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EFFECTS OF NEOADJUVANT INTRAPERITONEAL/SYSTEMIC CHEMOTHERAPY ON PERITONEAL METASTASES FROM GASTRIC CANCER

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ABSTRACT

Background: Adjuvant chemotherapy is thought to improve postoperative survival in gastric cancer (GC) patients with peritoneal metastasis (PM). Effects of neoadjuvant intraperitoneal/systemic chemotherapy (NIPS) were studied. **Materials and Methods:** Exploratory laparoscopy was performed in 55 GC-patients with PM. PM was evaluated using the peritoneal cancer index (PCI). A peritoneal port was introduced, and a series of 3-week cycles of NIPS was performed. Four weeks after 3 cycles of NIPS, laparotomy for cytoreductive surgery (CRS) was performed. **Results:** During NIPS, patients had grade 3 and 4 side effects, respectively. Before NIPS, cytology was positive in 39 (75%) patients, and changed from positive to negative in 28 (71.8%) after NIPS. PCI was significantly lower after NIPS (7.63±9.28) than before NIPS (10.6±8.38) (P=0.006). There was complete disappearance of PM in 5 (9.1%) patients, decrease in PCI in 21 (38.2%), and increase in PCI level in 12 (21.8%) patients. After NIPS, The GC in 9 patients were diagnosed as inoperable. Cytoresuction was complete in 40 of 46 patients who received laparotomy. Down-staging by NIPS was found in 14.5% (8/55) of patients. Overall median survival time (MST) after NIPS was 21.9 months, and 5-year survival rate was 18.2%. The MST was 24.1 months in the 40 patients who received complete cytoreduction was 24.1 months and 9.6 months in the 6 patients who received incomplete cytoreduction, and 9.6 patients with inoperable GC ($p<0.05$). **Conclusions:** NIPS is a safe and effective method to eradicate peritoneal free cancer cells and to reduce the PCI to less than cutoff level before cytoreductive surgery, and thereby to increase rate of complete cytoreduction and improve prognosis after CRS. Peritoneal metastasis (PM) from gastric cancer (GC) has usually been considered a lethal disease with short median survival time.[1] The traditional therapies for GC-PM are systemic chemotherapy, palliative surgery, and best supportive care. However, the prognosis of GC-PM after systemic chemotherapy or palliative surgery alone is approximately half a year.[2] In 2016, the Peritoneal Surface Oncology Group International proposed a novel treatment that combined cytoreductive surgery (CRS) with perioperative chemotherapy (POC) for PM from GC.[3] The comprehensive treatment was performed with curative intent for selected patients with PM,[4,5] and indicated for GC-PM with limited peritoneal cancer index (PCI).[6] The treatment combines removal of all the macrosocopic tumors using peritonectomy techniques (complete cytoreduction) with the eradication of residual micrometastasis by intraperitoneal chemotherapy just after CRS.[7] In GC-PM, however, complete cytoreduction is sometimes difficult because of high PCI and diffuse involvement in the small bowel or its mesentery. 8 The most important prognostic factor after the comprehensive treatment is suggested to be PCI.[9] In gastric cancer, a PCI cutoff level of.[12] is an independent prognostic factor, and survival is significantly better in patients with PCI below this cutoff level.[9] In contrast, patients with PCI above the cutoff level have poor prognosis even after complete cytoreduction plus POC.[9] However, 70% of patients with PM show PCI above the cutoff level at the time of diagnosis.[8] Neoadjuvant chemotherapy (NAC)may reduce PCI to lower than cutoff levels.[10] Yonemura Y reported that a combination of neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC) and neodjuvant intraperitoneal/systemic chemotherapy (NIPS) significantly reduces intraperitoneal tumor burden and eradicates peritoneal free cancer cells.[10,11] In this paper, the effects of NIPS were studied by assessing changes in PCI level, and cytological status before and after NIPS. This is the first report to verify the reduction of PCI score after NIPS.

KEYWORDS: Gastric Cancer, Peritoneal Metastasis, Hyperthermic Intraperitoneal Chemoperfusion, Neoadjuvant intraperitoneal/systemic chemotherapy.

PATIENTS AND METHODS

Exploratory laparoscopy and placement of intraperitoneal (IP) port: Exploratory laparoscopy was performed in 55 GC-patients with PM referred to the Peritoneal Surface Malignancy Centre of Kishiwada Tokushukai Hospital and Kusatsu General Hospital between November, 2012 and October, 2018. At exploratory laparoscopy, PCI score and cytologic status were determined.

Under general anesthesia, exploratory laparoscopy was performed according to the previous report.[10,11]

The ascitic fluid was examined cytologically. When no ascites was found, the recovered peritoneal lavage fluid after intraperitoneal administration of 200 ml of saline was used for cytological examination. Biopsy specimens were routinely taken from the peritoneal nodules. PM in the entire abdominal cavity was quantitatively evaluated using PCI.

Then, a peritoneal port system (Hickman Subcutaneous port; BARD, Salt Lake City, UT, USA) was introduced into the abdominal cavity, and the tip was placed in the cul-de-sac of the pelvis. Two weeks after laparoscopy, a series of 3-week cycles of NIPS was started.

Specifically, S1 was administered orally twice daily at a dose of 60mg/m^2/day for 14 consecutive days, followed by a 7-day rest period. Docetaxel and cisplatin were administered intraperitoneally (IP) at a dose of 30 mg/m^2 with 500 ml of normal saline on day 1. The same dose of docetaxel and cisplatin were administered intravenously (IV) on day 8 after standard premedication. The treatment course was repeated every 3 weeks for 3 courses.

Cytoreductive surgery: Four weeks after the last NIPS cycle, laparotomy for CRS and HIPEC was performed, and PCI and cytologic changes were studied. During the period after the last NIPS, patients were selected for CRS by laparoscopy, or imaging with contrast enhanced CT, or positron emission tomography or both. Patients diagnosed as having progressive disease or diffuse involvement of the small bowel or its mesentery were excluded from receiving CRS.

Ethical standards: Institutional review board approval was obtained on October, 26, 2012, for our study entitled "A study of the safety and efficacy of cyroreductive surgery and NIPS for the treatment of peritoneal metastasis from gastrointestinal cancer". All patients were informed about the adverse events of the procedure and gave their written informed consents to participate.

Eligibility criteria: The eligibility criteria included: (1) histologically or cytologically proven PM from gastric cancer; (2) absence of hematogenous metastasis and remote lymph node metastasis; (3) age 85 years or younger; (4) Eastern Clinical Oncology Group scale of performance status 3 or less; (5) good bone marrow, liver, cardiac, and renal function; (6) absence of severe adhesion in the peritoneal cavity; and (7) absence of other severe medical conditions or synchronous malignancy.

The clinicopathologic characteristics of two groups are given in Table-1.

Evaluation of complications

Complications were graded according to the system of classification established by Dindo and colleagues.[12]

STATISTICAL ANALYSES

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patients interviews. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA), and statistical significance was defined as a P-value <0.05.

RESULTS

The 55 patients in this study had a mean age of 55.7±12.8 (rang 26 to 85 years old). There were 27 male and 28 female patients; 40 patients with synchronous and 15 with metachronous PM:.2, 16, and 37 patients with macroscopic type of 2, 3, and 4, respectively, and . and 48 patients with poorly differentiated adenocarcinoma (**Table 1**).

Grade 3 and 4 side effects were experienced in 3 (5.5%) and 4 patients (7.3%), but no grade 5 complication was found. The grade 3 complications in 1, and 2 patients, respectively, were general malaise and appetite loss.

Four patients were admitted to hospital for diarrhea (N=1), port infection (N=1), and severe general malaise (N=2). They completely recovered after treatment, and were discharged.

After NIPS, 46 (83.6%) patients received laparotomy and 40 (72%) patients received complete cytoreduction. However, Because of disease progression and involvement in small bowel involvement, the GC in 9 (10.9%) patients was judged to be inoperable.

Before NIPS, cytology was positive in 39 (75%) patients, and changed to negative in 28 (71.8%) after NIPS. In contrast, 2 (15.4%) of 13 patients with negative cytology before NIPS changed to positive after NIPS. There was a statistically significant difference in peritoneal cytological status after NIPS (**Table 2**).

PCI after NIPS (7.63±9.28) was significantly lower than that before NIPS (10.6±8.38) (P=0.006) (**Table 3**).

PCI level before NIPS was ≤11 in 39 patients (70.9%), and ≥ 12 in 16 (29.1%) patients. (table 4) In 8 patients, PCI changed from ≥ 12 before NIPS to PCI ≤ 11 after

NIPS. (P<0.019). Final pathological stage of 55 patients were stage 2 in 2, stage 3 in 6, and stage 4 in 47 patients, respectively. Down-staging by NIPS was found in 14.5% (8/55) of patients.

After NIPS, there was complete disappearance of PM in 5 (9.1%), (**Table 5**), decrease in PCI in 21 (38.2%) patients, and increase in PCI level in 12 (21.8%) patients. **Table 3** shows the changes in lesion size scores in each of the 13 peritoneal sectors. Lesion size scores in the central sector (sector 0), were significantly lower after NIPS than before NIPS (p=0.028).

After NIPS, the tumors in 9 patients were inoperable due to high PCI and diffuse involvement of the small bowel and its mesentery. Cytoreduction was complete in 40 of the 46 patients, who received laparotomy. Total gastrectomy and distal gastrectomy with D2 lymphadenectomy were performed in 29 and 2 patients, respectively. Peritonectomy was performed in 42 patients.

Postoperative Grade 3, 4, and 5 complications were found in 5 (10.1%), 2 (4.1%), and 1 (2.0%) patient, respectively. One patient died because of bleeding from hepatic artery branch. Grade 3 complications were pancreatic fistula in 2 patients, and abdominal abscess in 2. Grade 4 complications were leakage from esophago-jejunostomy in 1 and renal failure in 1.

Median survival time (MST) after NIPS was 21.9 months, and 5-year survival rate was 18.2%. The MST was 24.1 months in the 40 patients with complete cytoreduction and 9.6 months in the 6 patients with incomplete cytoreduction in 9 patients with inoperative tumor (P<0.05).

Table 1: Patients' characteristics and pathological findings.

No of cases	**55**
Age (mean ±S.D. (range))	55.7±12.8 (26~85)
Male/female	27/28
Synchronous/metachronous	40/15
Macroscopic type	
Type 2	2
Type 3	16
Type 4	37
Histologic type	
Intestinal type	7
Diffuse type	48
Lymph node metastasis	
pN0	17
pN1	13
pN2	15
pN3	4
pNX	6

Table 2: Cytological status before and after NIPS.

Before NIPS	**After NIPS**		
Cytology	**Negative**	**Positive**	
Negative	11	2	13
Positive	28	11	39 (75.0%)
	39	13 (25.0%)	52

Table 3: Lesion size scores of each peritoneal sectors and PCI scores before and after NIPS.

	Lesion size (mean ± S.D.)		
Sectors	**Before NIPS**	**After NIPS**	**p**
0: central	0.90±1.07	0.40±0.88	0.028
1: right upper	0.76±1.02	0.50±0.95	NS
2: epigastrium	0.58±0.85	0.36±0.28	NS
3: left upper	0.64±0.90	0.41±0.74	NS
4: left flank	0.28±0.59	0.21±0.56	NS
5: left lower	0.36±0.73	0.25±0.65	NS
6: pelvis	0.57±0.90	0.50±0.86	NS
7: right lower	0.40±0.63	0.39±0.70	NS
8: right flank	0.25±0.65	0.29±0.71	NS
9: upper jejunum	0.34±0.80	0.23±0.60	NS
10: lower jejunum	0.37±0.77	0.26±0.65	NS
11: upper ileu	0.31±0.72	0.26±0.66	NS
12: lower ileum	0.35±0.73	0.26±0.67	NS
Total PCI	10.6±8.38	7.63±9.28	0.006

Table 4: Number of patients with above and below PCI cutoff values before and after NIPS.

	After NIPS		
before NIPS	**PCI ≤ 11**	**PCI ≥ 12**	
PCI ≤ 11	33	6	39 (70.9%)
PCI ≥ 12	8	8	16
	41 (74.5%)	14	
P=0.019			

Table 5: Changes after NIPS.

Changes	**No of cases**
Complete disappearance of PM	5 (9.1%)
Decrease in PM	21 (38.2%)
No change in PM	17 (30.9%)
Increase in PM	12 (21.8%)

DISCUSSION

Meta-analyses by Coccolini et al. clearly showed the significant reduction of recurrence after cytoreductive surgery folowed by NAC as compared with CRS without NAC in advanced gastric cancer.[13] The aims of NAC for GC-patients with PM are to 1) preoperatively treat micrometastasis existing outside surgical field in lymph nodes and peritoneum, 2) reduce macroscopic PM and PCI, resulting in preservation of the intact peritoneum as much as possible, and 3) increase the incidence of

complete cytoreduction.[14] Neoadjuvant systemic chemotherapy alone did not improve long-term survival in patients with PM and MST between 5.0 and 12.5 months.[15,16,17] Additionally, no 5-year survivor was reported after systemic chemotherapy alone.[15,16] The reason is thought to be the blood-peritoneal barrier, which limits the amount of drugs reaching the peritoneal cavity after systemic therapy.[18] In order to further improve the outcomes of GC-PM, intraperitoneal chemotherapy has been performed.[19] Compared with systemic therapy, intraperitoneal chemotherapy can lead to a higher concentration of drugs in the peritoneal cavity and prolong maintenance of significantly higher concentrations of anticancer drugs when drugs with higher molecular weight are used.[20] High concentration of anti-cancer drugs kill peritoneal free cancer cells and cancer cells in the subperitoneal lymphatic vessels.[21] However, cancer cells growing in the deep subperitoneal tissue cannot be eradicated by intraperitoneal chemotherapy alone due to the existence of peritoneal-blood barrier. To address this limitation of intraperitoneal chemotherapy, combined therapy using intraperitoneal and systemic administration was developed, and was named NIPS.

This intraperitonjeal-systemic bidirectional drug delivery method can widen the treatment area to include not only in the peritoneal cavity but also subperitoneal tissues and lymphatic vessels.[22,23] We already reported the direct effects of LHIPEC and NIPS. LHIPEC combined with 3 courses of NIPS was found to reduce PCI by 4.9, convert positive cytology to negative in 71.2% (22/31) of patients,[11] and cause complete disappearance of PM in 11.5% (6/52) of patients.[11]

However, the direct effects of NIPS alone on PM from GC have not been reported, so far. The present study used changes in PCI and cytologic status to show the direct effects of NIPS. After 3 cycles of NIPS, peritoneal metastasis disappeared in 5 (9.1%) patients; positive cytology was converted to negative cytology in 71.8% (28/39) of patients; and PCI was decreased in 21 (38.2%) patients but was unchanged in 17 patients The mean decrease in decreased mean PCI after NIPS was 2.07. These results indicate that NIPS effectively eradicates peritoneal free cancer cells and reduces PCI level. As a result, down-staging after NIPS was brought in 14.5% (8/55) of patients. According to Valle et al., without NAC, cytoreduction was completed in only 30% of patients, because of higher PCI levels.[8] After NIPS, cytoreduction was complete in 40 (72.7%) patients.

Complete cytoreduction has been considered key to improving long-term survival after CRS in GC patients with PM.[25] After complete cytoreduction, PCI cutoff level is an independent prognostic factor. From the analysis of 9 trials including 748 GC- patients with PM, Coccolini F et al. proposed a PCI cutoff level of 12. In the present study, the PCI in 8 of 16 patients with PCI $\geq$ 12 before NIPS decreased to PCI $\leq$ 11 after NIPS. Among the 8 patients with PCI $\leq$ 11 after NIPS 5 patients received complete cytoreduction. The MST of the present study was 21.9 months, and the 5-year survival rate was 18.2%. These results indicate that NIPS plus CRS could offer better long-term survival than systemic chemotherapy alone in GC patients with PM.

During NIPS, grade 3 and 4 side effects were found in 3 (5.5%) and 4 (7.3%) patients. However, these patients recovered from the side effects after appropriatet treatments. Additionally, postoperative Grade 3, 4, and 5 complications were found in 5 (10.1%), 2 (4.1%), and 1 (2.0) patient, respectively. Morbidity/mortality after NIPS and CRS were at rates similar to thoee previously reported treatement with CRS.[26,27,28]

CONCLUSIONS

NIPS is a safe and effective method to eradicate peritoneal free cancer cells and to reduce PCI to less than its cutoff level before cytoreductive surgery, thereby to increase rate of complete cytoreduction and improve prognosis after CRS.

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All authors declare that there was no actual or potential conflict of interest. This study did not receive any financial support.

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