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Prophylaxis with Intraoperative Chemohyperthermia against Peritoneal Recurrence of Serosal Invasion-Positive Gastric Cancer

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Abstract. Continuous hyperthermic peritoneal perfusion (CHPP) with a solution which contains 30 mg mitomycin C and 300 mg cisplatin has been introduced as a prophylactic treatment for peritoneal recurrence after curative resection of 79 advanced gastric cancers. The control group consisted of 81 patients with advanced gastric cancer who underwent curative surgery during the same period. CHPP was performed for 60 minutes by perfusing MMC- and CDDP-containing saline solutions warmed at 43.5°C by a special CHPP device. In patients with pathologically confirmed serosal invasion-positive tumors, the survival rate of the CHPP group was significantly higher than that of the control group. A survival advantage for stage IV patients was also obtained by CHPP. However, there was no survival advantage between the CHPP group and the control group with serosal invasion-negative tumors. Adverse effects were observed in four patients who underwent CHPP: One developed severe bone marrow suppression, and transient hyperazotemia was observed in the other three. There was no difference in the incidence of mortality and morbidity between the two groups. These results indicate that CHPP is a safe, readily available prophylactic therapy for peritoneal recurrence after gastric cancer surgery.

Gastric cancer is the second most common cause of cancer deaths worldwide after lung cancer [1]. Despite the introduction of a variety of multimodal therapies, the surgical results for advanced gastric cancer are discouraging, with an overall 5-year survival of 10% to 30% [2–4]. The most frequent site of recurrence is the peritoneum, and many patients with serosal invasion-positive tumor succumb to peritoneal metastasis even after a curative resection is done [5]. The control of peritoneal dissemination is one of the final goals for the treatment of gastric cancer. However, the results of adjuvant systemic chemotherapy are disappointing because the peritoneal cavity is thought to be a pharmacologic sanctuary [6]. Therefore trials of direct intraperitoneal administration of anticancer drugs in aqueous solution have been performed, but the results of these trials are also unsuccessful [7, 8].

There is a renewed interest in the effectiveness of hyperthermia, and the combination of hyperthermia and chemotherapy has proved to enhance the respective anticancer actions. Hence we decided to perform a study of multidisciplinary therapy combining surgery, intraperitoneal chemotherapy, and local hyperthermia for the treatment of peritoneal dissemination [9]. We have developed a novel technique, called continuous hyperthermic peritoneal perfusion (CHPP), which uses a solution that contains mitomycin C (MMC) and cisplatin (CDDP) as prophylactic treatment for peritoneal recurrence after surgery for gastric cancer. This article documents the studies performed to evaluate the effectiveness of the prophylaxis for peritoneal recurrence of gastric cancer.

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Patients and Methods

The technique (CHPP) was applied to 79 gastric cancer patients with macroscopic serosal invasion and no peritoneal metastasis. The control group in this study consisted of 81 patients with macroscopic serosal invasion and no peritoneal dissemination during the same period who were treated by surgery alone. The total 160 patients had consecutively undergone curative surgery in the Second Department of Surgery, Kanazawa University between 1984 and 1992. Histologic serosal invasions were confirmed in 57 (70%) patients of the control group and 63 (80%) of the CHPP group. As shown in Table 1, there is no difference in background factors between these two groups. Patients with active liver disease (e.g., liver cirrhosis or hepatitis) were excluded from the study.

Distal gastrectomy was performed in 44 (55%) and 34 (43%) patients, total gastrectomy in 10 (12%) and 24 (30%), and left upper abdominal evisceration (LUAE) [10] in 27 (33%) and 21 (27%) in the control and CHPP groups, respectively (Table 2). In 40 (49%) of the control group and 42 (53%) of the CHPP group, the removal of paraaortic lymph nodes around the left renal vein in combination with the resection of level 1, 2, and 3 station lymph nodes (D4 gastrectomy) was performed [11].

In the control group, death related to surgery occurred in two (2.5%) patients, who died of anastomotic leak of the esophagojejunostomy. Of the 79 patients of the CHPP group, two died of anastomotic leakage and one died of sepsis due to bone marrow suppression (Table 2).

After resection of the tumor and completion of the reconstructions, the peritoneal cavity was expanded by a peritoneal cavity expander (Tomiki Medical Co., Kanazawa, Japan) (Fig. 1). The peritoneal cavity expander is used to enable maximal fluid–surface

Table 1. Background factors for patients in the control and CHPP-treated group.

Factor	Controls (n = 81)	CHPP-treated (n = 79)
Age (years)	59.2 ± 13.6	57.5 ± 11.7
Sex (male/female)	57:23	44:32
Histologic type (diff./poorly diff.)	28:53	18:61
Macroscopic type (localized/infiltratong)	27:54	20:59
Histologic serosal invasion (negative/positive)	24:57	16:63
Nodal involvement (negative/positive)	19:62	14:65
Stage		
I	7	1
II	22	14
III	17	32
IV	35	32
Liver metastases	0	0

None of the factors showed significance between the two groups.

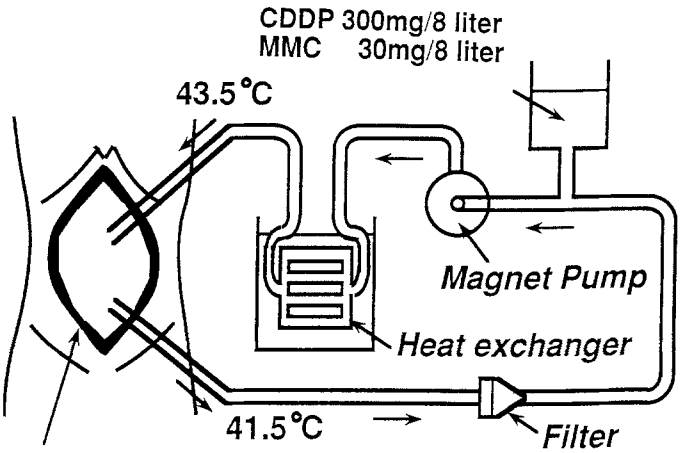

Fig. 1. Schema of the continuous hyperthermic peritoneal perfusion (CHPP). Eight liters of warmed saline with 30 mg of MMC and 300 mg of CDDP, which are heated at 43.5°C by the CHPP device, are perfused in a closed circuit.

Table 2. Operation and postoperative deaths.

Parameter	Controls	CHPP-treated
Operation		
Subtotal gastrectomy	44	34
Total gastrectomy	10	24
LUAE	27	21
Lymph node dissection		
D2	41	37
D4	40	42
Postoperative deaths		
Leakage	2	2
Chemotherapy deaths	—	1

contact within the peritoneal compartments and even heating of every abdominal cavity. Four silicone tubes (10 mm in diameter) were then placed in both sides of the pelvic and right and left subphrenic cavities for infusion and discharge of a heated saline solution. These four tubes were connected with a CHPP device (Tomiki Medical) and the infusate, heated at 43°C, was introduced into the peritoneal cavity through two subphrenic tubes attached to a magnetic pump. Because this magnetic pump can deliver 30 liters of saline solution per minute, every intraperitoneal cavity is evenly heated. The abdominal cavity was filled with 8 liters of saline, which contained 30 mg MMC and 300 mg CDDP, and the infusate was circulated at a rate of 30 L/min. Thermister probes (Tateishi Electric Co., Osaka, Japan) attached to a thermometer (Omron HEH-TM4, Tateishi Electric Co.) were placed in the inflow and outflow tubes at the entrances of the abdominal cavity and in the pelvic and right and left subphrenic cavities. The inflow and outflow temperatures were maintained at 43.5°C and 41.5°C, respectively. The perfusion was performed for 60 minutes after the temperature in the abdominal cavity reached at 41.5°C.

All patients in both groups were given 400 mg UFT [a combination of 1-(2-tetrahydrofuryl)-5-fluorouracil and uracil in a molar ratio of 1:4] per day orally on consecutive days for the first 2 to 3 postoperative weeks.

Peritoneal perfusates and peripheral blood were sampled regularly in three patients until 24 hours from the beginning of CHPP. MMC concentrations in the perfusates and plasma were measured by a thin agar plate method [12], and CDDP concentrations in the same samples were estimated by atomic absorption spectrophotometry [13].

The data are presented as the mean ± SD of the mean. Statistical analyses of the data were performed by χ^2 or the Student t-test. Survival curves were estimated by using the Kaplan-Meier method, and outcomes from different groups of patients were compared by the generalized Wilcoxon test. Throughout this report, the general rules for Gastric Cancer Study of the Japanese Research Society of Gastric Cancer are used for the description and classification of variables [14].

Results

Overall survival curves of the two groups are shown in Figure 2. The 5-year survival rate of the CHPP group was better than that of the control group, but there was no significant difference in survival curves between these two groups (p = 0.052). In patients with serosal invasion-negative tumors, a survival advantage could not be found after CHPP (Fig. 3). In contrast, the survival of patients with serosal invasion-positive tumors in the CHPP group was significantly higher than the survival of those in the control group (p = 0.016) (Fig. 4). In patients with stage IV disease the difference in survival between the groups was also significant (p = 0.0001) (Fig. 5).

The MMC and CDDP concentrations in the perfusates remained high during CHPP and showed four- to sixfold equivalents to the peak plasma concentration (PPC) after administration of 20 mg MMC and 100 mg CDDP per square meter from the peripheral vein [15] (Figs. 6, 7). In contrast, drug concentrations of each drug in the peripheral vein showed significantly lower levels than those in perfusates. They gradually decreased after CHPP and could not be detected 12 hours after CHPP.

Postoperatively, leukopenia (white blood cell count below 3×10^8/L) and thrombocytopenia (platelet count below 10^{10}/L) developed in only one patient of the CHPP group. This patient died of sepsis on the 35th postoperative day. Hyperazotemia (creatinine

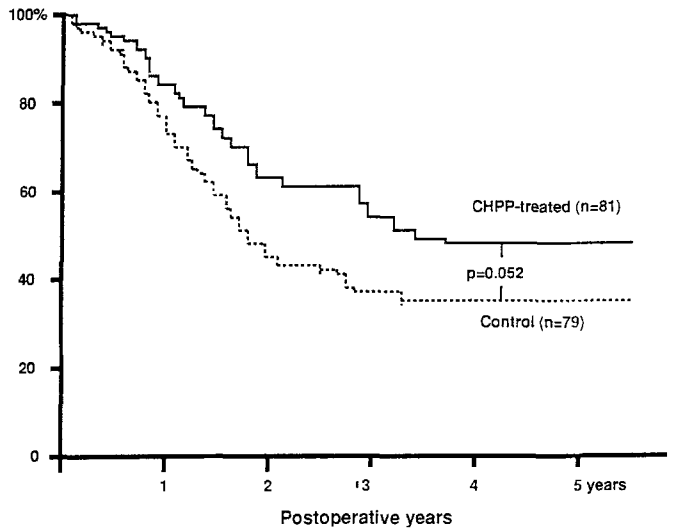

Fig. 2. Overall survival curves of the CHPP and control groups.

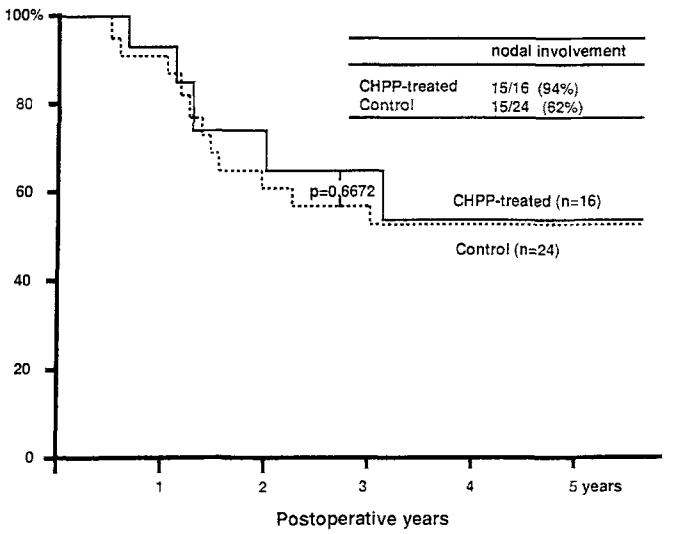

Fig. 3. Survival curves of patients with histologically proved serosal invasion-negative tumor, according to the treatment.

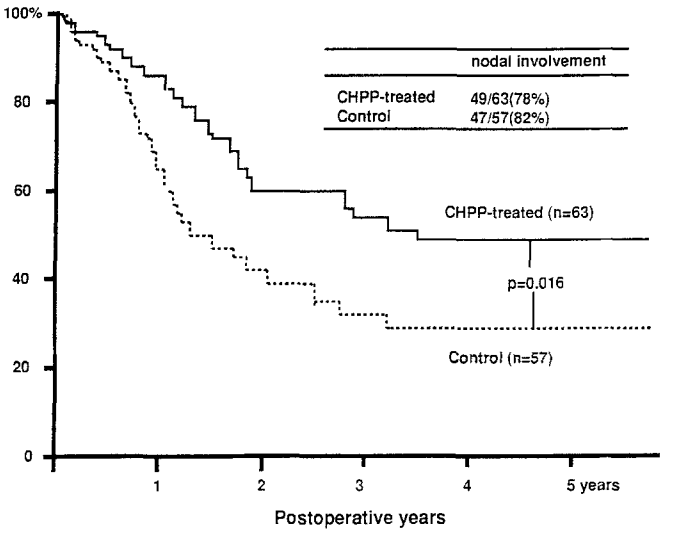

Fig. 4. Survival curves of patients with histologically proved serosal invasion-positive tumor, according to the treatment.

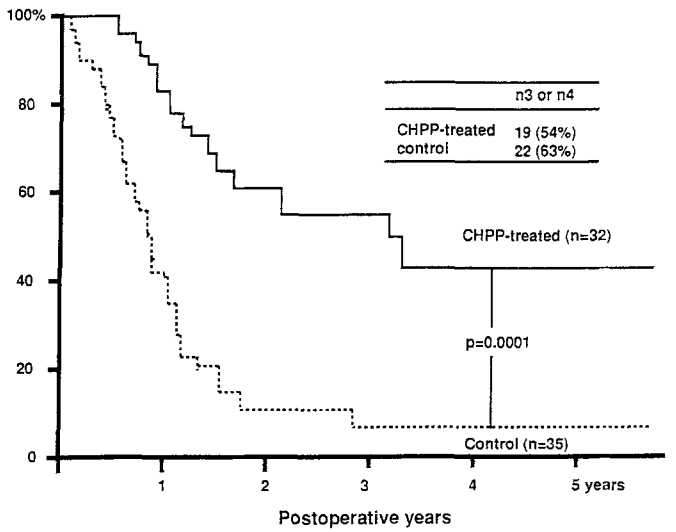

Fig. 5. Survival curves of patients in stage IV of the disease, according to the treatment.

concentration >5 mg/dl) was observed in three patients, but the serum creatinine levels normalized within 3 weeks.

Discussion

Despite improvements in operative technique and adjuvant chemotherapy, the postoperative prognosis for serosal invasion-positive gastric cancer is still poor. In about half of the gastric cancer patients with serosal invasion, viable cancer cells are found by peritoneal lavage [16]. These exfoliated cancer cells from the serosal surface are the origin of the peritoneal recurrence after curative surgery.

In patients with serosal invasion-positive tumors, invisible peritoneal metastasis has already developed in the abdominal cavity, and these foci cannot be completely resected by surgical techniques. To treat these micrometastases, several methods have been tried, but the results were disappointing [4, 8, 9, 17].

In vivo and in vitro studies have shown that hyperthermia is an antitumor agent as soon as it reaches 42.5°C, acting as a cytotoxic agent for tumoral cells [18]. It inhibits DNA replication and RNA and protein synthesis [19]. Furthermore, it affects membrane stability and alters the membrane permeability of cancer cells, resulting in increased intracellular permeability of anticancer drugs [20]. As a result, the addition of hyperthermia in the presence of an anticancerous drug leads to synergistic enhancement of each other's action [21]. In this context, hyperthermia is a hopeful prospect for treating a refractory disease.

Recently, several investigators reported that intraoperative chemohyperthermia is effective for treating the peritoneal dissemination of gastrointestinal cancer [22–24]. Direct introduction of heat plus anticancerous drugs into the peritoneal cavity seems judicious because it acts directly on peritoneal dissemination with high extracellular concentration and low drug transition to the peripheral vein [25]. We previously reported that about 50% of 14

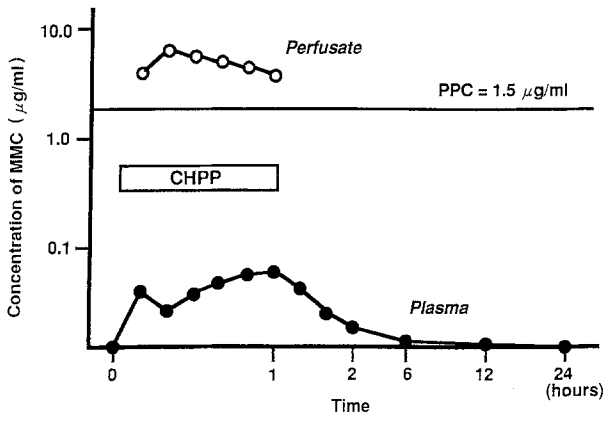

Fig. 6. Mitomycin C (MMC) concentrations in plasma and perfusate ($n = 4$). The peak plasma concentration (PPC; 1.5 μg/ml) means the peak plasma concentration of MMC after administration of 20 mg/m^2 of MMC from the peripheral vein [29]. The MMC concentration in the perfusate was significantly higher than that in plasma. The peak concentration of MMC in the perfusate was 3.2 ± 0.8 μg/ml at 10 minutes. In contrast, peak MMC concentration of plasma was only 0.08 μg/ml, and the level gradually decreased after CHPP.

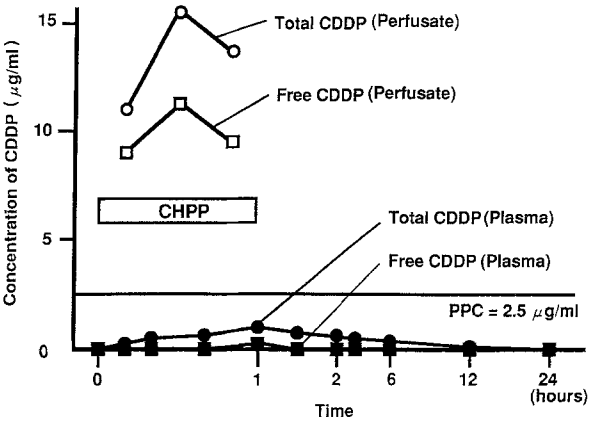

Fig. 7. Cisplatinum (CDDP) concentrations in plasma and perfusates. PPC of CDDP, administered at a CDDP dose of 100 mg/m^2 via the peripheral vein is 2.5 μg/ml [29]. Concentration of free and total CDDP in the perfusate at 20 minutes were 8.65 ± 1.01 and 10.82 ± 1.85 μg/ml, respectively. The concentration of free and total CDDP reached peak levels of 11.6 ± 1.97 μg/ml and 15.62 ± 2.36 μg/ml at 40 minutes, respectively. However, the free and total CDDP concentrations in plasma revealed low levels (<2.0 μg/ml) during CHPP, and no free CDDP could be detected at 2 hours after CHPP.

patients with peritoneal dissemination treated by CHPP showed a partial or complete response [9]. In addition, the most favorable and objective result obtained with CHPP was the drying up of ascites [26].

The effect of chemotherapy is thought to have an inverse correlation with the tumor burden [27]. Thus the postoperative period immediately after resection of a tumor might even be the optimal time for chemohyperthermia, as the tumor burden would be minimal during this time. In 1988 Koga et al. introduced CHPP for the prophylaxis of peritoneal recurrence of gastric cancer and reported the safety and prophylactic effect against peritoneal recurrence [22]. They used MMC in combination with hyperthermia. In other experiments, MMC and CDDP have been singled out for their synergistic anticancer effects with hyperthermia. In addition, our colleagues Ohyama et al. reported that these drugs were also sensitive to gastric cancer by in vitro chemosensitivity test [28]. Based on these results, we used MMC and CDDP in combination with hyperthermia.

In this trial, prophylactic effects were observed in patients with serosal invasion-positive tumors or with stage IV disease. However, this treatment cannot kill cancer cells that have penetrated deeply into the subperitoneal layers [29]. Therefore CHPP may not be recommended for treatment of a bulky mass but can be recommended for treatment of occult peritoneal metastases.

Fujimoto et al. reported that gastric cancer cells in the abdominal cavity vanished after intraoperative chemohyperthermia. CHPP may wash out intraperitoneal free cancer cells, leading to the prevention of the attachment of these free cancer cells to the mesothelium [29].

When treating patients with CHPP, anastomotic leakage and adhesive ileus are the most important concerns. In the present study, the most frequent complications were anastomotic leakage, but there was no difference in the incidence of anastomotic leakage in patients with surgery alone and those with surgery coupled with CHPP. Three patients with transitory renal failures and one with bone marrow suppression were observed and could have been related to the side effects of MMC and CDDP. These complications must be carefully treated.

Our CHPP technique is a simple, readily available prophylactic therapy for peritoneal recurrence after gastric cancer. It would be of interest to evaluate CHPP in patients with gynecologic malignancies, particularly ovarian cancers because of their frequent peritoneal dissemination.

Résumé

La perfusion continue hyperthermique (CHPP) avec une solution contenant 30 mg de mytomycine C (MMC) et 300 mg de cisplatine (CDDP) a été utilisée comme traitement prophylactique pour prévenir la récidive péritonéale chez 79 patients avec un cancer gastrique avancé réséqué. Un groupe composé de 81 patients avec un cancer gastrique avancé qui ont eu une chirurgie à visée curatrice pendant la même période de temps a servi de contrôle. La CHPP, perfusion de MMC et de CDDP mélangés au sérum physiologique réchauffé à 43.5°C par un appareil spécial, était administrée pendant 60 minutes. Lorsque l'envahissement séreux a été confirmé par l'examen anatomopathologique, la survie des patients ayant eu la CHHP était significativement plus longue que lorsque les patients n'avaient pas eu de CHHP. La survie des patients classés stade IV était également améliorée. Il n'y avait aucune amélioration, par contre, de la survie lorsque la couche séreuse n'était pas envahie. Des effets secondaires ont été observés chez quatre patients qui ont une CHHP: un a développé une aplasie médullaire sévère, alors que les trois autres n'ont eu qu'une hyperazotémie transitoire. Il n'y avait, en définitive, aucune différence de mortalité ou de morbidité entre les deux groupes. Ces résultats indiquent que la CHPP est sûre et facilement disponible comme thérapie prophylactique contre la récidive péritonéale après résection de cancer gastrique.

Resumen

La perfusión hipertérmica peritoneal continua (CHPP) con una solución que contiene 30 mg de mitomicina C y 300 mg de cisplatino ha sido introducida como tratamiento profiláctico para prevenir recurrencia peritoneal luego de la resección curativa en 79 pacientes con cáncer gástrico avanzado. El grupo control consistió en 81 pacientes con cáncer gástrico avanzado que fueron sometidos a cirugía curativa en el mismo período de tiempo. La CHPP fue realizada durante 60 minutos con solución salina con MMC y CDDP calentada a 43.5°C por medio de un sistema de CHPP. En los pacientes con invasión serosa confirmada histológicamente, la tasa de sobrevida del grupo CHPP fue significativamente mayor que la del grupo control. También se detectó una ventaja de sobrevida en los pacientes en estado IV tratados con CHPP. Sin embargo, no se encontró ventaja en cuanto a sobrevida entre el grupo CHPP y el grupo control en los pacientes con tumores negativos para invasión serosa. Efectos adversos fueron registrados en 4 pacientes con CHPP:1 desarrolló severa depresión de la médula ósea, e hiperazotemia transitoria fue observada en los otros 3 pacientes. Sin embargo, no se halló diferencia en cuanto a mortalidad y morbilidad entre los dos grupos. Estos resultados indican que la CHPP es una modalidad terapéutica segura y fácilmente disponible para prevenir la recurrencia peritoneal luego de cirugía por cáncer.

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