Successful Treatment of Recurrent Gastric Cancer with Chemotherapy for More than 6 Years: A Case Report

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A 66 year-old male underwent a distal gastrectomy with D2 dissection in April 2003. Pathological findings showed a well-differentiated carcinoma with a depth of m, n2, stage II. Six months later, a computed tomography revealed multiple lymph node swellings in the para-aortic lesion; we judged this to be a recurrence of the gastric cancer. As treatment, paclitaxel was administered weekly on days 1, 8, and 15, in combination with doxifuridine for 5 days per week, on a 28-day cycle. Following three courses of chemotherapy, the lymph nodes had almost disappeared. This therapy was continued until January 2007. Because of the appearance of a Virchow lymph node, S-1 + cisplatin was administered. Following administration of the altered chemotherapy regime, a computed tomography displayed a significant reduction in Virchow lymph node swelling. Four years and ten months following the initiation of chemotherapy, the patient displayed jaundice. A computed tomography revealed lymph node swelling in the hepato-duodenal region. Following bile duct drainage, he received four cycles of paclitaxel and doxifuridine therapy. The patient then received S-1 monotherapy for 5 months. He died in February 2010, 6 years and 3 months after the recurrence in the stomach cancer. (Kitakanto Med J 2010; 60: 265~270)

Key Words: paclitaxel, doxifuridine, gastric cancer, S-1

Introduction

Metastatic gastric carcinoma remains an incurable disease, with a median survival period of only 4-8 months. Systemic chemotherapy plus supportive care, compared with best supportive care alone, has been shown to provide both a survival benefit and a positive impact on the quality of life of patients with unresectable or metastatic gastric cancer in randomized studies.1 In Japan, the current standard therapy in advanced and recurrent gastric cancer patients is S-1 (+CDDP). S-1 prolongs the median survival period of patients; this increase is, however, only modest, with an increase in the median survival period of only 11~13 months.2-3 As such, there is a continuing need for better therapies.

Paclitaxel and doxifuridine (S-DFUR) act synergistically when combined in advanced gastric cancer both in vitro and in vivo, without overlapping toxicities. S-DFUR is an intermediate of capecitabine and is converted to S-FU by thymidine phosphorylase (TP). TP, which is a member of the pyrimidine nucleoside phosphorylase (PyNPase) family and exists predominantly in humans, is a potent tumor-associated angiogenesis factor that is preferentially expressed in malignant cells.4-5 Paclitaxel enhances the efficacy of S-DFUR, probably by inducing TP activity, as demonstrated in human cancer xenograft models.6

Here, we report the successful treatment of a patient with recurrent gastric carcinoma using the new chemotherapeutic combination of paclitaxel and S-DFUR for more than 3 years. Following progression of the disease, we successfully treated this patient for a total of over 6 years with chemotherapy treatment (including S-1 + CDDP).

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Fig. 1. Endoscopic examination prior to operation revealed a IIc lesion in the lesser curvature of the gastric angle (A) CT demonstrated a large lymph node swelling around the left gastric artery (B) FDG–PET showed the accumulation lymph node (Max SUV = 5.1) (C).

Fig. 2. Six months following the operation, the CT scan revealed the multiple lymph node swellings in para-aortic lesion.

Case Report

A 66-year-old male was admitted to the department of surgery due to lymph node swelling (left gastric artery region) in February 2003. Endoscopic examination showed a IIc lesion in the lesser curvature of the gastric angle (Fig. 1A). A histological examination of biopsy specimens from the lesion showed well differentiated adenocarcinoma. Computed tomography (CT) demonstrated a large lymph node swelling around the left gastric artery (Fig. 1B). FDG–PET showed the accumulation lymph node (Max SUV = 5.1; Fig. 1C). Distal gastrectomy with D2 dissection was performed in April. Pathological findings showed well a differentiated carcinoma with a depth m, n2 (stage II by the Japanese Classification of Gastric Carcinoma 13th edition).

Then, 6 months later, a CT scan revealed multiple lymph node swellings in the para-aortic lesion (Fig. 2), which was judged to be a recurrence of the gastric cancer. Paclitaxel (80mg/m²) was administered as a 60-min infusion weekly on days 1, 8, and 15 with 5’-DFUR (333mg/m²) at 800mg/day for 5 days per week, on a 28-day cycle. After three courses of chemotherapy, the lymph nodes almost disappeared as judged by CT (Fig. 3). This therapy continued until January, 2007 with only minor changes in the protocol (Fig. 4). Because of the appearance of a Virchow lymph node (Fig. 5), S-1 (100mg/body) was administered from February 2007 per the schedule outlined in Fig. 6. Following the change in chemotherapy regimen, a CT scan showed a reduction of the Virchow lymph node swelling (Fig. 7). Four years and 10 months after the initiation of chemotherapy, the patient displayed jaundice and a CT scan showed lymph node swelling in the hepato-duodenal region. After bile duct drainage, the patient again received four cycles of PTX and 5’-DFUR therapy. CPT-11 and CDDP therapy were
then administered; however, he refused this therapy due to grade-2 diarrhea. S-1 monotherapy was then administered for 5 months. He received best supportive care only from September 2009, and he died in February 2010, 6 years and 3 months after the recurrence of his stomach cancer.

The serum carbohydrate antigen (CA) 19-9 level and the carcinoembryonic antigen (CEA) levels are shown in Fig. 8. The only adverse drug reaction of grade 3 or higher was grade 3 leucopenia, observed when S-1+CDDP therapy was administered. Toxicity associated with the regimens was evaluated according to the National Cancer Institute’s Common Toxicity Criteria, version 3.0.
Fig. 5. PET-CT showed the appearance of a Virchow lymph node in January 2007.

Fig. 6. S-1 and CDDP schedule

Fig. 7. CT scan displayed a reduction in the swelling of the Virchow’s lymph node following the administration of S-1.
Discussion

Despite the progressive improvement in detection methods, gastric cancer is still associated with the highest mortality of all malignancies in Japan. A median survival time of 3–4 months has been reported for non–resectable or recurrent gastric cancer with supportive care alone; thus, chemotherapy is indispensable in decreasing mortality.\(^3\) The use of a single agent, such as 5-FU, cisplatin, paclitaxel, 5′DFUR, or mitomycin C, for gastric cancer usually results in a response rate of 10–30%.\(^6\) Paclitaxel is a recently developed anticancer drug that promotes the polymerization of tubulin and inhibits the depolymerization of microtubules. The effect of paclitaxel on microtubular dynamics could account for the cell cycle block that it produces during mitosis.\(^5\) Recent studies have demonstrated that when administered weekly, paclitaxel is both more active and safer than monthly administration of the drug\(^6\) and as such, is one of the most suitable treatment regimens for outpatients with gastric cancer.\(^5\),\(^11\)

5′-DFUR (which is a prodrug and an intermediate metabolite of capecitabine) is converted by a PyNPs to 5-FU and displays anti-tumor activity.\(^11\) TP, a member of the PyNPs family, is involved in the salvage pathway of pyrimidine nucleoside synthesis and converts capecitabine and 5′-DFUR to 5-FU. As a result, TP has an essential role in the expression of the anti-tumor activity of 5′-DFUR. Preclinical studies have demonstrated that treatment with paclitaxel up-regulated intra-tumoral TP and, as such, is likely to enhance the toxicity of 5′-DFUR by up-regulating TP in normal organs.\(^4\) In contrast, Sawada and colleagues\(^6\) reported that paclitaxel did not elevate PyNPs activity in the intestinal tract of mice. Additionally, the toxicity of paclitaxel does not appear to be synergistic with 5′-DFUR in preclinical models, although the efficacy of these compounds in combination was additive-to-synergistic. In contrast, paclitaxel and 5-FU or UFT (a mixture of tegafur and uracil) in combination showed only additive activity.\(^5\) Thus, it seems unlikely that paclitaxel greatly enhances TP activity in normal organs or enhances the toxicity of 5′-DFUR. Accordingly, we were able to successfully treat this patient for more than 3 years without severe side effects. Weekly paclitaxel and 5′-DFUR therapy was effective and well-tolerated.

In Japan, since 2007, the first-line standard therapy for unresectable or recurrent gastric cancer patients is S-1+CDDP.\(^3,\)\(^3\) First line therapy for this patient started before 2007. We used paclitaxel and 5′-DFUR combination therapy for this patient, followed by S-1+low dose CDDP as a second-line therapy. The second-line therapy continued for 20 months. Following this, we used CPT-11+CDDP; however, the patient refused this therapy because of grade 2 diarrhea and we returned to S-1 treatment.

In conclusion, paclitaxel plus oxifluoridine first-line therapy and S-1 plus low-dose CDDP second-line therapy were effective and well-tolerated and should be further investigated in cases of non–resectable or recurrent gastric cancer.
References


