A Case of Recurrent Peritoneal Cancer in Which an Antitumor Effect Was Obtained Using a Combination of Etoposide and a Chinese Herbal Medicine with Maintenance of Daily Life

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The patient was a 50-year-old multiparous female (gravida/para 4/2) who had divorced. She was followed up for 1 year and 5 months after completion of initial treatment for peritoneal cancer (preoperative chemotherapy + optimal surgery + chemotherapy). A gradual increase in the tumor marker CA125 occurred, and computed tomography and ultrasonography showed bilateral neck, left supraclavicular and right axillary lymphadenopathy. The patient wanted to continue her job. Therefore, she was treated with etoposide (25 mg) daily for 3 weeks and TJ-48 (juzen-taihoto, 7.5 g) daily for 4 weeks, and then followed up. After two weeks, swelling of lymph nodes had been reduced or eliminated and tumor marker CA125 was negative. The only adverse reaction was slight numbness and the patient continued to work while receiving the same drugs orally for 2 years and 8 months without any symptoms or recurrence. This case shows that a combination of etoposide and TJ-48 has an antitumor effect on recurrent progressive peritoneal cancer while allowing a patient to work and have a normal daily life.

Key words: peritoneal cancer, etoposide, juzen-taihoto

INTRODUCTION

Molecular targeted drugs have had a marked effect in treatment of gynecologic cancer [1]. However, these drugs are expensive and the financial burden on patients can be severe. In contrast, etoposide is an antineoplastic drug that was initially produced from podophyllotoxin extracted from Berberidaceae rhizome in 1966, and is relatively inexpensive [2]. The Chinese herbal medicine TJ-48 (juzen-taihoto) decreases adverse reactions caused by anticancer drugs and is effective in treatment of various recurrent cancers [7, 9, 13, 15, 16]. In the case reported here, we used combination therapy of etoposide and TJ-48 for advanced peritoneal cancer. As far as we are aware, this is the first case report of etoposide and juzen-taihoto (TJ-48) treatment for recurrent peritoneal cancer. This treatment allowed the patient to continue with her work without disturbance of daily life.

CASE REPORT

The patient was a 50-year-old multiparous female (gravida/para 4/2) who had divorced. She was diagnosed with stage IV peritoneal cancer, and received 4 cycles of neoadjuvant chemotherapy of Paclitaxel and carboplatin (TC), followed by optimal surgery of abdominal total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy and peritoneal tumor resection. The pathological diagnosis was poorly differentiated adenocarcinoma (high grade serous carcinoma), metastatic lymph nodes, pleural effusion and ascites cytology of class V (adenocarcinoma). Postoperatively, 6 cycles of adjuvant TC chemotherapy were administered, with follow-up observation (Fig. 1).

One year and five months after the initial treatment, the level of the tumor marker CA125 gradually increased. Computed tomography and ultrasonography showed bilateral neck, left supraclavicular and right axillary lymphadenopathy. The patient strongly desired to continue her daily work, and after consultation, she was treated with etoposide at 25 mg/day for 3 weeks and juzen-taihoto (TJ-48) at 7.5 g/day for 4 weeks, and then followed up. She continued to work with further oral treatment with these drugs for 2 years and 8 months without symptoms or recurrence (Fig. 2). Swelling of lymph nodes was reduced or eliminated and tumor markers became negative (Fig. 3). The only adverse reaction was grade 1–2 numbness in the fingers and feet (CTCAE ver. 4). Currently, at 1 years and 7 months since the end of oral treatment, there are no signs of recurrence, but mild numbness of the fingers and feet continues.

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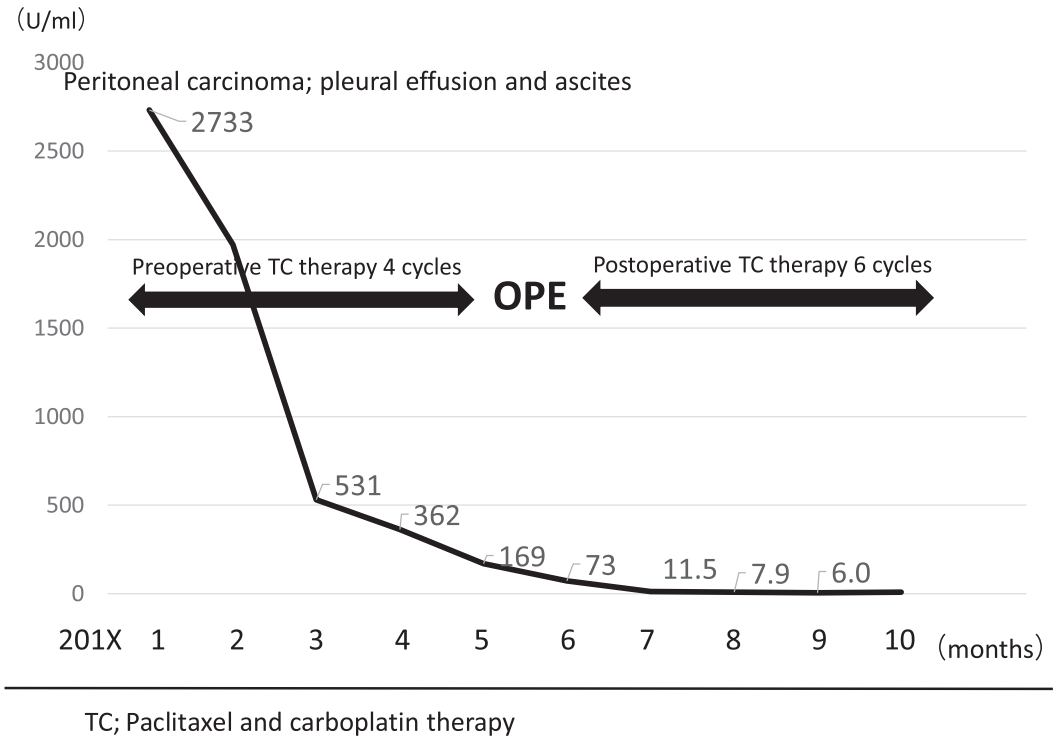

Fig. 1 Changes in CA125 during initial treatment.

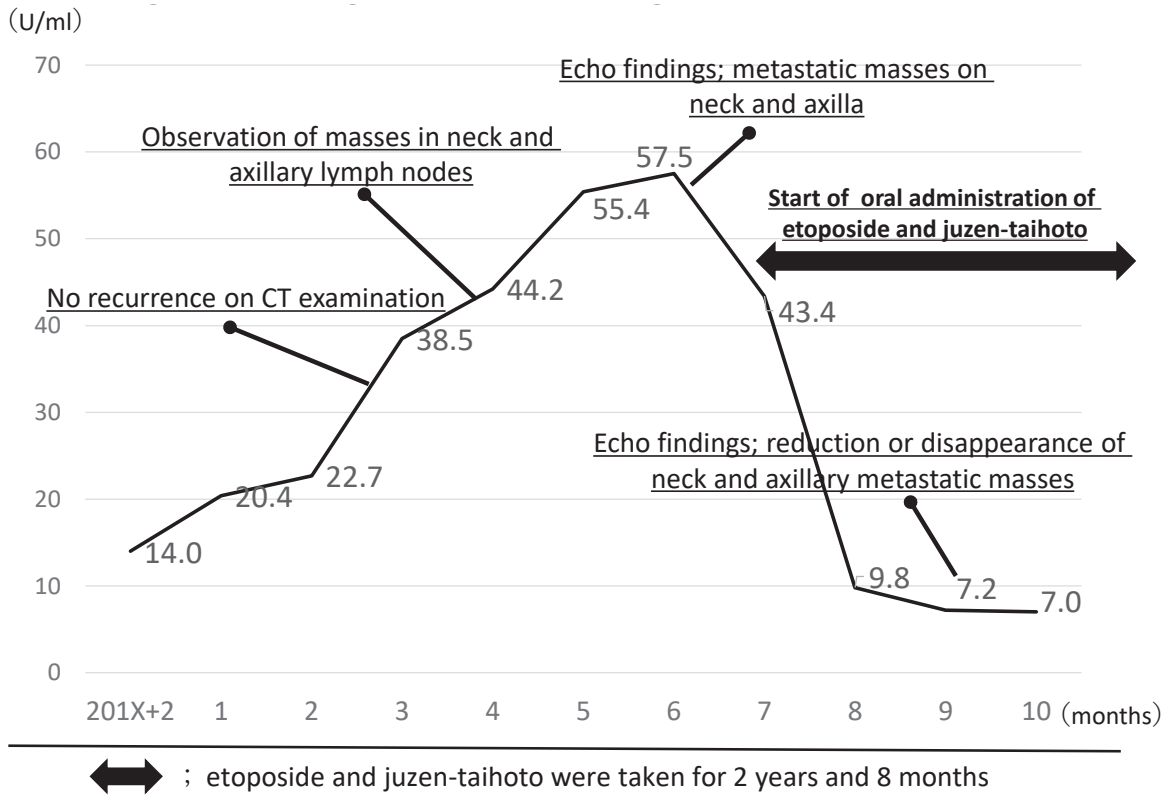

Fig. 2 Changes in CA125 during treatment after recurrence. Etoposide and juzen-taihoto were ultimately taken for 2 years and 8 months.

DISCUSSION

Chemotherapy for recurrent peritoneal cancer is performed using guidelines for ovarian cancer treatment, in which platinum-based multidrug therapy is recommended [1]. Combination treatment with molecular targeted drugs such as bevacizumab can improve the prognosis of recurrent cases, but these drugs are expensive and a financial burden on patients. Serious complications including gastrointestinal perforation and thromboembolism may also occur [3]. In our case, treatment of recurrent peritoneal cancer with a combination of etoposide and TJ-48 reduced or eliminated metastasized lymph nodes and CA125 and caused

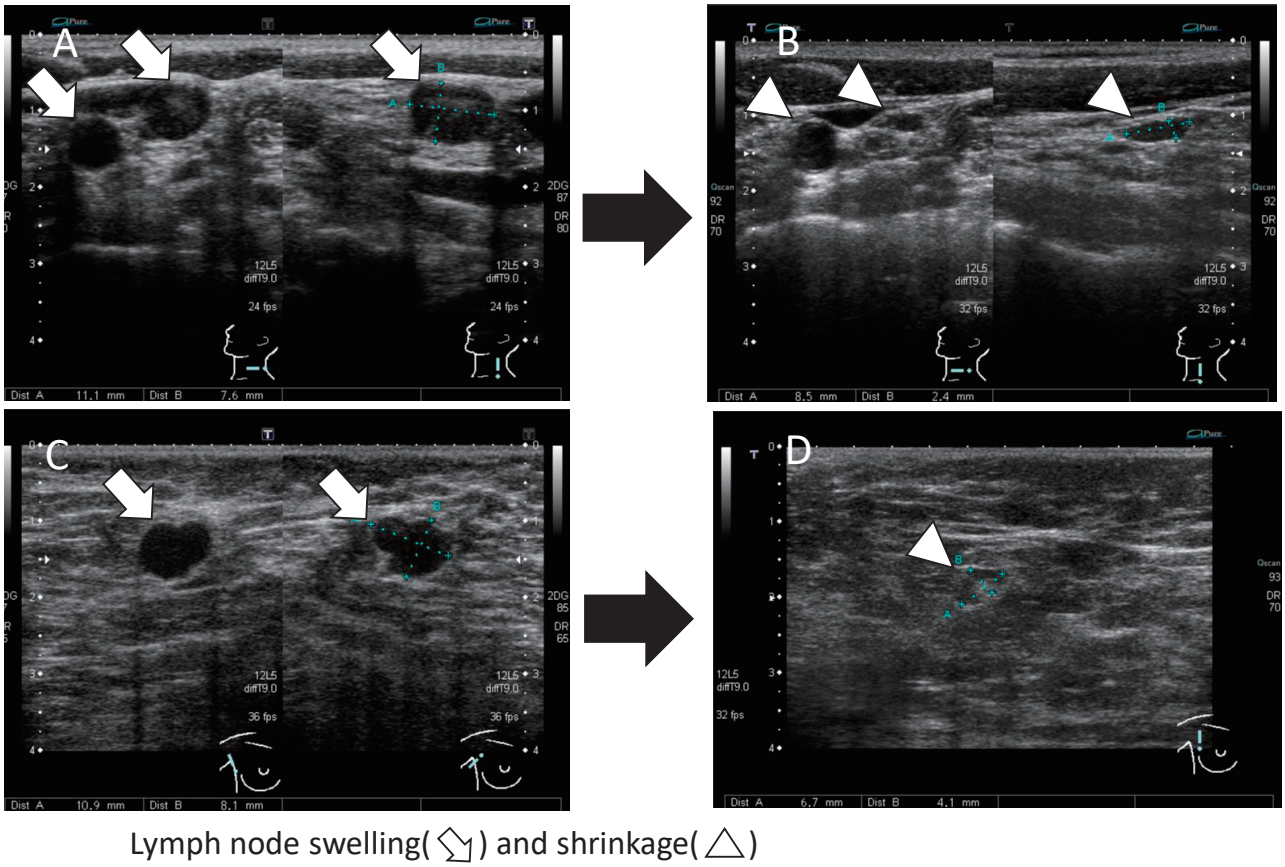

Fig. 3 Echo findings showed decreases and elimination of neck (A, B) and axillary (C, D) lymph node swelling.

almost no adverse reactions. The patient was divorced and supported her family as a single mother. For this reason, effective treatment was required that also permitted the patient to work and to maintain her quality of life (QOL).

Our treatment plan was based on oral administration proposed by a senior oncologist [4, 5, 8]. The oncologist had used the combination of etoposide and TJ-48 in several patients with recurrent ovarian cancer and had found reduced or eliminated tumors and lower tumor markers. This drug combination can be used for a long period and long-term outcomes can be judged over several years. There are many case reports of treatment with a combination of anticancer drugs and Chinese herbal medicine. This approach is considered to be empiric treatment, but its therapeutic efficacy has been shown.

Etoposide is an antineoplastic drug that was first obtained from podophyllotoxin, a crystalline material extracted from Berberidaceae rhizome, in 1966. The mechanism of action is formation of a complex with topoisomerase II that causes DNA breaks in cancer cells and inhibits DNA recombination and duplication [2]. The major adverse reactions are myelosuppression, anaphylactic shock, pneumonitis, and gastrointestinal symptom, including nausea and vomiting. In Japan, etoposide was approved in March 1987. Injections and capsules are on the market, with the indications for capsules being small cell lung cancer, malignant lymphoma, cervical cancer and recurrent ovarian cancer [6, 12].

TJ-48 is a Chinese herbal medicine that is effective for severe wasting, general malaise and anorexia after surgery and other treatment. TJ-48 has 10 herbal components: Astragalus root, cinnamon bark, Rehmannia root, peony root, Cnidium rhizome, Atractylodes lancea rhizome, Angelica root, ginseng root, Hoelen, and licorice. The enhancement of immunity by TJ-48 combined with anticancer treatment may relieve myelosuppression, and TJ-48 itself has been shown to have a strong antitumor effect in animal experiments [7, 9, 10]. In particular, Astragalus root, Rehmannia root, peony root, Cnidium rhizome and Angelica root are thought to act as a biological response modifiers that improve immunocompetence, inhibit expression of cytokines that cause inflammation, activate tumor-specific cytotoxic T cells, increase natural killer cell activation and INF-γ, and inhibit angiogenesis [9, 11, 17, 18]. There are clinical reports of tumor-reducing effects of TJ-48 on recurrent ovarian, liver and lung cancers [13–15]. In gynecology, TJ-48 has been shown to enhance the effect of HPV vaccine on cervical cancer [19].

Our treatment regimen for recurrent peritoneal cancer was continuous 21-day oral etoposide at 25 mg/day and 7-day drug withdrawal, and 28-day oral TJ-48 at 7.5 g/day for 2 years and 8 months. The oral etoposide dose is 25 and 50 mg and the package insert for recurrent ovarian cancer recommends a dose of 50 mg/day for 21-day and 7-day drug withdrawal [8]. However, we have experienced cases of severe myelosuppression after continuous 10-day oral administration of 50 mg etoposide, resulting in treatment withdrawal or hospitalization to prevent susceptibility to infection. Therefore, we used a daily dose of 25 mg in combination with TJ-48 and observed the condition of the patient. This regimen led to relief of myelosuppression, gastrointestinal symptoms such as nausea and

vomiting, peripheral neuropathy including numbness, and general malaise. Imaging and tumor marker tests were conducted periodically and treatment was continued for approximately 2 years and 8 months. After completion of treatment, the patient has had no recurrence to date.

Chinese herbal medicine is commonly used for adverse reactions of myelosuppression, anorexia and general malaise [2, 7, 16]. Our case shows that a combination of oral etoposide with the Chinese herbal medicine TJ-48 can be used for continuous cancer treatment while allowing the patient to have a normal daily life without decreased QOL. As described above, there are many case reports of an antitumor effect of TJ-48, while etoposide has efficacy for advanced or recurrent cancer. In combination, these drugs may relieve adverse reactions and have an antitumor effect.

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