Cisplatin–5-Fluorouracil Therapy with Remarkable Effect and 5-Year Survival for Paraaortic Lymph Node Metastases of Rectal Carcinoma in Females: A Case Report

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A 68-year-old woman was admitted because of a rectal carcinoma with huge paraaortic lymph node metastases. Low anterior resection with regional lymph node dissection was performed, leaving the paraaortic mass. After the operation, cisplatin–5-fluorouracil therapy was used as supplemental chemotherapy. The metastatic lymph nodes shrunk remarkably in response to anticancer drugs. We evaluated the effect of chemotherapy as a partial response. The physical condition of the patient was well controlled for more than 4 years until she was admitted again because of cardiac failure accompanied by relapse of abdominal lymph node swelling. She died of cardiac failure 5 years and 3 days after the operation.

Key words: rectal carcinoma — paraaortic lymph node — cisplatin—5-fluorouracil

INTRODUCTION

Nowadays chemotherapy is mainly used for the treatment of recurrent or unresectable colorectal cancer. However, there are no anticancer drugs effective as single agents for colorectal cancer. Therefore, various protocols involving the combination of 5-fluorouracil (5FU) with other drugs have been tried. Cisplatin (CDDP)—5FU therapy is one of those based on the concept of biochemical modulation and is widely used for gastric and esophageal carcinoma (1–7). In contrast, as for colorectal carcinoma, many authors have reported that leucovorin (LV)—5FU therapy is effective in clinical studies (8–12). However, there are three reports that CDDP—5FU therapy is effective for advanced colorectal carcinoma (13–15). We treated a 68-year-old woman who suffered from rectal carcinoma with huge paraaortic lymph node metastases. She received CDDP—5FU therapy after low anterior resection with only regional lymph node dissection, which greatly reduced metastatic lymph nodes and improved her quality of life (QOL) and she survived for 5 years.

CASE REPORT

A 68-year-old woman showed constipation, appetite loss and body weight loss. Barium enema and abdominal computed tomography (CT) at another hospital revealed rectal carcinoma with huge paraaortic lymph node swelling. She was subsequently referred to Tokyo Hitachi Hospital and admitted on June 29, 1993. The patient’s past history was unremarkable except for appendectomy. As for her family history, her mother died of gastric carcinoma. An elastic hard tumor, 8 cm in diameter, was palpable at the umbilical region, which corresponded to paraaortic mass. With regard to laboratory findings, the blood cell count showed severe anemia [hemoglobin (Hb) 6.5 g/dl] and carcinoembryonic antigen (CEA) was extremely elevated to 140.3 ng/ml. Barium enema showed a severe stenosis 7 cm in length above the peritoneal reflection of the rectum (Fig. 1). Abdominal CT showed a huge paraaortic lymph node swelling (Fig. 2).

After anemia had been corrected by blood transfusion, operation was performed for the purpose of preventing subsequent obstruction of the rectum on July 9, 1993. At laparotomy, there was a little ascitic fluid (cytology was negative for malignancy) and paraaortic lymph node swelling extending from celiac axis to the bifurcation of the aorta was seen. The main tumor, 7 cm in diameter, was located in the rectum (above the peritoneal reflection) and showed serosal invasion and regional lymph node swelling (Fig. 3). Since the clinical
stage was T4N2M1 (stage IV) and radical operation was not indicated, low anterior resection of the rectum with only regional lymph node dissection was performed. In the resected specimen, the main tumor was a circular, 7 × 6.5 cm, ulcerative and infiltrative shaped carcinoma (Fig. 4, top). Microscopically, the tumor was composed of well-differentiated adenocarcinoma invading the serosa (pT4) and metastases were observed in 14 of 17 regional lymph nodes (Fig. 4, bottom).

After the operation, we decided to give CDDP–5FU therapy as supplemental chemotherapy. Fig. 5 shows the process of chemotherapy. The first course started on August 16, 1993 (post-operative day 39) and was as follows: CDDP 50 mg/m² was administered for 3 h on day 1 and 5FU 500 mg/m² was administered for 24 h on days 1–5. In the second course, we gave oral UFT (TAIHO, Tokyo, Japan) at 600 mg/day instead of 5FU infusion from September, then the dose of UFT was reduced to 400 mg/day from November and 300 mg/day from December referring to the protocol of Suga et al. (16). Moreover, a total of four courses of CDDP were also administered.
CDDP/SFU for metastasis of rectal cancer

in September 1993, November 1993 and March 1994. During the second course of CDDP, she suffered from atrial fibrillation because of rapid water loading. Therefore, CDDP administration with water loading was performed more slowly (for 12 h) for the third and fourth courses. As a result, the only side effect was slight anorexia. After four courses of CDDP, the dose of UFT was increased to 400 μg/day and continued until numbness appeared in her limbs in December 1994, because such a phenomenon might be one of the side effects of UFT. When UFT intake was finished, no chemotherapy or radiotherapy was performed until she died.

As for subjective symptoms, the abdominal distension due to the huge paraaortic mass was decreased and anorexia also improved after the first course of chemotherapy. Abdominal CT showed evident reduction of paraaortic lymph node on September 2, 1993 (2 weeks after the first course of chemotherapy) (Fig. 6, top). After three courses of chemotherapy, the lymph node became much smaller and remained only around the root of the inferior mesenteric artery on December 5, 1993 (Fig. 6, bottom). With regard to tumor markers, the CEA level decreased from 140.3 ng/ml (pre-operation) to 11.5 ng/ml (post-operation), 3.9 ng/ml after the first course of the chemotherapy and finally 1.3 ng/ml after three courses of chemotherapy (Fig. 5). The CEA level then remained in the normal range until the patient was rehospitalized in May 1998. Thus, she showed a remarkable response to chemotherapy in the clinical manifestations, the CT images and the tumor marker CEA.

We evaluated the effect of chemotherapy as a partial response (PR), which is defined as a >50% reduction of the sum of all measurable lesions lasting for at least 4 weeks according to World Health Organization (WHO) criteria (17).

After the operation, she attended hospital as an outpatient while carrying out daily activities for 4 years and 10 months. However, she was admitted to our hospital again because of dyspnea and edema in May 1998. Examination revealed cardiac failure due to endocarditis. After admission, abdominal distention recurred and the widespread swelling of the mesenteric and paraaortic lymph nodes was diagnosed by abdominal CT on July 8 (Fig. 7). The CEA level rose to 8.8 ng/ml in June and 13.2 ng/ml in July. In addition, the levels of anti-thrombin III (ATIII) (69%), platelet (Pit) (7 x 10^4/μl) and prothrombin time (PT) (70%) decreased and the levels of D-dimer (482 ng/ml) and fibrin degradation product (FDP) (7.5 μg/ml) increased on May 14, 1998. These data showed abnormalities of the coagulation system. She died of cardiac failure 5 years and 3 days after the operation. Autopsy revealed bacillary endocarditis that was assumed to have originated from vegetation on a heart valve. We thought the vegetation was related to hypercoagulability due to cancer relapse. Autopsy also revealed that the swelling of the mesenteric and paraaortic lymph node was metastases of rectal carcinoma.
DISCUSSION

The concept of biochemical modulation has recently been the focus of considerable attention in cancer chemotherapy. The purpose of biochemical modulation is to increase the effect of an anticancer drug, that is, to increase antitumor effects and reduce side effects by changing the pharmacokinetics of the effector (anticancer drug) with a modulator.

CDDP–5FU chemotherapy is based on the concept of biochemical modulation. As the mechanism of modulation, CDDP promotes methionine synthesis in cells by suppressing the intake of extracellular methionine. This promotion of methionine synthesis accelerates the folic acid metabolic circuit and increases 5,10-methylene tetrahydrofolic acid (5,10-CH2FH4), which forms a ternary complex with fluorodeoxyuridine monophosphate (FdUMP, metabolic product of 5FU) and thymidylate synthase (TS). The reaction lowers TS activity and inhibits deoxyribonucleic acid (DNA) synthesis (7,18,19).

As for colorectal carcinoma, LV–5FU therapy is commonly used in Western countries (8–12). Moreover, several authors have reported that there are no advantages with CDDP–5FU therapy for colorectal carcinoma (19–21). In contrast, in Japan LV–5FU is not yet established from the viewpoint of protocol, side effects and cost performance. CDDP–5FU therapy has the same mechanism as LV–5FU therapy from the point of increasing TS inhibition (11,12). It is usually applied to gastric and esophageal carcinoma and many authors have reported its efficacy (1–7). In addition, one paper reported that CDDP–5FU therapy is effective for colorectal carcinoma (13). Therefore, we selected CDDP–5FU therapy as supplemental chemotherapy. However, with radical chemotherapy the duration of response is usually less than 1 year in colorectal carcinoma (14,22). In our case, the duration of response was more than 4 years, the QOL of the patient was much improved and she survived for 5 years after the operation. There are no case reports that CDDP–5FU therapy was effective for advanced colorectal cancer for more than 4 years. One of the reasons why cancer relapse was suppressed for such a long time may be the application of UFT, which is a combination of uracil and tegafur. The uracil in UFT slows degredation of 5-FU by dihydropyrimidine dehydrogenase (DPD), which results in sustained concentrations of 5-FU in blood and tumor tissues (23,24).

Recently, several authors have reported that the combination of continuous administration of 5FU with a low-dose daily infusion of CDDP is more effective and side effects due to the protocol are milder than the combination with bolus injection of CDDP (7,14,15). When we gave CDDP–5FU (UFT) therapy to this patient, the protocol was not yet established. Therefore, we selected a protocol of CDDP bolus injection of those days. In our case, CDDP might not act as a modulator of 5FU so much, but CDDP itself might be effective on metastatic lymph nodes.

In conclusion, we experienced a valuable case where CDDP–5FU was very effective for paraaortic lymph node metastases of rectal cancer in a female. Although there are many reports on the efficacy of LV–5FU therapy for colorectal cancer in Western countries (8–12), we think that CDDP–5FU (UFT) therapy may be useful for the treatment of colorectal cancer by an appropriate protocol and the prevention of side effects such as vomiting and renal disorders.

References


