Case report

Weekly paclitaxel for a patient with advanced gastric cancer

SHIGETAKA YAMAMOTO¹, YASUHIRO TANAKA¹, TOSHINORI ITO², TOYOKAZU AONO¹, YOSHIKAZU MORIMOTO¹, TORU KITAGAWA², and YOUJIROU KURIHARA¹

¹Department of Surgery, Osaka Prefectural General Hospital, 3-1-56 Mandaihigashi, Sumiyoshi-ku, Osaka 558-8558, Japan

²Department of Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Abstract

A 56-year-old woman diagnosed with gastric cancer was admitted to our hospital for operation on May 15, 2001. The operation was performed on May 23. The tumor formed a large mass from the antrum to the head of the pancreas, and cancer cells were detected in the ascitic fluid microscopically. During the operation, resection was impossible, and so 100 mg of cisplatin (CDDP) was infused into the abdominal cavity. After the operation, she experienced continuous nausea and there was a discharge of 1200–1600 ml of digestive fluid per day from her nasogastric tube. On July 17, a new regimen, of 4-week courses of chemotherapy, with weekly administrations of 65 mg/m² of paclitaxel, along with premedication for 3 weeks, followed by 1 week of rest, was started. After the first of these 4-week courses, the discharge from her nasogastric tube decreased to 200–600 ml per day, and the tube was removed 78 days after insertion. Oral intake of food increased smoothly, and she was discharged on September 14. After another, short, hospitalization, she was discharged on October 20, and she has been coming to our outpatient clinic once a week. After paclitaxel was started, gastric fiberoscopy and computed tomography (CT) scan showed reduction of the tumor. Of special note was the disappearance of ascitic fluid after two courses, rated as a “partial response” (Japanese classification). There was a decrease in hemoglobin, but neither leukocytopenia nor a decrease in platelets was found. Neuropathy was slight and no treatment was needed. Now, after 1 year, 11 courses of chemotherapy have been administered at the outpatient clinic. These results suggest weekly administration of paclitaxel to be a promising treatment for advanced gastric cancer with peritoneal dissemination. The therapeutic efficacy should be confirmed by further clinical trials.

Key words Paclitaxel · Advanced gastric cancer · Peritonitis carcinomatosa

Introduction

Although successful results achieved in clinical trials of paclitaxel in patients with ovarian, breast, and lung cancer have been reported in many studies, there have been only a few published studies of such clinical trials of paclitaxel in patients with gastric cancer. At present, there is no clear consensus regarding the appropriate dosage or method of administration of paclitaxel for gastric cancer. Recently, successful results achieved using a regimen of weekly administration of paclitaxel in patients with breast cancer and ovarian cancer have been reported, but, to date, only a few such trial studies in patients with gastric cancer have been reported. Here, we report one patient in whom a regimen of weekly administration of paclitaxel appears to have been successful in treating advanced gastric cancer.

Case report

A 56-year-old woman with symptoms of heartburn and epigastralgia that had started in January 2001 was diagnosed with gastric cancer by her family doctor, and she was admitted to our hospital for operation on May 15, 2001. At that time, her abdomen was flat but slightly firm. No superficial lymph nodes were detected, and digital examination showed no signs of Schnitzler metastasis. She had slight anemia, but icterus was not detected. On hematological examination, liver and renal functions were normal, and carcinoembryonic antigen (CEA) was 1.1 ng/ml. Gastric fiberoscopy showed a large irregular ulcerous lesion with swelling of the folds and stiffness of the gastric wall extending from the upper dorsal to the middle body of the stomach (Fig. 1A), and this was diagnosed histologically as poorly differentiated adenocarcinoma. Abdominal computed tomography (CT) scan showed thickness of the body of the stomach, but no solitary lesions in the liver and no

Fig. 1A,B. Gastric fiberscopy **A** before operation showed a large irregular ulcerous lesion with swelling of the folds and stiffness of the gastric wall, extending from the upper dorsal to the middle body of the stomach and **B** although a partial irregular ulcer still remained, the swelling of the folds and stiffness of the gastric wall were alleviated 6 months after the start of paclitaxel administration

lymph node swelling. A small amount of ascitic fluid was found in the Douglas pouch. Although peritonitis carcinomatosa was not ruled out by the results of the examinations, an operation was performed on May 23.

The tumor was found to occupy both the gastric body and the angle, and had invaded the transverse mesocolon and jejunal mesentery near the Treitz ligament, forming a giant mass from the antrum to the head of the

pancreas. Ascitic fluid was also found throughout the abdominal cavity, and cancer cells were detected in it. Neither resection nor anastomosis was able to be performed because of the extensiveness of the cancer, and so, after 100mg of cisplatin (CDDP) was injected into the abdominal cavity, the operation was finished.

She began eating 7 days after operation, but only small amounts, and she experienced continuous nausea. On June 5, a nasogastric tube was inserted because of vomiting. Chemotherapy, with 5-fluorouracil (5-FU) and CDDP was started on June 7, but was stopped after 1 week because the nausea became severe. Discharge of digestive fluid from the nasogastric tube was 1200–1600ml per day. Because of general fatigue, she remained in bed all day and her performance status was grade 3. On July 17, weekly administration of paclitaxel with a short course of premedication was started, to be given in 4-week courses, with 3 weeks of administration followed by 1 week of rest. In this regimen, 500ml of normal saline with vitamins was administered as a 3-h drip-infusion. After 30min of infusion, 10mg of dexamethasone, 5mg of chlorpheniramine maleate, 20mg of famotidine, and 0.3mg of ramosetron hydrochloride were administered intravenously. After another 30min of infusion, a dose of 65mg/m² of paclitaxel was admixed with the residual normal saline and administered for the remaining 2h.

After the first course of this chemotherapy regimen, discharge from her nasogastric tube decreased to 200–600ml per day and urine volume increased. During the second course, the nasogastric tube was removed, 78 days after insertion. Oral intake of food increased smoothly, without nausea or vomiting, and she was discharged on September 14 (Fig. 2). Although administration of 600mg/day of doxifluridine had been started on September 4, it was stopped because of diarrhea, and she was readmitted to our hospital for intravenous drip-injections for 10 days. Since being discharged, she has been coming to our outpatient clinic once a week for treatment.

At 3 months after the operation, that is, 1 month after the start of paclitaxel administration, CT scan showed ascitic fluid, swelling of the gastric wall, and swelling of the greater omentum caused by remnant inflammation from peritonitis carcinomatosa (Fig. 3A). After the second course was finished though, the ascitic fluid had completely disappeared and reduction in the peritoneal lesions was found (Fig. 3B). Now, after 11 courses of chemotherapy, CT scans show no recurrence of ascitic fluid. This was rated as a “partial response” according to the Japanese classification system for gastric carcinoma [1]. At 6 months after the start of paclitaxel administration, gastric fiberscopy showed that, although a partial irregular ulcer still remained, the swelling of the folds and stiffness of the gastric wall were alleviated (Fig.

Fig. 2. Case history. 5-FU, 5-fluorouracil; CDDP, cisplatin; CEA, carcinoembryonic antigen; NG, nasogastric; NC, no change; PR, partial response

Table 1. Clinical trials of paclitaxel for gastric cancer

Author	Dosage (mg/m ²)	Interval	Combination	Rate of efficacy (%)	MST (months)
Cascinu et al. [5]	225	Every 3 weeks	None	22	8
Ajani et al. [6]	200	Every 3 weeks	None	17	8
Yamada et al. [7]	210	Every 3 weeks	None	23	11
Garcia et al. [8]	210	Every 3 weeks	None	11	5.8
Murad et al. [9]	175	Every 3 weeks	5-FU	65	12
Kollmannsberger et al. [4]	175	Every 3 weeks	5-FU, CDDP	51	14
Kim et al. [10]	175	Every 3 weeks	5-FU, CDDP	51	6.5
Kuo et al. [11]	80	Weekly	5-FU, leucovorin	46	9

MST, median survival time; 5-FU, 5-fluorouracil; CDDP, cisplatin

1B). No increase in CEA has been seen since the start of this regimen.

As for hematological side effects, although hemoglobin decreased to 7.9g/dl in the first course and a blood transfusion was performed, hemoglobin has remained at over 10g/dl since the third course. Leukocyte levels have remained at over 3000/mm³ through all courses and no decrease in platelets has been seen. While hemoglobin and leukocyte levels have tended to decrease toward the end of the third week of each course, they have repeatedly recovered during the fourth (rest) week. Increases in alanine aminotransferase and alkaline phosphatase were also found. Some clinical symptoms, such as disturbances of taste, flushing of the face, numbness of the bottom of the feet, and pain in the ribs, along with grade 2 alopecia, were found, but they were slight and no treatment was needed.

Discussion

In recent reports of the efficacy of paclitaxel for advanced or recurrent gastric cancer, the target lesions of

the chemotherapy were liver or lung metastases, gastric primary lesions, and intraabdominal lymph nodes. There are hardly any reports on the efficacy of paclitaxel for disseminated peritoneal lesions because it is difficult to evaluate efficacy in such cases. Regarding the concentration level of paclitaxel in ascitic fluid after its intravenous infusion, O'Boyle et al. [2] have reported that 0.112μM of paclitaxel was detected 7h after intravenous infusion of 175mg/m² of paclitaxel, and 0.26μM of paclitaxel was detected after 22h, which was the same as the level in serum after 6h. Wiernik et al. [3] have reported that although paclitaxel was not detected in ascitic fluid during a 6-h intravenous infusion of 175mg/m² of paclitaxel, it was detected subsequently, and its concentration in the ascitic fluid increased for several hours thereafter, reaching a maximum concentration of 0.25μM, remaining for at least 12h, and then stabilizing at a level approximately 40% above that in plasma. In that same study, one patient had a massive amount of ascitic fluid due to metastatic adenocarcinoma from an unknown primary organ, yet there was only minimal sonographic evidence of ascitic fluid after 6 months of treatment with paclitaxel. Kollmannsberger et al. [4]

Fig. 3A,B. Computed tomography (CT) scans showed **A** ascitic fluid, swelling of the gastric wall, and swelling of the greater omentum 1 month after the start of paclitaxel administration; **B** the ascitic fluid had completely disappeared and reduction in peritoneal lesions was found after the second course was finished

have reported remission, including complete response, for 7 of 15 patients with advanced gastric cancer with peritoneal lesions, and Cascinu et al. [5] have reported an improved response for peritoneal lesions even in patients classified as stable. In our patient, the complete disappearance of the ascitic fluid and reduction of the primary gastric lesions were detected by CT scan 3 months after the start of paclitaxel. Clinical symptoms improved dramatically. Discharge volume from the nasogastric tube decreased after only one 4-week course of paclitaxel and, during the second course, the tube was able to be removed and the patient could take foods orally.

All of the clinical trials of paclitaxel for gastric cancer reported up to the present, and listed in Table 1, were performed with administration every 3 weeks [4–10],

except for one [11]. With a single administration of paclitaxel every 3 weeks in one dose of 200–225 mg/m², antitumor efficacy has been reported at 11%–23%, and median survival time has been reported at 5.8–11 months. Furthermore, combination chemotherapy; for example, paclitaxel and 5-FU, or paclitaxel, 5-FU, and CDDP, has shown an improvement in these results, with antitumor efficacy at 46%–65% and median survival time at 6.5–14 months. Many reports have also shown that pretreatment with other anticancer drugs had no influence on the efficacy of paclitaxel; although there was pretreatment in our chemotherapy course, our patient showed a partial response.

Some of the benefits of weekly administration of paclitaxel have already been reported, and some can be seen quite clearly in our patient. Weekly administration of paclitaxel gives no time for progression of the tumor, by shortening the intervals between drug administrations [12], and there are reports of the effectiveness of weekly administration without severe side effects in patients with breast cancer and lung cancer [13,14]. In studies where paclitaxel was administered every 3 weeks, rates of leukopenia above grade 3 were 4.8%–11% with paclitaxel only, and 6.8%–34% with combined chemotherapy [4–10]. The rate of occurrence of disturbance of nerves in the extremities over grade 1 was high, at 22%–75% [4–10]. In our patient, clinical symptoms, such as disturbance of taste, flushing of the face, numbness of the bottom of the feet, and pain in the ribs were seen, but no treatment was needed because of the slight degree of the symptoms. Most of these symptoms appeared after the eighth course of chemotherapy. Some hematological side effects were observed, but they disappeared after the 1 week of rest in each 4-week course.

We cannot say conclusively to what extent our results are attributable to the weekly administration of paclitaxel, or to the inclusion of a week of rest in each 4-week course, or whether our use of doxifluridine in combination with paclitaxel, albeit for a short time, may have affected the outcome. Yet, in this patient, weekly administration of paclitaxel with a 1-week rest period appears to have led to a partial response and improved performance status dramatically. Because there have been so few studies using either weekly administration of paclitaxel alone or using paclitaxel in combination with other drugs in patients with gastric cancer, we believe that this case is noteworthy and clearly points to the need for further clinical trials to confirm the therapeutic efficacy of paclitaxel in such cases. Paclitaxel could prove to be effective in the treatment of peritoneal disseminated lesions in cases of gastric cancer which previously were difficult to treat.

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