Advanced Gastric Cancer Patient with Peritonitis Carcinomatosa Successfully Treated with a Combination Therapy of Paclitaxel and TS-1, but Relapsed with Multiple Bone Metastasis and Died from Rapidly Progressive Meningitis Carcinomatosa

—Advanced Gastric Cancer with Metachronous Peritonitis Carcinomatosa and Meningitis Carcinomatosa—

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Abstract

A 59-year-old man diagnosed as gastric cancer with peritonitis carcinomatosa was treated with paclitaxel and TS-1; 60 mg/m²/day of paclitaxel was given on days 1 and 8, and 60-80 mg/m²/day of TS-1 was given for 2 weeks. Six courses of combination therapy were administered, and the ascites disappeared completely. Because multiple bone metastases occurred, we attempted combination therapy with cisplatin and irinotecan hydrochloride; 50 or 30 mg/m²/day of cisplatin was given on day 1 or day 15, and 70 mg/m²/day of irinotecan hydrochloride was given on days 1 and 15. The patient achieved a remarkable response, however, intracranial dissemination occurred and he died from rapidly progressive meningitis carcinomatosa.

Key words: gastric cancer, peritonitis carcinomatosa, meningitis carcinomatosa, chemotherapy

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Introduction

Although intraperitoneal dissemination is the route for most types of metastasis in gastric cancer (1), early diagnosis is difficult, and many cases are diagnosed as advanced peritonitis carcinomatosa with massive ascites. As it is difficult to completely cure peritonitis carcinomatosa; patients have very poor prognoses. Meningitis carcinomatosa, an invasion into the meninges and diffuse metastasis of a malignant tumor, occurs in 5-8% of all malignant diseases (2, 3). The prognosis for meningitis carcinomatosa is extremely poor (4).

Only one case with gastric cancer that meningitis carcinomatosa metachronously occurred after the patient achieved a complete response for peritonitis carcinomatosa with chemotherapy, has been previously reported (5). Here, we report a rare case of advanced gastric cancer that was successfully treated with a combination chemotherapy regimen of paclitaxel (PTX) and TS-1, resulting in complete disappearance of ascites. The patient, however, relapsed with multiple bone metastases and died from acutely progressive meningitis carcinomatosa.

Case Report

A 59-year-old man with complaints of abdominal fullness and loss of appetite was transferred to our hospital for further examination and therapy in July 2007. Upper GI endoscopy revealed type-3 gastric cancer (Fig. 1A). Biopsy was
performed. The histological diagnosis was poorly differentiated adenocarcinoma. A computed tomography (CT) scan of the chest and abdomen demonstrated bilateral pleural effusion and a moderately large amount of ascites in the upper abdomen (Fig. 2A), respectively. Cytologic examination of the peritoneal fluid showed class-V adenocarcinoma. The patient was diagnosed as having gastric cancer with peritonitis carcinomatosa.

For combination therapy with PTX and TS-1, 60 mg/m²/day of PTX was given intravenously on days 1 and 8, and 60 mg/m²/day of TS-1 was given orally from day 1 to day 14. Improvement in appetite and relief from the sensation of abdominal fullness was achieved 8 days after initiation of the first course of combination therapy. After 2 courses of combination therapy, abdominal CT scan revealed that the ascites had disappeared completely (Fig. 2B). Upper GI endoscopy showed the reduced fold convergence, and the central depressed area covered by regenerated epithelium was becoming smooth. The redness of the cancerous lesion lessened (Fig. 1B). Serum carcinoembryonic antigen (CEA) level decreased from 633.0 ng/mL to 130.1 ng/mL. Serum creatinine (S-Cre) level, which previously had increased to 1.43 mg/dL, decreased to 0.83 mg/dL and normalized after 2 courses of combination therapy. Upper GI endoscopy after 5 courses of combination therapy showed the primary gastric lesion to be a small, flat, red lesion surrounded by the fold convergence and a shallow ulceration on the side of the lesser curvature (Fig. 1C). The tissue biopsied from the edge of the shallow ulcer revealed tubular adenocarcinoma (“tub-2”). Although we suspected that the primary lesion had progressed, an abdominal CT scan showed no ascites and no swollen lymph nodes (Fig. 2C).

We performed the 6th course of combination therapy. Adverse reactions of the combination therapy of PTX and TS-1 were Grade-1 anemia, leukocytopenia, and alopecia and Grade-2 peripheral numbness in the extremities. Lumbago,
which appeared from mid-November 2007 during the 6th course of combination therapy, rapidly worsened. Serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and CEA levels in the third week of November 2007 increased to 681 IU/L, 235 IU/L and 674 ng/mL, respectively. A systemic bone scan at the end of November 2007 revealed multiple bone metastases in the lumbar region (Fig. 3). We suspected that resistance to the combination of PTX and TS-1 had developed.

As an inhibitor of bone resorption, 4 mg of Zometa® (zoledronic acid hydrate) was given intravenously in early December 2007. Furthermore, second-line combination therapy with cisplatin (CDDP) and irinotecan hydrochloride (CPT-11) was administered; 50 or 30 mg/m²/day of CDDP was given intravenously on day 1 or day 15, and 70 mg/m²/day of CPT-11 was given intravenously on days 1 and 15. After one course of second-line combination therapy, the patient achieved temporary relief of lumbar pain and improved laboratory data on bone metastasis. Specifically, serum ALP, LDH and CEA levels decreased from 1,153 IU/L, 514 IU/L and 1,178.0 ng/mL to 870 IU/L, 134 IU/L and 429.4 ng/mL, respectively. The second-line combination therapy of CDDP and CPT-11 was considered effective. Additionally, upper GI endoscopy after the second-line therapy showed that the primary gastric lesion improved (Fig. 1D). Adverse reactions of the CDDP/CPT-11 combination therapy were Grade-1 anemia and Grade-2 nausea, vomiting, and loss of appetite. During the first course of the second-line combination therapy (day-10), ALP and LDH levels re-increased, lumbar pain re-worsened, and mild headache appeared. Although a brain CT scan was performed (Figs. 4A, 4B), no abnormality was detected.

Headache, however, increased from the beginning of January 2008, and dysarthria, involuntary movement, and consciousness disorder appeared from mid-January 2008. Brain CT scan revealed severe brain edema and apparent dilatation of cerebral ventricles (Figs. 4C, 4D). We diagnosed the condition as meningitis carcinomatosa that had developed from meningeal invasion of tumor cells, due to exacerbations of the lumbar metastatic lesion. Although we considered the need for cerebral spinal fluid (CSF) examination, intrathecal methotrexate (MTX), and a ventriculo-
Figure 4. Brain CT scan findings. (A, B) After 1 course of combination therapy with cisplatin (CDDP) and irinotecan hydrochloride (CPT-11): No abnormality was found. (C, D) When the patient experienced worsening of headache: Severe brain edema and apparent dilatation of cerebral ventricles were observed.

peritoneal (VP) shunt procedure, the patient’s consciousness disorder rapidly progressed, his general condition quickly worsened, and the patient died in mid-January 2008. Lastly, because of the rapid worsening of neurological symptoms of involuntary movement, consciousness disorder and so on, severe lumbar pain due to worsened lumbar metastatic lesion, and a growing tendency to renal failure, lumbar puncture requiring the chest-knee position, enhanced MRI and enhanced CT were not performed.

Discussion

Only one case with gastric cancer that meningitis carcinomatosa metachronously occurred after the patient achieved a complete response for peritonitis carcinomatosa with chemotherapy, has been previously reported (5). In the current case report, the ascites had completely disappeared, and the patient maintained an absence of ascites prior to death. The tumor, however, had relapsed with multiple bone metastases. Although the second-line combination therapy with CDDP and CPT-11 was temporarily effective, intrameningeal dissemination occurred, and the patient died from acutely progressive meningitis carcinomatosa. A possible explanation is that chemotherapeutic drugs vary in antitumor effectiveness in various organs and sites of tumor lesions.

Intrameningeal metastasis occurs in 4-15% of solid tumors, 20% of malignant melanomas, 11% of small cell lung cancers, 5% of breast cancers, 5-15% of leukemias and malignant lymphomas, and 1-2% of primary brain tumors; and the most common histological type of meningeal metastatic tumor is adenocarcinoma (6, 7). The incidence of intrameningeal metastasis is 0.16-0.69% of gastric cancers, and the most common site for metastasis of solid tumors is intrameningeal metastasis (4). Furthermore, the most common macroscopic types of gastric cancer with metastasis of the meninges are type-3 or type-4, and poorly differentiated adenocarcinoma and signet ring cell carcinoma are the most common histological types (4, 8, 9).

The metastatic pathways of tumor cells to the meninges include: (a) hematogenous spread, (b) direct invasion of metastatic tumors, (c) intraperitoneal dissemination of primary brain tumors, (d) migration of tumor cells in head and neck cancer to peripheral nerves, and (e) mechanical dissemination of cells in metastatic brain tumors by surgical procedures (6). In the present patient, the metastatic pathway was considered to have been direct invasion of tumor cells from the metastatic lesion in the lumbar region to the meninges.

Recent clinical trials of chemotherapy have assessed not only the survival period, but also the quality of life for patients. In the present patient, the ascites rapidly decreased and completely disappeared, the patient became symptom-
free after first-line combination therapy, and the patient was able to return to normal social and work activities for 4 months prior to relapse. This first-line course of treatment was considered to have clinically very significant results in terms of temporarily maintaining a high quality of life.

Anecdotal reports on intraperitoneal administration of anticancer drugs for advanced gastric cancer with peritonitis carcinomatosa have shown favorable results (10-12). Although we judged that intraperitoneal anticancer therapy may have been sufficiently indicated as an option for our patient, intraperitoneal therapy in which the recommended dosage of anticancer drug has not been adjusted individually can result in severe adverse reactions. The reasons include the poor performance status of most peritonitis carcinomatosa patients and the great individual variation in the rate of absorption of anticancer drugs from the peritoneum.

TS-1 is an oral anticancer drug that is relatively effective for peritonitis carcinomatosa. Inaba et al previously reported that in patients with gastric cancers and peritonitis carcinomatosa, 1-year and 2-year survival rates and median survival time (MST) were 63.2%, 23.7% and 437 days, respectively (13). TS-1 may become more widely used for peritonitis carcinomatosa in patients with gastric cancer, especially those who are able to swallow. Additionally, it has been reported that taxanes (such as PTX) with greater antitumor effects may accumulate in the intraperitoneal fluid, and intravenous administration of PTX may stabilize drug concentration in intraperitoneal fluid to approximately 40% higher than that in plasma (14). Anecdotal reports of remarkable responses of gastric cancers with peritonitis carcinomatosa to systemic chemotherapeutics have been published (15-18). The present patient, treated systemically with a first-line combination regimen of PTX and TS-1, demonstrated a complete response.

Patients with meningitis carcinomatosa have an extremely poor prognosis, as median survival is 4 weeks if untreated and 2-4 months if treated (4). Although intrameningeal methotrexate (MTX) has been administered to patients with meningitis carcinomatosa, the effectiveness is transient. Recently, patients with meningitis carcinomatosa have maintained a relatively high quality of life after a ventriculo-peritoneal (VP) shunt procedure and intrameningeal administration of anticancer therapies (19). Despite the fact that the number of patients with meningitis carcinomatosa has been very small, the incidence may increase in the near future, due to improved prognosis and extended long-term survival of cancer patients receiving new anticancer drugs. We should consistently note the appearance of the symptoms of increased intracranial pressure. If the diagnosis of intrameningeal dissemination is confirmed and the therapies of ventriculo-peritoneal (VP) shunt procedure and intrameningeal administration of anticancer drugs are started earlier, we expect the further prolongation of survival for gastric cancer patients with meningitis carcinomatosa.

References
