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Case report

Weekly administration of paclitaxel attenuated rectal stenosis caused by multiple peritoneal recurrence 8 years after the resection of gastric carcinoma

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Abstract

We report a patient with rectal stenosis caused by peritoneal recurrence 8 years after a curative resection of advanced stage gastric carcinoma; the recurrence was effectively treated with the weekly administration of paclitaxel. The patient was a 66-year-old Japanese woman who was admitted to our hospital complaining of abdominal pain and frequent bowel movements. She had undergone total gastrectomy, due to advanced-stage gastric carcinoma with extensive lymph node metastasis, 8 years before, and had taken an oral anticancer agent, fluoropyrimidine, for 4 years after the operation. Colonofiberscopy performed on admission revealed circumferential rectal stenosis located 10 cm from the anal verge. Barium enema study demonstrated extensive poor expansion of the upper and lower rectum and irregularity of the descending colon. Abdominal computed tomography (CT) scanning revealed wall thickening in the rectum and descending colon. These findings were compatible with rectal stenosis caused by the peritoneal recurrence of gastric carcinoma. Weekly administration of paclitaxel was started. The abdominal symptoms soon disappeared when the second cycle of paclitaxel was completed, and they have not appeared since then. The rectal stenosis was attenuated, as confirmed by imaging analyses. Weekly paclitaxel has been effective for more than 13 months, suggesting that the patient is in a state of tumor dormancy of recurrent gastric carcinoma.

Key words Gastric carcinoma · Peritoneal dissemination · Rectal stenosis · Weekly paclitaxel

Introduction

Recurrent gastric carcinoma is a difficult disease status for which few treatment modalities are available. Peritoneal dissemination is the type of recurrence that most frequently occurs in gastric carcinoma, and it is extremely difficult to deal with [1]. Longterm survival of patients with peritoneal dissemination is desperately awaited, as the mean survival at present is less than 6 months [1]. Although anticancer chemotherapy is the primary treatment available for the majority of patients with diffuse peritoneal metastasis, response to anticancer chemotherapy is extremely poor. In particular, for the majority of the patients with peritoneal recurrence, first-line anticancer chemotherapy has already been given when they were in an advanced stage before the time of operation, and following the operation, and recurrence then appears as a consequence of resistance to the first-line anticancer chemotherapy. Nonetheless, anticancer chemotherapy appears to provide a significant survival advantage over best supportive care [2]. However, no effective second-line chemotherapy has yet been available for gastric cancer patients who have not responded to or who have relapsed after an initial response to first-line chemotherapy. Therefore, an effective second-line anticancer chemotherapy regimen is expected for the treatment of recurrent peritoneal dissemination of gastric carcinomas.

We report herein a patient with rectal stenosis caused by the peritoneal dissemination of recurrent gastric carcinoma resected 8 years previously. Repeated weekly administration of paclitaxel has been effective for more than 13 months. The patient is considered to be in a state of tumor dormancy of recurrent gastric carcinoma.

Case report

A 66-year-old Japanese woman was admitted to our hospital with complaints of abdominal pain, loose stools, and frequent bowel movements. The patient had undergone total gastrectomy associated with D3 lymph node dissection and Roux-en-Y reconstruction

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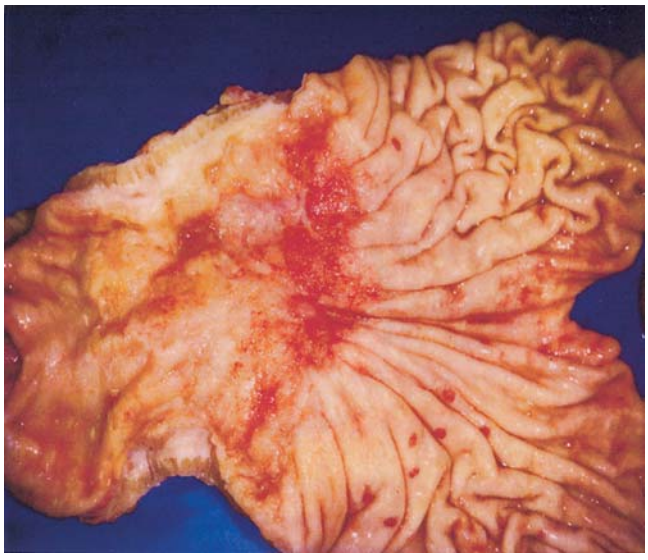

Fig. 1. Resected specimen obtained 8 years before the current admission. Type 4 diffuse type gastric carcinoma was noted in the body and antrum of the stomach

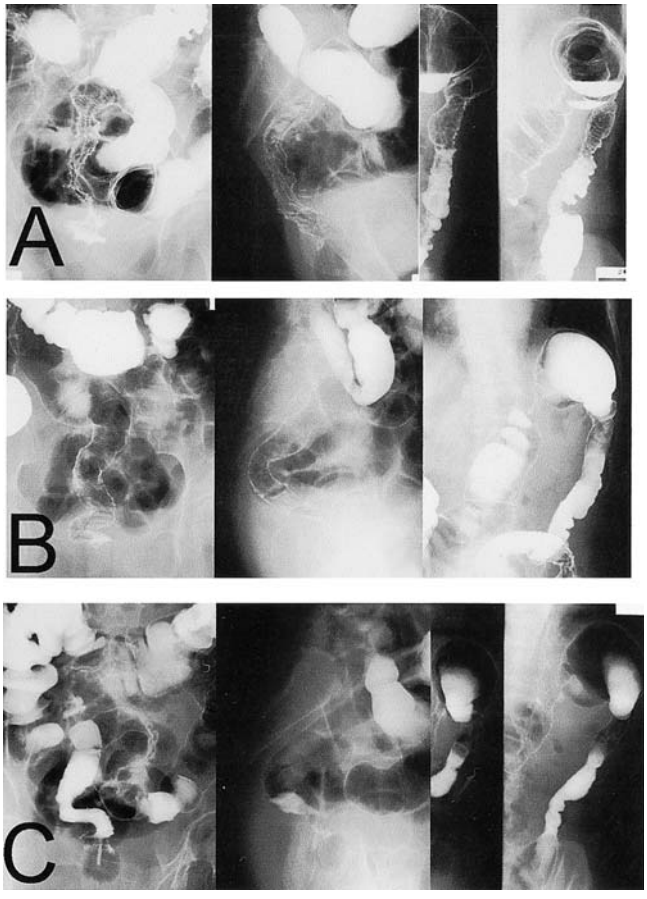

Fig. 2A–C. Barium enema studies; **A** on admission, revealing circumferential stenosis of the upper rectum, descending colon, and transverse colon. Sequential images of barium enema **B** 4 months and **C** 8 months after the start of weekly paclitaxel, demonstrating attenuation of the extent of rectal stenosis, which was maintained for more than 10 months

under the diagnosis of advanced gastric carcinoma, in December 1993. The resected specimen obtained at the gastrectomy is shown in Fig. 1. The pathological findings of the resected, primary gastric carcinoma, expressed in accordance with the Japanese Classification of Gastric Carcinoma [3] were mucinous carcinoma, se, INF γ, intermediate, ly 3, v 1, DM (−), and PM (−); also, 8 of 40 dissected regional lymph nodes were metastatic. Metastasis of the lymph nodes was positive in nos. 3, 4sb, 4d, 5, 6, and 8 according to the Japanese Classification of Gastric Carcinoma [3]. The pathological stage was stage IIIa. The patient was followed up at the outpatient clinic of our department for 8 years after the gastrectomy, without any interruption. No recurrence was found for 8 years, although there was a gallbladder stone and fluctuating serum carbohydrate antigen (CA) 19-9 level, being above the normal value in a range of 60 to 90 U/ml, which was likely to have been caused by the presence of the gallbladder stone. Uracil plus tegafur (UFT), 450 mg per day, was given orally for 4 years after the surgical resection and was discontinued in October 1998.

Abdominal pain, loose stools, and tenesmus appeared in January 2002. The number of bowel movements had been increasing, with these symptoms having started from November 2001 and becoming exacerbated. Digital examination of the rectum revealed irregular rectal mucosa and circumferential stenosis 10 cm from the anal verge. The patient was admitted to our hospital for further examination and treatment. Barium enema performed in January 2002 revealed circumferential stenosis of the upper rectum, the descending colon, and the transverse colon (Fig. 2A). Colonofiberscopy also revealed a mucosal irregularity extending circumferentially, with the rectum being stenotic 10 cm from the anal verge (Fig. 3A). These lesions were diffuse and extended through 13 cm from the anal verge. Another stenosis of the descending colon was noted just proximal to the splenic flexure. The patient was menopausal at the time of the diagnosis of rectal stenosis, and gynecological examination on admission revealed no abnormal findings in the uterus; the patient did not complain of dysmenorrhea or of periodical lower abdominal pain. Computed tomography (CT) scanning and magnetic resonance imaging (MRI) of the pelvis revealed circumferential wall thickening of the upper rectum, extending approximately 7 cm (Figs. 4, 5). Endoscopic biopsies were taken from the irregular mucosa, and no carcinoma was found. While recurrent gastric carcinoma was not histologically confirmed, comprehensive findings obtained from the imaging

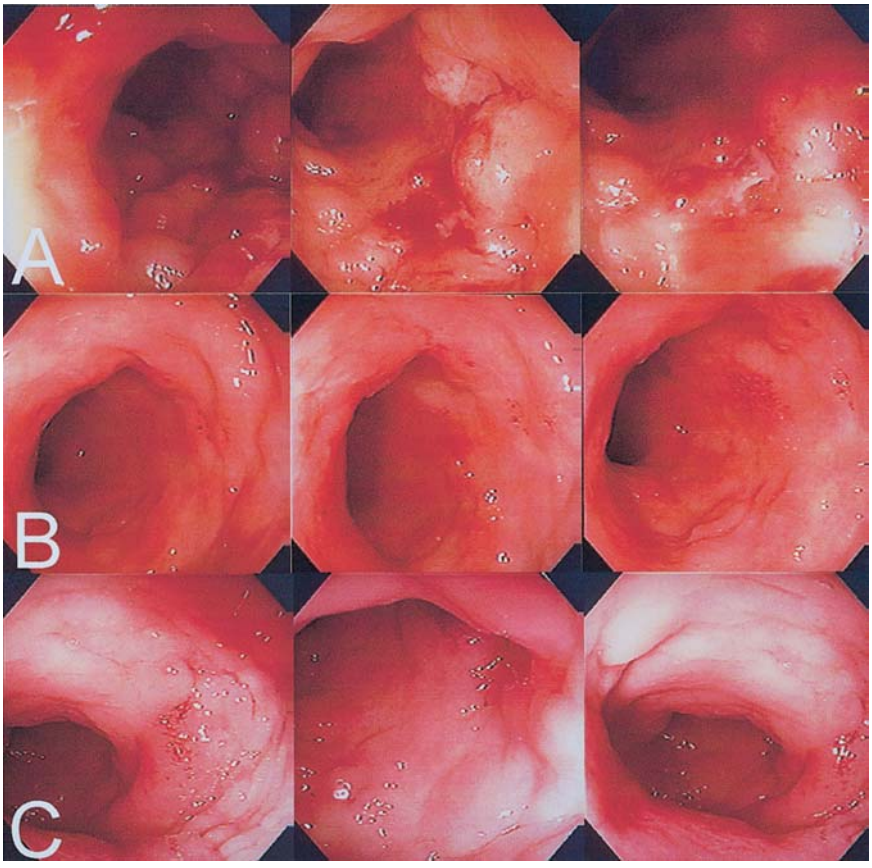

Fig. 3A–C. Colonofiberscopic findings; **A** on admission, revealing mucosal irregularity extending though 23 cm from the anal verge. Sequential colonofiberscopic findings **B** 4 months and **C** 8 months after the start of weekly paclitaxel, demonstrating attenuation of the extent of rectal stenosis, which was maintained for more than 10 months

analyses and the previous history of gastric carcinoma indicated that these multiple stenoses should be clinically diagnosed as being caused by the peritoneal dissemination of the gastric carcinoma that had been resected previously.

Because surgical intervention was absolutely not feasible, a weekly paclitaxel regimen was selected to be administered as a second-line anticancer chemotherapeutic regimen. To minimize paclitaxel-associated hypersensitivity reaction, the patient was treated with the short-course prophylactic regimen developed originally by Wiernik et al. [4] shortly prior to the administration of paclitaxel. The short-course prophylactic regimen includes intravenous administration of dexamethasone, 50 mg of ranitidine, and oral administration of diphenhydramine, given 30 min prior to a 1.5-h intravenous administration of paclitaxel. Paclitaxel, 80 mg per m^2, corresponding to 108 mg per body, was administered weekly on days 1, 8, and 15 as one cycle of the regimen, from March 2002. The next cycle was started on day 29 and the cycles were to be repeated, unless severe or problematic side effects occurred. Because no side effect had occurred at the final dose of the first cycle of paclitaxel, the patient was discharged from the hospital and the cycles of paclitaxel were then continued in an outpatient setting.

The symptoms of tenesmus and diarrhea were soon alleviated, 3 weeks after the initial dose of the first cycle, and they had completely disappeared at the end of the second cycle. Sequential barium enema findings and sequential colonofiberscopic findings at the end of the fourth cycle and at the end of eighth cycle are shown in Fig. 2B,C and Fig. 3B,C, respectively. The extent of the stenosis and mucosal irregularity were attenuated after the fourth cycle of paclitaxel administration, and these features were maintained for at least 10 months during the course of the weekly paclitaxel treatment. Hypersensitivity reactions such as stridor, urticaria, and flushing have not appeared during the course of repeated cycles of paclitaxel administration, although there have been a few episodes of bone marrow suppression, (including leukopenia of grade 1), which were successfully treated with subcutaneous injections of human recombinant granulocyte colony stimulating factor, 100 μg.

As of April 2003, the patient was still receiving repeated cycles of weekly paclitaxel in the outpatient setting, without any dose reductions, and 14 cycles of

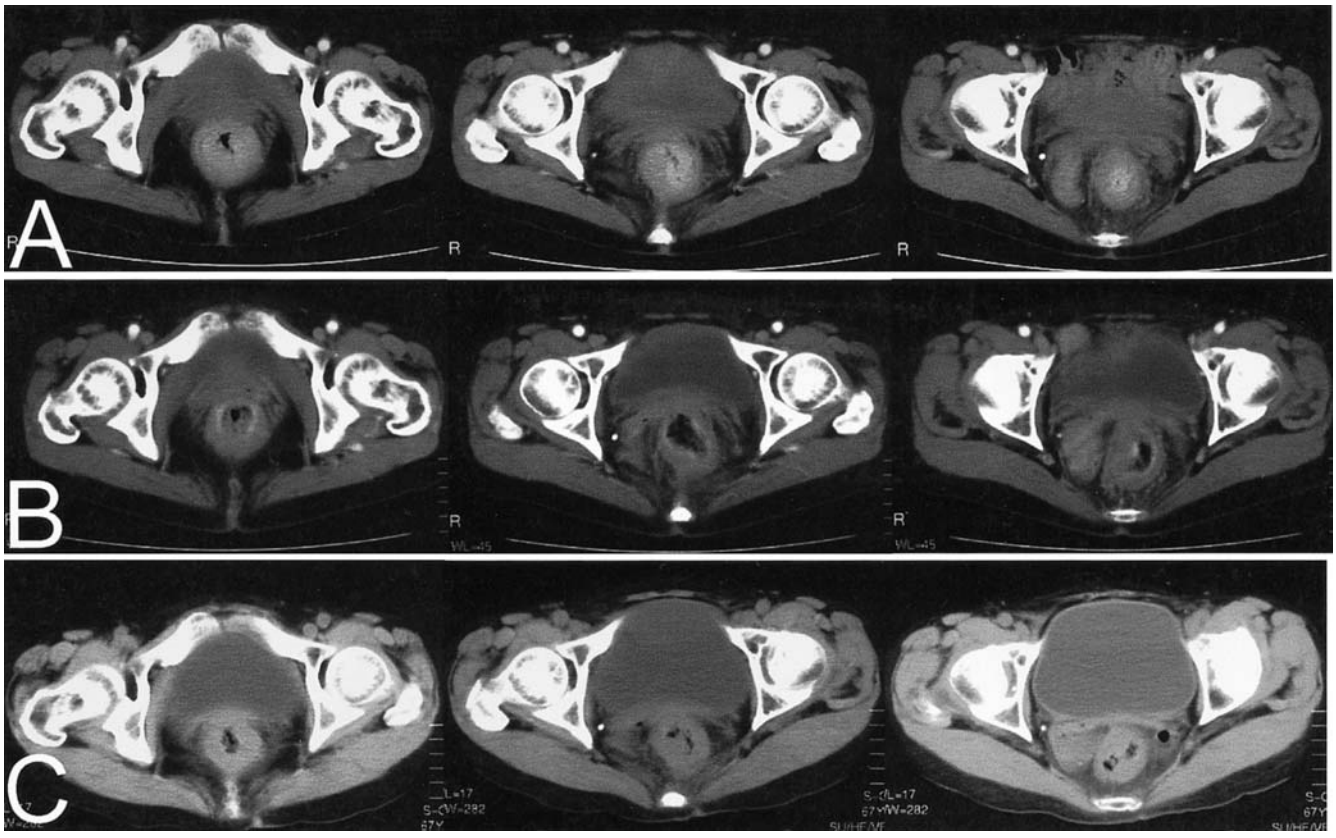

Fig. 4. A Abdominal computed tomography (CT) scanning on admission, revealing circumferential wall thickening of the rectum, which continuously extending through the upper rectum and rectosigmoid portion. Sequential images of pelvic CT scanning **B** 4 months and **C** 8 months after the start of weekly paclitaxel, demonstrating attenuation of the extent of rectal stenosis, which was maintained for more than 10 months

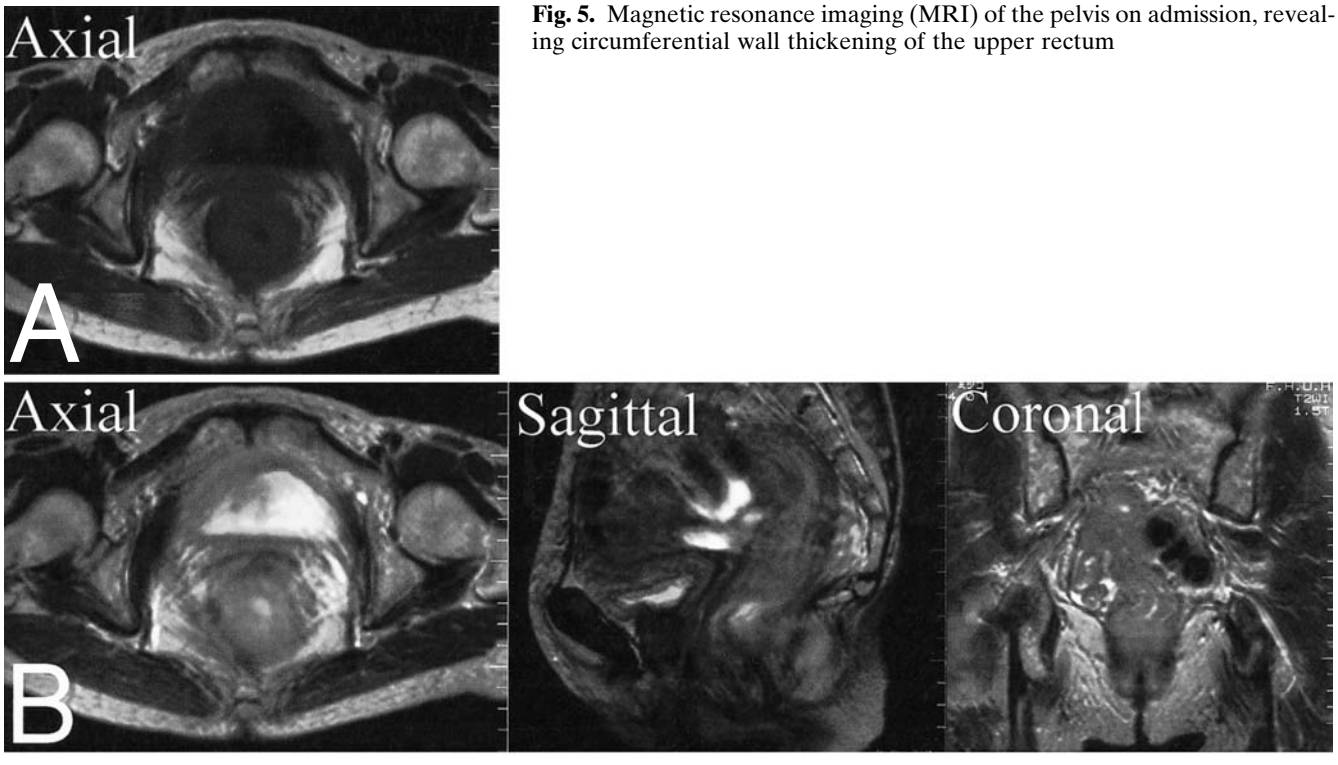

Fig. 5. Magnetic resonance imaging (MRI) of the pelvis on admission, revealing circumferential wall thickening of the upper rectum

paclitaxel had been completed. The patient has been in good shape without any changes in bowel habit. This stable condition of the patient with the weekly administration of paclitaxel indicates that the recurrent gastric carcinoma has been in a tumor dormancy status for 13 months since the start of the weekly administrations of paclitaxel.

Discussion

The reasons that this case report warranted publication are twofold. (1) This is a rare case of circumferential rectal stenosis extending to the upper rectum presented as a late peritoneal recurrence of gastric carcinoma resected 8 years previously. While gastric carcinoma occasionally recurs within 5 years after operation, late peritoneal recurrence more than 5 years after surgery is a relatively rare event, but such recurrence is extensive in some patients. Although some predictive factors for late recurrence have been noted [5–7], the precise mechanism of late recurrence is unknown. (2) Weekly administration of paclitaxel was effective for creating a state of tumor dormancy in a patient with recurrent gastric carcinoma.

It has been reported that approximately 50000 persons per year died from gastric carcinoma in recent years in Japan [8] thus, gastric carcinoma remains a major health problem in Japan, as well as worldwide. In particular, the survival rate of metastatic gastric carcinoma has been reported to be poor, and the 2-year survival rate is only 10% [9]. Peritoneal dissemination, one type of recurrence that is generally characteristic of gastric carcinoma, has been reported to definitely be a poor predictor of survival [10]. Other than the primary rectal carcinoma, peritoneal metastasis may be a cause of circumferential rectal stenosis, which has been reported to show rectal narrowing and rigidity as radiological features [11]. In the present patient, the late peritoneal recurrence of gastric carcinoma occurred 8 years after the primary resection. The multiple circumferential stenoses were considered to have been caused by peritoneal dissemination of recurrent gastric carcinoma. Although recurrent gastric carcinoma causing the multiple stenoses of the colorectum was not histologically confirmed, the findings obtained by barium enema and colonofiberscopy were characteristic of metastatic carcinoma that extended from the serosal side of the colonic wall. The fact that there were no abnormal findings in the uterus on the gynecological examination done on admission could rule out the possibility that the rectal stenosis was caused by endometriosis. Histologically, poorly differentiated adenocarcinoma associated with mucinous fluid is frequently seen in patients with metastasis to the rectum [12]. It has generally been demonstrated that curative resection is impossible to perform in such patients and the patients die within 12 months after the metastasis is found in majority of these cases. It has been reported that there is late recurrence in only 6% of surgically resected gastric carcinomas. The important factors predicting early recurrence have been reported to be tumor size and the extent of lymph node metastases [6]. The present patient was at high risk of early recurrence after resection in terms of tumor size and extensive lymph node metastasis, in contrast to previously reported patients.

In the present patient, weekly administration of paclitaxel was effective for the treatment of circumferential rectal stenosis that had resulted in tenesmus and loose stools. Paclitaxel is an anticancer chemotherapeutic agent derived from the bark of the Pacific yew tree, *Taxus brevifolia*, and it acts as an antimitotic agent by binding to microtubules [13]. Its cytotoxicity is mediated through the promotion of microtubule assembly and the subsequent inhibition of normal disassembly, including the formation of extremely stable microtubule bundles. Cell division consequently stops at G2/M in the cell cycle [14,15]. A recent report has demonstrated that paclitaxel elicits its anticancer effect by the induction of p53-independent apoptosis [16]. Anticancer effects of paclitaxel have been demonstrated subclinically [13,17,18] and clinically in breast [19], ovarian [20], and nonsmall-cell lung cancers [21]. Because paclitaxel has a unique mechanism underlying its anticancer effect, paclitaxel is expected to elicit a different spectrum of anticancer effects from those of previously available agents.

This effectiveness may be supported by the finding that an effective concentration of paclitaxel in the ascitic fluid and/or peritoneal cavity was obtained after the intravenous administration of paclitaxel [4,22]. Although ascites was not found in the present patient, it is possible that the effectiveness of paclitaxel was related to the effective concentration of paclitaxel that was maintained in the recurrent lesions. Therefore, the effectiveness of weekly paclitaxel in the present patient may lead to an expectation that this regimen could be useful for the treatment of peritoneal disseminated lesions of gastric carcinoma. This novel chemotherapeutic regimen has been reported primarily in patients with recurrent breast carcinoma, and clinical efficacy in patients with primary breast carcinoma has also been reported [19]. While the administration of paclitaxel for the treatment of gastric carcinoma has been reported in recent years [23–28], paclitaxel was administered every 3 weeks at a dose from 175 to 225 mg per m^2. However, recent trends in anticancer chemotherapy have shown a paradigm shift, implying that the weekly administration of smaller doses is preferred [29,30]. This trend has been

based on the dose-density concept that enables the effective inhibition of cancer cell proliferation by curtailing of the dose interval [30].

Paclitaxel was frequently given as a continuous infusion in previous years [31]. The rationale for a continuous infusion is based on the fact that severe hypersensitivity reaction occurred, which has led to the cessation of many phase I clinical trials of bolus doses of paclitaxel with a shorter infusion schedule [32]. A chemotherapeutic regimen using continuous infusion was selected to minimize the severe hypersensitivity reaction that was recognized in the early phase I clinical trials [4,33–38]. The primary benefits of weekly administration of paclitaxel are considered to be the minimization of toxicity and the ability to administer this chemotherapeutic regimen in the outpatient setting. Yamada et al.[39] stated that, for their 3-h infusion regimen, a short-course premedication regimen offerred a safe and convenient alternative to the standard premedication [32], and their approach facilitates the administration of paclitaxel in an outpatient setting.

For the present patient, weekly administration of paclitaxel was selected as the second-line anticancer chemotherapeutic regimen after the oral administration of a fluoropyrimidine (UFT), because paclitaxel has been shown to elicit a different spectrum of anticancer effects [40,41]. This difference may be explained by the fact that paclitaxel elicits its effects through different mechanisms from those of other anticancer agents [13,16]. The effectiveness of paclitaxel as a second-line chemotherapeutic regimen for recurrent and advanced gastric carcinomas has been reported recently , in which weekly paclitaxel was effective after resistance was shown to TS-1 [40,41]. The present case provides further evidence that supports these reports, suggesting that weekly administration of paclitaxel is a feasible choice of second-line anticancer chemotherapy after resistance has been shown to fluoropyrimidines. In particular, good quality of life of the patient was maintained for 13 months, which was the longest period of tumor dormancy during the repeated weekly administration of paclitaxel that has ever been reported in the literature, as far as we aware. We are now planning to use weekly administration of paclitaxel as a solid second-line chemotherapeutic regimen for recurrent and/or advanced gastric carcinoma; further accumulation of cases is required to determine the overall response rate and characteristics of the anticancer spectrum after resistance to first-line chemotherapy.

For the present patient, no neurological side effects were observed during the course of the paclitaxel cycles. Neurotoxicity has been reported to be the nonhematological side effect most frequently observed during the use of paclitaxel [42], and to occur in a dose-dependent manner [42,43]. The frequency of neurotoxicity of an extent higher than grade 1 has been reported to be 22%–75% [24–28,39]. The dose of paclitaxel used in these studies was 175–210 mg/m^2 infused for 3 h every 21–28 days. No neurotoxicity was observed in previously published reports of patients receiving weekly paclitaxel [40,41,44]. The absence of toxic neurological effects in the present patient confirmed evidence supporting findings that weekly administration of paclitaxel has minimal neurotoxicity.

In summary, weekly administration of paclitaxel was effective in controlling rectal stenosis caused by the peritoneal dissemination of recurrent gastric carcinoma 8 years after gastrectomy. This regimen was effective for maintaining good quality of life in the patient, with minimal toxic side effects. The anticancer effect seen in the present patient suggests that weekly paclitaxel could be an important second-line anticancer chemotherapeutic regimen for patients with recurrent gastric carcinoma, and that the regimen could be performed with minimal side effects in an outpatient setting.

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