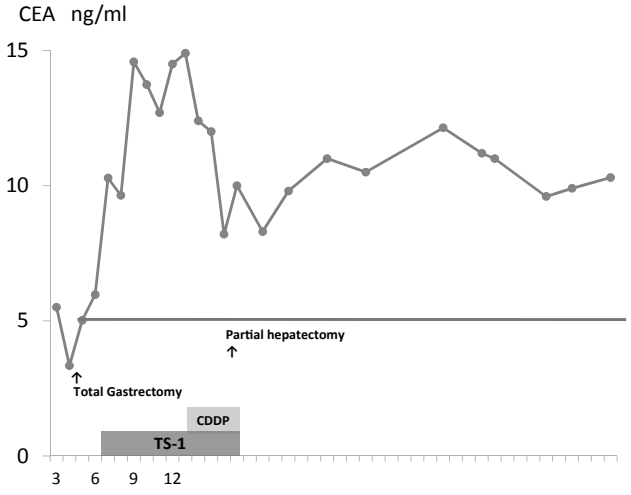

Fig. 5. The serial changes of CEA levels

DISCUSSION

Clinical trials of S-1 plus CDDP for advanced gastric cancer have yielded good responses and the treatment was well tolerated. In this S-1 plus CDDP versus S-1 alone in RCT in the treatment for advanced gastric cancer, it has been verified that overall survival is better in patients with advanced gastric cancer with S-1 plus CDDP than with S-1 alone[3,13]. Therefore, S-1 plus CDDP holds promise of becoming a standard first-line treatment for patients with advanced gastric cancer. In fact, there have been reports that combined use of S-1 and CDDP achieved complete response for gastric cancer with multiple liver metastases[2,6,7,18]. Including our case, the referral to surgical oncology is a crucial step for the documentation of pathological complete response. Anyway, it has been established that the strategy of combined use of S-1 and CDDP provides a promising treatment for far advanced gastric cancer with a limited number of liver metastases.

Early tumor detection, standardized surgical treatment including lymph node dissection and appropriate adjuvant therapy have improved the survival of patients with primary gastric cancer in Japan[22]. However, distant metastases of gastric cancer to the liver jeopardize the likelihood of a cure of the disease and the liver is considered a major site of treatment failure. Liver resection has been widely accepted as an effective treatment for metastatic colorectal cancer, and the indications for this procedure have been expanded to include all technically resectable metastases numbering four or more[12,15,28]. However, the benefits of a surgical approach to metastatic gastric cancer have remained debatable. This is because of extrahepatic diseases and advanced cancer progression such as peritoneal dissemination or extensive lymph node metastases[14,29]. Therefore, the indications of surgical resection of liver metastases in advanced gastric cancer are generally accepted as follows: (1) Peritoneal metastases or intensive periaortic lymphadenopathy are not found. (2) Liver ?metastasis lesions are resectable and curability B has to be achieved[9]. It has been reported that the recurrence rate after hepatectomy of gastric cancer metastases is 54.0%, which is considered to be high, and that the resection rate after hepatic recurrence is only 23.0%[8].

A previous report documented that the rate of liver metastases from gastric cancer was 4-14%, while the rate of hepatic resection remained at only 1-21%[18]. Out of patients who underwent liver resection for the treatment of metastases arising from gastric cancer, a few have survived long-term. These reports indicate that the 5-year survival and MST (mean survival time) after hepatectomy for metastases from gastric cancer range from 11.0 to 42.0% and from 12.0 to 21.4 months, respectively[1,20,21,27]. Recent reports revealed that all patients who sur-

vived for more than 5 years after initial hepatectomy had a solitary metastasis, and no patient with multiple metastatic disease survived beyond 3 years[10,16,24]. These reports indicated that the number of liver metastases, solitary or multiple, is a significant predictive factor and patients with a solitary liver metastasis are good candidates for surgical resection, whereas the number of liver metastases arising from colorectal cancer is no longer considered an important predictor of long term survival[15,25].

We herein reported a case of metachronous liver metastases of gastric cancer, in which a pathologically complete response of gastric liver metastases was confirmed histologically after 3 cycles of combined chemotherapy with S-1 and CDDP. The patient survived till September 2014, 30 months after hepatic resections of liver metastases. The patient had not received any chemotherapy, because she herself refused to undergo chemotherapy due to a severe adverse event. However, a favorable prognosis has been observed and no recurrences has been detected up to now by CT/MRI and PET images, although the tumor marker has not returned to under the normal level (CEA < 5 ng/ml). A previous report showed that the absence of serosal invasion was another influential factor for a good prognosis after hepatectomy, because the dissemination of malignant cells to the abdominal cavity is as fatal and controllable as extensive lymph node metastases and scattered liver lesions[13]. Thus, serosal invasion of primary gastric cancer is a significant poor prognostic factor following resection of gastric liver metastases. In conclusion, strict observation is needed for the development of peritoneal recurrences, because our case was positive in serosal invasion of primary gastric cancer.

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