Continuous Hyperthermic Peritoneal Perfusion for the Prevention of Peritoneal Recurrence of Gastric Cancer: Randomized Controlled Study

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We performed continuous hyperthermic peritoneal perfusion (CHPP) or continuous normothermic peritoneal perfusion (CNPP) combined with cisplatin (CDDP) 300 mg/kg and mitomycin C (MMC) 30 mg/kg in an attempt to prevent peritoneal recurrence after surgery for gastric cancer. Twenty-two patients were treated with perfusion using about 10 liters of saline heated to 41° to 42°C (CHPP group); 18 patients were treated with saline heated to 37° to 38°C (CNPP group); and 18 patients underwent only gastric surgery without perfusion (control group) in a randomized control study. There were two deaths (9%) due to peritoneal recurrence in the CHPP group, four (22%) in the CNPP group, and four (22%) in the control group. The 1-, 2-, and 3-year survival rates were 95%, 89%, and 68%, in the CHPP group; 81%, 75%, and 51%, in the CNPP group; and 43%, 23%, and 23%, in the control group, respectively. There was a significant difference between the three survival curves by the log-rank test (p < 0.01). This difference showed that CNPP and CHPP are both effective procedures for preventing peritoneal recurrence. The maximum concentrations in the perfusate of total and free CDDP with 300 mg administration were 12.2 and 10.1 μg/ml, respectively, at the end of the perfusion, and the maximum concentrations of total and free CDDP in plasma were 2.1 and 1.0 μg/ml, respectively. The maximum concentrations of MMC in perfusate and plasma with 30 mg administration were 1.00 and 0.05 μg/ml, respectively, which are intraperitoneally cytotoxic but systemically safe concentrations.

Advanced gastric cancer with serosal invasion is associated with a high risk of peritoneal recurrence, predicting a poor prognosis. Extended surgical intervention with lymph node resection or systemic anticancer chemotherapy does not improve the prognosis in the patient with peritoneal recurrence. It is important to prevent peritoneal recurrence, although no means of prophylaxis is available.

Koga et al. [1] introduced continuous hyperthermic peritoneal perfusion (CHPP) combined with mitomycin C as a prophylactic treatment for peritoneal recurrence after surgery for gastric cancer. The CHPP is done with saline heated to 42°C and containing anticancer drugs that have synergistic effects with the hyperthermia. We previously performed CHPP with cisplatin (CDDP) and mitomycin C (MMC) to prevent peritoneal recurrence and reported better results in the CHPP group than in the controls with respect to survival time after operation [2]. The real and enhanced effects of hyperthermia were not directly proved by this study, however. It is uncertain that perfusion with saline heated to body temperature (37°-38°C) plus chemotherapy has the same effect as CHPP. Since March 1988 we have performed CHPP and continuous normothermic peritoneal perfusion (CNPP) with CDDP and MMC in a randomized control study to determine which modality had the most preventive effect: perfusion, chemotherapy, hyperthermia, or some combination.

Patients and Methods

Fifty-eight patients with advanced gastric cancer and serosal invasion underwent treatment at the Second Department of Surgery, Kanazawa University between March 1988 and March 1992 and were entered into the study. All underwent curative resection, and 40 of the 58 were treated with CHPP or CNPP before closure of the abdominal wound. Of these 40 patients, 22 were treated with perfusion using about 10 liters of saline heated to 41° to 42°C (CHPP group); and 18 were treated in a similar manner but by saline heated to 37° to 38°C (CNPP group). The remaining 18 patients (control group) underwent only gastric surgery without the perfusion. The study was randomized.

The preheated perfusate containing 300 mg of CDDP (Nihon Kayaku Co. Ltd., Japan) and 30 mg of MMC (Kyouwa Hakkou Co. Ltd., Japan) was infused into the peritoneal cavity through a peritoneal cavity expander (PCE; Nihon Kayaku Co. Ltd., Japan) (Fig. 1). The peritoneal cavity was expanded by a PCE large enough to allow the small intestine to float in the perfusate, and the perfusate infused to the peritoneal cavity was circulated by manual stirring (Fig. 2). (Refer to an earlier paper [3] for details of the procedures.) The intraperitoneal temperatures were simultaneously and continuously monitored with Copper-Constantan thermocouples (type IT-18; Sensortek Co. Ltd., U.S.A.) in Douglas’ pouch and bilateral subphrenic
Fig. 1. Continuous hyperthermic peritoneal perfusion (CHPP). The patients operated for gastric cancer with macroscopic curative resection were treated by perfusion in the peritoneal cavity with about 10 liters of saline heated to 41° to 42°C (CHPP group); 18 patients were treated in a similar manner by saline heated to 37° to 38°C (CNPP group). The preheated perfusate containing 300 mg of cisplatin (CDDP) and 30 mg of mitomycin C (MMC) was infused into the peritoneal cavity through the peritoneal cavity expander (PCE) (Nihon Kayaku Co., Ltd., Japan).

Fig. 2. Peritoneal cavity expander (PCE) is an acrylic cylinder with a spindle-shaped cross section. The peritoneal cavity was sufficiently expanded by the PCE to allow the small intestine to float in the perfusate. The perfusate infused into the peritoneal cavity was stirred by the surgeon.

cavities. After the perfusion the perfusate was quickly drained and the abdomen closed with careful intraperitoneal observation.

The pharmacokinetics of CDDP and MMC were analyzed under CHPP. The concentrations of total and free CDDP and of MMC in the perfusate and the plasma were measured before perfusion, every 10 minutes from the start to the finish of perfusion, and 20, 40, 60, and 120 minutes and 6, 12, and 24 hours thereafter. Survival curves were obtained using the method of Kaplan-Meier. The log-rank test (p value) was used for a comparison of the curves. Patient characteristics was described according to the TNM classification, and the general rules for a gastric cancer study [4] established by the Japanese Research Society for Gastric Cancer were followed.

Results

Thermal profiles for CHPP and CNPP are shown in Figure 3. Each procedure was started when intraperitoneal temperatures reached 41°C with CHPP or 37°C with CNPP. The intraperitoneal temperatures were adjusted to 41° to 42°C in the CHPP group and to 37° to 38°C in the CNPP group for 60 minutes.

Patient characteristics are summarized in Table 1. Of the patients with metastatic peritoneal dissemination (P1), one was in the CHPP group, one in the CNPP group, and three in the control group. (P1 level dissemination is defined as a few seedings only near the stomach [4].) It is frequently possible to resect P1 level dissemination curatively. We have thought that the patients with P1 level dissemination in this series could have undergone complete resections. There were no significant differences in the background features of the patients in the CHPP, CNPP, and control groups.

Twenty-two patients died of recurrent disease after surgery: 5 (23%) in the CHPP group, 6 (33%) in the CNPP group, and 11 (61%) in the control group (Table 2). Recurrence sites included the peritoneum in 10 patients, liver in 5, lymph nodes in 4, local site in 1, and others in 2. There were 2 (9%) deaths due to peritoneal recurrences (9%) in the CHPP group, 4 (22%) in the CNPP group, and 4 (22%) in the control group.

Survival curves, using the method of Kaplan-Meier, of the three groups are shown in Figure 4. The median times of follow-up were 35 months in the CHPP group, 37 months in the CNPP group, and 31 months in the control group. The numbers of survivors at a definite time of follow-up were 17 in the CHPP group; 13 in the CNPP group; and 9 in the control group. The 1-, 2-, and 3-year survival rates were 95%, 89%, and 68% in the CHPP group; 81%, 75%, and 51% in the CNPP group; and 43%, 23%, and 23% in the control group, respectively. There was a significant difference between the three survival curves using the log-rank test (p < 0.01).

The maximum concentrations in the perfusate of total and free CDDP with 300 mg administration were 12.2 and 10.1 μg/ml, respectively, at the end of the perfusion (Fig. 5). The maximum plasma concentrations of total and free CDDP with 300 mg administration were 2.1 and 1.0 μg/ml, respectively, at