Concurrent Proton Beam Radiotherapy and Systemic Chemotherapy for the Metastatic Liver Tumor of Gastric Carcinoma: a Case Report

Takeshi Gohongi1, Koichi Tokuuye2, Hiroyuki Iida1, Reiko Nakai1, Naoto Gunji1, Yasuyuki Akine2 and Kazuo Orii1

1Department of Surgery, Tsukuba-Gakuen Hospital, Tsukuba, Ibaraki and 2Department of Radiation Oncology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

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We report a case of a woman with a metastatic liver tumor from gastric carcinoma, who has been successfully treated with concurrent proton beam therapy and systemic chemotherapy. A 76-year-old woman underwent distal gastrectomy with regional lymph node dissection for advanced gastric carcinoma on January 17, 2002. She received five courses of sequential chemotherapy with methotrexate–5-fluorouracil after the surgical resection. A metastatic liver tumor was detected in the caudate lobe of the liver by computed tomography at 6 months after the surgical resection. We employed concurrent proton beam therapy and systemic chemotherapy which consisted of 5-fluorouracil (250 mg/body per day, as a 24-h intravenous injection for 4 weeks) and low dose cisplatin (10 mg/body on days 1–5 every week for 4 weeks). Proton beam therapy targeting the metastatic liver tumor was performed in a daily fraction of 3 Gy, 5 days per week, with a total dose of 66 Gy over 30 days. The tumor disappeared 3 months after the treatment and no recurrence has been observed for 2 years after termination of the treatment. Throughout the entire course of treatment, the patient received injections of granulocyte stimulating factor subcutaneously for grade 3 leukopenia. She never complained of abdominal symptoms, such as epigastralgia, nausea or diarrhea. Liver failure related to proton irradiation has not been observed. This concurrent proton beam radiotherapy with systemic chemotherapy could be an effective treatment modality for metastatic liver tumor from gastric carcinoma.

Key words: chemoradiotherapy – 5-fluorouracil – gastric carcinoma – metastatic liver tumor – proton

INTRODUCTION

Gastric carcinoma is one of the most common gastrointestinal malignancies in Japan for which the primary curative treatment is surgical resection including systematic dissection of lymphatic tissues. The prognosis of patients with advanced gastric carcinoma is still poor because of its high relapse rate even after curative resection. Systemic adjuvant chemotherapy has been studied extensively in past decades. However, an effective chemotherapeutic regimen in a post-operative setting has yet to be identified. Patients die from the development of symptomatic metastatic disease arising from unresected microscopic metastases. Liver metastasis is one of the most common failure patterns of gastric carcinoma after surgery along with peritoneal dissemination and extensive lymph node metastases. We report a case of a woman with a metastatic liver tumor from gastric carcinoma successfully treated with concurrent proton beam therapy and systemic chemotherapy.

CASE REPORT

A 76-year-old woman was referred to our hospital for appetite loss and nausea in December 2001. On physical examination, her conjunctiva was slightly anemic and laboratory tests showed her hemoglobin level to be 8.2 g/dl. Gastric endoscopic examination revealed a type 3 lesion on the lesser curvature of the antrum. Pathological examination of biopsy specimens showed moderately differentiated adenocarcinoma. Barium gastroscopy showed almost complete obstruction at the pyloric ring and barium flow was not observed in the duodenum (Fig. 1a). Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated no metastases in the lung, liver or brain, but multiple swollen lymph nodes along the common hepatic artery, whose sizes were 20 mm in maximum diameter (Fig. 1b). She previously underwent an appendectomy for acute appendicitis at age 45 and cholecystectomy for...
gallbladder stones at 50. At laparotomy on January 17, 2002, the tumor was located in the antrum and there was extensive lymph node swelling along the common hepatic artery but no peritoneal dissemination. She underwent distal gastrectomy and systematic dissection of regional lymph nodes encompassing the common hepatic artery, left gastric artery and celiac artery. Pathological examination of the resected specimen revealed that moderately differentiated adenocarcinoma of the stomach invaded the depth of the serosa membrane. Metastases in regional lymph nodes were detected in the infrapyloric, greater curvature and anterior superior group of the common hepatic artery nodes. Conclusive stage grouping according to the Japanese Research Society for Gastric Carcinoma proved to be stage IIIb (T3, N2, P0, H0). As adjuvant chemotherapy we applied methotrexate (MTX)/5-fluorouracil (5-FU) sequential chemotherapy (MTX; 150 mg/body, 5-FU; 900 mg/body, every 2 weeks). After five courses of the systemic chemotherapy, a metastatic liver tumor was detected by abdominal CT, whose size was 40 mm in diameter (Fig. 2). The tumor was located in the caudate lobe and appeared to involve the main trunk of the portal vein and inferior vena cava. There were no other metastases in the lung or brain, and no lymph node swelling or peritoneal dissemination. ECOG (Eastern Cooperative Oncology Group) performance status of the patient was grade 2 at the time of diagnosis because of shortness of breath after daily exercise and general fatigue, although respiratory function and laboratory tests showed no abnormality. After we informed her of the disease status, we opted for non-surgical therapy in consideration of her poor performance status. We chose concurrent proton beam therapy and systemic chemotherapy for the metastatic liver tumor from gastric carcinoma after the patient gave her informed consent for this treatment. Chemotherapy consisted of systemic infusion of 5-FU at a daily dose of 250 mg/body continuously for 4 weeks and cisplatin at a daily dose of 10 mg/body on days 1−5, 8−12, 15−19 and 22−26 (Fig. 3).

In the treatment of proton beam therapy, a clinical target volume was firstly contoured in the radiographically demonstrated gross tumor with 5 mm adjacent normal tissue on each CT image of the treatment planning CT and on the cranio-caudal dimension. Six treatment ports [anterior, posterior, right anterior oblique (330°, 300°), right posterior oblique (210°)], a 10 mm treatment margin for uncertainty of the
positioning and a 5 mm respiratory-gaiting margin to caudal direction for uncertainty of respiratory gaiting were determined. Optimal parameters were calculated for the beam delivery system including a length of the spread-out Bragg peak, range of proton beams, and shapes of compensating bolus and a collimator size. Dose distribution obtained using a pencil-beam algorithm showed that the tumor was satisfactorily covered within the 100% dose level and the dose of the surrounding liver tissue was acceptably low (Fig. 4). Patient positioning was adjusted by fluoroscopy at each treatment session and respiratory-gated irradiation was used to minimize irradiation of normal liver tissue. The proton beam was delivered concurrently with chemotherapy in a daily fraction of 3 Gy, 5 days a week, with a total dose of 66 Gy for 30 days (Fig. 3). During the course of the therapy, leukopenia of grade 3 was observed through days 10–21 according to the National Cancer Institute-Common Toxicity Criteria (version 2.0) and she received subcutaneous injections of granulocyte stimulating factor (GCSF) of 75 μg [50 μg/m² × body surface area (1.5 m²)] every day from day 10 to 13 and day 21 to 23. After the injections of GCSF, her white blood cell count (WBC) recovered to >3000/mm³. Although she experienced general fatigue throughout the therapy, she never complained of abdominal symptoms, such as epigastralgia, nausea or diarrhea during or after the treatment. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and γ-glutamyl transferase (γ-GTP) were within the normal range. Gastritis or gastric ulcer in the residual stomach was not observed by gastric endoscopy after the therapy. Three months after the treatment, the metastatic tumor in the caudate lobe had completely disappeared and volume reduction of non-cancerous liver was not observed on abdominal CT or MRI (Fig. 5). Oral administration of 300 mg of tegafur has been continued in the outpatient clinic and she has been free of recurrence on both blood and radiological examination for 2 years after termination of the therapy (Fig. 6).

DISCUSSION

Despite recent advances in the treatment of metastatic liver tumors, the prognosis of patients with metastatic liver tumor from gastric carcinoma is still dismal (1). Curative resection of a metastatic liver tumor from gastric carcinoma could be achieved when non-curable factors such as peritoneal dissemination and extensive lymph node metastases do not exist (2). However, metastatic liver tumors are frequently accompanied by peritoneal dissemination and multiple metastases in both lobes of the liver (3), resulting in a curative resection rate of only 10–15% among all hepatic resections of metastatic liver tumors from gastric carcinoma (4). In addition, surgical resection is often difficult because of risk factors related to the general status of patients. Although the tumor was solitary and there was no other recurrence in this case, we had to plot strategies other than surgical resection because of the poor general condition of the patient.
Chemotherapy via the systemic route or arterial infusion through a catheter in the hepatic artery has been widely studied in past decades. Patients with metastatic liver tumors from gastric carcinoma who have survived more than 5 years with systemic chemotherapy or a combination of hepatic resection, systemic chemotherapy and hepatic arterial infusion have been reported (5,6). However, we considered that the recurrent tumor in this case might be less sensitive to chemotherapeutic drugs, because MTX–5-FU sequential chemotherapy had already been applied as a post-operative adjuvant therapy. Therefore, we chose proton beam radiotherapy along with chemotherapy as the treatment for the metastatic liver tumor in the caudate lobe. Proton beams have relatively similar biological effectiveness both on the tumor and on the surrounding normal tissue to X-rays, while dose distribution is completely different from conventional X-ray radiotherapy (7). Proton beam therapy has an advantage over conventional X-ray radiotherapy for treating deep-seated tumors, since its dose distribution is more localized to tumors while delivering a lesser dose to the dose-limiting normal tissues (8). It enables the delivery of higher doses of radiation to target tumors with reduced normal tissue complications. Clinically it is widely used to treat various malignancies such as ocular melanoma, skull base tumor, lung cancer, esophageal cancer, hepatocellular carcinoma and prostate cancer (9). However, there is no report so far of proton beam therapy to metastatic liver tumors from gastric carcinoma. It would be difficult to achieve curative treatment to the tumor in the caudate lobe with conventional X-ray radiotherapy because it is located adjacent to the residual stomach and the tolerance dose of the liver is limited. Use of proton beam therapy makes it possible to avoid side effects related to the irradiation of the normal gastric body while delivering a high dose to the target tumor with curative intent. In this case, the metastatic liver tumor has been completely regressed and no recurrence has been detected for 2 years after the therapy. The patient has been free of epigastralgia or upper abdominal discomfort, which may be related to gastritis or gastric ulcer of the residual stomach. Radiation-induced hepatic injury and volume reduction of the irradiated liver have not been observed either by CT, MRI or laboratory tests. The superiority of proton beams may have contributed to achieving local control of the metastatic liver tumor from gastric carcinoma and have been beneficial for survival.

Regarding chemotherapy, we chose a concomitant low dose of 5-FU/cisplatin (FP therapy) to enhance the radiation effects on the local tumor as well as to control distant micrometastases. FP therapy is a well-established regimen for the recurrence of various gastrointestinal malignancies (10,11), including gastric carcinoma (12,13), and has a mechanism of biochemical modulation of 5-FU anti-tumor effect different from MTX–5-FU sequential chemotherapy (14). Also, both drugs have been reported to be radiosensitizers, which enhance the anti-tumor effects of irradiation (15), in addition to its direct effect on microscopic nests of cancer cells in the whole body. Although the dose of 5-FU and cisplatin was chosen to be low in this case, mainly in order to seek radiosensitizing effects and to reduce severe hematological and gastrointestinal toxicities (16), the patient experienced hematologic toxicity of grade III during the therapy and received GCSF injections with success. Total WBC count and number of granulocytes must be carefully monitored during the therapy to avoid life-threatening complications due to severe bone marrow suppression.

In conclusion, concurrent proton beam therapy with systemic chemotherapy using 5-FU and low-dose cisplatin appeared effective and feasible for the metastatic liver tumor from gastric carcinoma after surgical resection.

References