

Clinical report

Local injection of M-CH combined with i.p. hyperthermic hypo-osmolar infusion is an effective therapy in advanced gastric cancer

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Treatment failure of surgically treated gastric cancer is attributed to the spread of gastric cancer cells into the abdominal cavity and lymphatic or hematogenic canals. In the present study, local injection of mitomycin C bound to activated carbon (M-CH) combined with i.p. hyperthermic hypo-osmolar infusion (IPHHOI) was intra-operatively administered to prevent lymph node recurrence and peritoneal recurrence of gastric cancer. Between April 1998 and August 1999, 79 patients with advanced gastric cancer were allocated randomly to two groups. Forty patients underwent M-CH plus IPHHOI combined with surgery (M-CH+IPHHOI group) and the remaining 39 underwent surgery alone (control group). Lymph node and peritoneal recurrence were significantly decreased in the M-CH+IPHHOI group compared to that in the control group ($p < 0.05$). The 1- and 2-year survival rates for the M-CH+IPHHOI group were 91.2 and 72.1%, and those for the control group were 78.9 and 45.5%. The M-CH+IPHHOI group reaped a significant survival benefit ($p = 0.0352$) compared to the control group. Although this study was conducted randomly for a small number of patients and short time, compared with the control group, the M-CH+IPHHOI group had a beneficial effect in preventing lymph node recurrence and peritoneal recurrence after curative gastrectomy for advanced gastric cancer. [© 2002 Lippincott Williams & Wilkins.]

Key words: Activated carbon, gastric cancer, i.p. hyperthermic hypo-osmolar infusion, surgery.

Introduction

The locations of recurrence of gastric cancer after surgery are the peritoneal cavity, lymph nodes and liver, suggesting that the indications for gastric

cancer surgery might be extended by multidisciplinary treatment, in particular using potent anticancer chemotherapy and physical therapy.

Small activated carbon particle (CH-40)-adsorbed anticancer drugs are used as lymphatic chemotherapy and to provide orientation for lymphadenectomy. Local injection of mitomycin C bound to activated carbon particles obtained a higher survival rate in patients with gastric cancer.¹ Hyperthermic hypo-osmolar solution is reported to kill gastric cancer cells quickly.² In a previous study, the 2-year survival rate of patients with serosal involvement increased by 23.1% when the peritoneal cavity was lavaged with 43°C distilled water as i.p. hyperthermic hypo-osmolar infusion (IPHHOI) therapy.³ The use of heated distilled water combined with 5-fluorouracil (5-FU) was reported to prevent tumor recurrence in the peritoneal cavity and liver in patients with advanced colorectal cancer.⁴

We currently use aggressive surgery combined with local injection of activated carbon particle adsorbing mitomycin C (M-CH) and i.p. infusion of heated double-distilled water to treat patients with advanced gastric cancer. Here we report the results of a prospective randomized study of the prophylactic efficacy of M-CH plus IPHHOI therapy against the recurrence of gastric cancer.

Patients and methods

Patients

All the patients in the current study were diagnosed microscopically as having gastric cancer and they

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each underwent curative surgery in Department of Gastrointestinal Surgery, Ningxia Hospital, Ningxia, PRC, between April 1998 and August 1999. Gastric cancer patients with macroscopic peritoneal, ovarian and/or hepatic metastases or cardiorespiratory lesions were excluded from this study. They were enrolled in this study after informed consent was obtained and were divided randomly into two groups at the time of surgery, one received M-CH plus IPHHOI therapy combined with surgery (M-CH+IPHHOI group) and the other received surgery alone (control group).

Forty patients received M-CH+IPHHOI plus surgery, while 39 received surgery without M-CH+IPHHOI treatment. The International Union Against Cancer TNM staging system was used to describe the depth of gastric wall invasion and the extent of lymph node metastases.⁵ The determination of the depth of invasion and lymph node metastases was based on histologic evidence in the resected specimens. Free cancer cells in the peritoneal cavity were examined in all of the cases. As shown in Table 1, there were no significant differences in age, gender, TNM classification, lymph node

metastases, free cancer cells in the peritoneal cavity, histologic type of tumor, type of surgery and lymphadenectomy or histologic curability between the two groups. D2, D3 or D4 lymphadenectomy was performed according to the stage, site and type of the gastric cancer (D2, complete removal of group 1 and 2 lymph nodes; D3, complete removal of group 1, 2 and 3 lymph nodes; D4, complete removal of group 1, 2, 3 and para-aortic lymph nodes).⁶ There were no surgery-related deaths.

M-CH injection

An aliquot of 2 ml of activated carbon particles suspension (CH-40; Mitsubishi Kasei, Tokyo, Japan) was mixed with 8 mg of mitomycin C. The mixture was shaken for 10 min so mitomycin C completely bound to carbon particles to form a combination of mitomycin C and carbon particles (M-CH).⁷ In the M-CH+IPHHOI group, after laparotomy, the M-CH was subserosally injected around the gastric tumor. The injection was performed very slowly over a period of

Table 1. Clinical patient data (M-CH+IPHHOI and control group)

Variable	M-CH+IPHHOI group (n=40)	Control group (n=39)	p values
Age (years)			
Gender (male/female)	58.5 ± 8.1	59.2 ± 9.1	0.642
TNM classification	27/13	24/15	0.757
Primary tumor			0.39
pT2	4	8	
pT3	16	13	
pT4	20	18	
Lymph node metastases			0.093
pN1	14	17	
pN2	26	22	
Positive free cancer cells	11	9	0.762
Type of surgery			0.401
distal subtotal gastrectomy	23	21	
proximal subtotal gastrectomy	7	6	
total gastrectomy	10	12	
Type of lymphadenectomy			0.083
D2	10	9	
D3	12	17	
D4	18	13	
Histology			0.512
well differentiated adenocarcinoma AC	8	6	
moderately differentiated adenocarcinoma AC	7	10	
poorly differentiated adenocarcinoma AC	25	23	
Histologic curability			0.735
curative surgery	33	34	
non-curative surgery	7	5	

about 3 min. In the control group, an equal volume of physiological saline was injected.

IPHHOI treatment

Before closure of the abdominal cavity, in the M-CH+IPHHOI group, 4000 ml of double-distilled water heated to 43–45°C was infused into the peritoneal cavity for 10 min. In the control group, room temperature normal physiological saline was infused.

Statistics

The Kaplan–Meier method was used to calculate the postoperative survival rate. Student's *t*-test, χ^2 -test and log-rank test were used to determine significant differences. $p < 0.05$ was considered significant.

Results

Pattern and site of recurrence

The pattern of recurrence and time to death due to recurrence in both groups are tabulated in Table 2. The sites of recurrence were determined by clinical findings based on radiological and/or echographic imaging or repeat laparotomy. There were five lymph node recurrences in the control group and one in the M-CH+IPHHOI group. There was a significant difference in the frequency of lymph node recur-

rence between the two groups ($p=0.025$; a versus g in Table 2). Peritoneal recurrence was observed significantly more frequently ($p=0.018$; b versus h in Table 2) in the control group compared to the M-CH+IPHHOI group. In the M-CH+IPHHOI group, totally six out of 40 patients died within 2 years, while in the control group 12 out of 39 patients died within 2 years, there was a significant difference between the two groups ($p=0.034$; f versus l in Table 2). The frequencies of liver and pleural recurrence did not differ between the two groups ($p > 0.05$).

Survival curve

The survival curves for the M-CH+IPHHOI group and control groups are shown in Figure 1. The 1- and 2-year survival rates for the M-CH+IPHHOI group were 91.2 and 72.1%, whereas those for the control group were 78.9 and 45.5%, respectively. The survival rates of the M-CH+IPHHOI group were significantly improved ($p=0.0352$, log-rank test) to those of the control group.

Postoperative morbidity

In the M-CH+IPHHOI group, one patient experienced minor anastomotic leakage, which was successfully managed without reoperation. One patient had incision rupture, which was treated by reoperation. In the control group, one patient experienced incision rupture which was treated by reoperation (Table 3).

Table 2. Pattern of recurrence and time to death due to recurrence in the M-CH+IPHHOI and control group

Site of recurrence	Postoperative time (months)								Total
	3	6	9	12	15	18	21	24	
M-CH+IPHHOI group									
lymph node				1					1 ^a
peritoneum			1						1 ^b
liver				1	1				2 ^c
pleura							1		1 ^d
other diseases								1	1 ^e
total			1	1	1	1	1	1	6 ^f
Control group									
lymph node			1	1	1		1		5 ^g
peritoneum		1	1	1	1		1	1	6 ^h
liver			1						1 ⁱ
pleura									0 ^j
other diseases									0 ^k
total		1	1	2	1	1	2	1	12 ^l

a versus g: $p=0.025$; b versus h: $p=0.018$; c versus i: $p > 0.05$; d versus j: $p > 0.05$; e versus k: $p > 0.05$; f versus l: $p=0.034$.

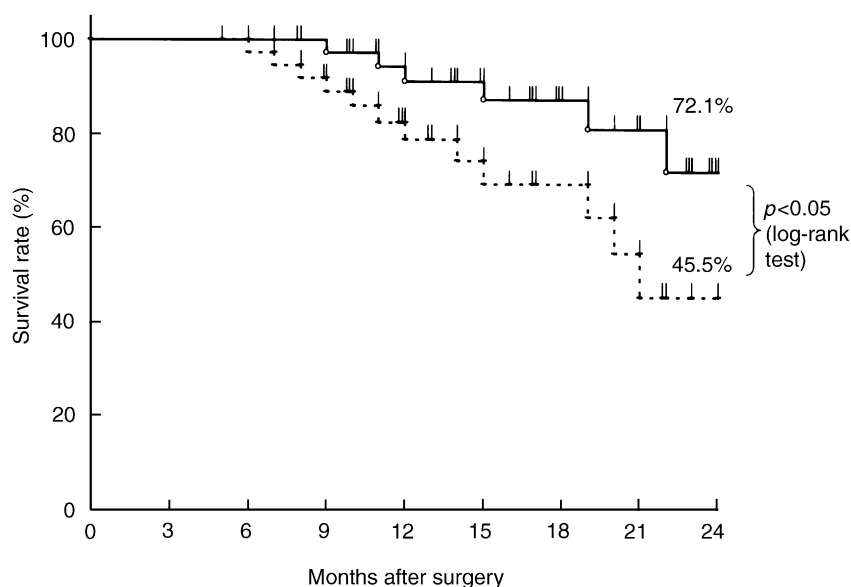


Figure 1. Survival curves of gastric cancer patients. Two-year survival rate of the M-CH+IPHHOI group is 72.1%, 2-year survival rate of the control group is 45.5%. A significant difference in survival was found between the M-CH+IPHHOI group and control group: $p=0.0352$ on log-rank test. Solid line: M-CH+IPHHOI group ($n=40$), local injection of mitomycin C bound to activated carbon particles (M-CH) combined with IPHHOI. Dashed line: control group ($n=39$).

Table 3. Postoperative morbidity

Variable	M-CH+IPHHOI group ($n=40$)	Control group ($n=39$)
Minor leakage of the duodenal stump	0/40	0/39
Leakage of the duodenal stump	0/40	0/39
Anastomotic leakage ^a	1/40	0/39
Incision rupture ^b	1/40	1/39

^aCompletely cured without reoperation.

^bHealed by reoperation.

Discussion

Gastrectomy with radical lymphadenectomy in advanced cancer improved the survival.⁸ Activated carbon particles (CH-40) are very small particles that are selectively taken up by the lymphatic system. Then regional lymph nodes containing CH-40 become blackened and are easily identified macroscopically even when the nodes are very small. This property of CH-40 facilitates thorough dissection of the lymph nodes during surgery.^{9,10} Activated carbon particles (CH-40) adsorb a large amount of anti-cancer drug on their surface and then release the drug reversibly.⁷ It was observed that metastatic lesions in lymph nodes degenerated after local

injection of M-CH.¹¹ Local injection of M-CH is reported to significantly increase the resection of lymph nodes and improve the survival rate in patients with advanced gastric cancer.¹²

It was reported that gastric cancer cells were detected at the time of laparotomy in the abdominal cavity even in some gastric cancer patients who clearly were demonstrated macroscopically to have no peritoneal metastases.¹³ In the case of advanced gastric cancer, the intracavity spread of tumor cells accounts for 53.8% of deaths due to recurrence after surgery.¹⁴ So it is very important to extirpate free tumor cells in the abdominal cavity. In the peritoneal cavity, instillation of hyperthermic hypo-osmolar solution rapidly kills free cancer cells and is harmless to healthy tissues.³ In the present study, heated double-distilled water was intraoperatively administered to prevent the peritoneal recurrence of gastric cancer.

Among the 40 patients treated with M-CH+IPHHOI in the present study, one died of lymph node recurrence and one died of peritoneal recurrence. Among the 39 patients in the control group, five and six died of lymph node recurrence and peritoneal recurrence, respectively. Decreased lymph node recurrence and peritoneal recurrence lead to a significantly ($p<0.05$) lower total recurrence rate in the M-CH+IPHHOI group than in the control group. M-CH+IPHHOI therapy effectively prevents lymph

node and peritoneal recurrence simultaneously, thus achieving the improved 1- and 2-year survival rates for the M-CH+IPHHO group compared to that in the control group.

Intraperitoneal hyperthermic perfusion (IHCP) has been using to prevent peritoneal recurrence. However, the continuous high temperature increases the internal pressure of the duodenum and upper jejunum or causes hyperemia with capillary dilatation of the mesenteric surface.¹⁵ In the present study, heated double-distilled water solution was i.p. infused over a short period so it did not injure the intestinal tract. In the M-CH+IPHHO group, only one patient experienced minor anastomotic leakage, which was successfully managed without surgery.

Although this study was performed on a small scale, combined therapy of local injection of mitomycin C bound to carbon particles along with IPHHOI has a beneficial effect in preventing lymph node recurrence and peritoneal recurrence after curative gastrectomy for advanced gastric cancer.

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