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Intraperitoneal Hyperthermo-Chemo-Perfusion in Treating Resectable Gastric Cancer: First Experience in Belarus

Overview and aims

Peritoneal carcinomatosis alongside other gastrointestinal malignancies is a common cause of death in patients with gastric carcinoma. It is a major problem encountered after serosa-invasive gastric carcinoma surgery. Despite recent advances in surgical procedures and adjuvant chemotherapies [1,2], no satisfactory outcomes have been reported, because of residual micrometastases and/or free-floating carcinoma cells present in the peritoneal cavity. The area of serosal tumour invasion has been shown to be positively correlated with the detection rate of intra-peritoneal cancer cells [3]. Furthermore, extensive lymph node dissection itself may be responsible for opening lymphatic channels, thereby spreading viable tumour cells [4]. Also, at the time of laparotomy, gastric carcinoma cells have been detected in the abdominal cavity, even in patients with no peritoneal metastases detected microscopically prior to surgery [5].

Hyperthermia has been developed as an anticancer therapy and employed clinically for its direct cytotoxic effect and synergy with some types of chemotherapeutic drugs. Hyperthermia also increases the depth of penetration of these drugs into tumour tissue. It mainly represents the pharmacodynamic features of drug-heat interaction (changes of the kinetics of the primary mode of drug action) [6].

Koga et al [7] were among the first to use Intraperitoneal Hyperthermo-Chemo-Perfusion (IHCP) as a prophylactic treatment for peritoneal recurrence after gastric cancer surgery. Since they released their data, a fairly large number of reports have been published demonstrating a successful application of IHCP in preventing peritoneal dissemination in gastric cancer patients. For example, administration of mitomycin C (MCC) based IHCP in combination with cisplatin (30mg MMC + 300mg cisplatin, 42-43°C, 60 minutes) helped increase the five-year survival in gastric cancer patients to 61% as compared with 42% in the control group [8]. Applying a similar IHCP regimen, Scaringi and colleagues [9] reported an increase in median survival to 23.4 months and that in median delay to recurrence to 18.5 months.

It was also established that the exclusion of cisplatin from the perfusate had no effect on the outcome of treatment. Using an IHCP regimen comprising 10mg/L MMC in 3-4L of infusate at 43-44°C for 120 minutes, Fujimoto et al [10] found that the four-year survival rate in the IHCP group was 76% against 58% in the control group. Similar results were reported using a dose of 10 mg/m^2 MMC at 43-44°C with a perfusion time of up to 90 minutes, which resulted in a 75% five-year survival rate. Interestingly, IHCP administration did not lead to an increase in complications or mortality [8,10,12].

According to the meta-analysis published by Xu and colleagues, the cohort of trials from Asian countries exhibited a trend towards a more significant curative effect than those from non-Asian countries [13]. It should be noted that there were few studies of IHCP efficacy conducted in Europe [9,14], and their results were mixed. That prompted us to conduct our own study.

Here, we report our preliminary results of a prospective randomised trial study of 68 patients with serosa-invasive gastric carcinoma carried out to evaluate the effect of surgery plus IHCP in the prevention of peritoneal metastases.

Patients and methods

Between 2008 and 2011, 68 patients with gastric cancer (stage stage II-IIIC, III-IV Borrmann type) were randomly assigned to two groups at the time of surgery. 39 patients underwent IHCP combined with radical gastrectomy plus D2 lymph node dissection (IHCP group). Twenty-nine patients underwent radical gastrectomy plus D2 lymph node dissection without IHCP (control group). There were 26 males and 42 females (age range – from 24 to 70). Patients over the age of 70 were not considered suitable for IHCP because of the anticipated incidence of serious complications. There were no significant differences in tumour location and pathologic type between patients treated with and without IHCP.

IHCP technique: IHCP was performed after gastrectomy/alimentary tract reconstruction and

IHCP appears to be helpful in decreasing peritoneal dissemination and has a potential for improving the survival rate among radically operated gastric cancer patients

wound closure. One inflow catheter (30F) was positioned beneath the left hemidiaphragm. Three outflow catheters (32F) were placed in the subhepatic area, in both the true and false pelvises. Temperature probes were placed on the inflow and outflow catheter tips. IHCP was administered for one hour with an automatic IHCP device (HT-1000 Thermochem (ThermaSolutions, Inc., USA)). Perfusate used was Ringer's solution (5-6L) mixed with cisplatin 50mg/m^2 + doxorubicin 50mg/m^2, warmed to an inflow temperature of 42°C.

Postoperative disease progression was detected by a combination of physical examination, periodic diagnostic imaging, computed tomography and ultrasonography. Disease progression with the development of peritoneal dissemination was detected by performing second-look laparoscopy. Chemotherapeutic side effects were assessed using CTCAE v 3 score.

Statistical analysis: Survival curves were calculated by the Kaplan-Meier method and compared by using the log-rank test. Student's t-test and Fisher's test were used to determine significant differences. The differences were judged to be significant at p value of less than 0.05.

Results

There was no difference between the two groups in the complication rates: 15.4% in the ICHP group and 6.9% in the control group (p = 0.45) (Table 1).

Gastrojejunal anastomotic leak occurred in two patients from the IHCP group leading to their death. Postoperative mortality rate was 5.1%. Development of gastrojejunal anastomotic leak in the IHCP group and its absence in the control group may be attributed to the influence of the IHCP procedure per se on the temperature of metal staples forming the anastomosis. In our view, an increase in their temperature could in some way contribute to such failure. No fatality was suffered by the control group.

IHCP-related complications: Evaluation of IHCP toxicity showed neither toxic complications of III-IV degree nor haematological toxicity (according to CTCAE v 3). IHCP-specific complications were observed, namely, postoperative fever of unclear genesis rising to 38°C and more and persisting for over three days. That complication was observed in two IHCP-treated patients and required administration of anti-inflammatory therapy.

As compared with the control group, the IHCP group showed a heightened degree of endogenous intoxication (up to III degree) with subsequent normalisation of laboratory test indicators by the tenth day after the surgery. The degree of endogenous intoxication in the control group was less pronounced (I-II degrees) and normalisation occurred earlier – from three to seven days after the surgery. An increase in endogenous intoxication in both groups was reversible and had no effect on the length of patient stay in hospital.

Table 1. Postoperative morbidity rate

Complications	IHCP group	Control group	P value
Gastrojejunal anastomotic leak	5.1% (2 patients)	-	0.5
Postoperative pneumonia	10.3% (4 patients)	6.9% (2 patients)	1.0
Overall morbidity rate	15.4% (6 patients)	6.9% (2 patients)	0.45

Table 2. Recurrence pattern among radically operated patients with gastric cancer

Recurrences	IHCP group	Control group	P value
Peritoneal metastases	12.8% (5 patients)	27.6 % (8 patients)	0.21
Hematogenous metastases	7.7% (3 patients)	6.9% (2 patients)	1.0
Disease progression	20.5% (8 patients)	34.5% (10 patients)	0.28
Time to development of peritoneal dissemination after surgery	6.9±1.12 months	10.6±0.98 months	0.02

Recurrence pattern with disease progression: Among the 68 patients, recurrences developed in 18 patients (Table 2).

No loco-regional recurrences were observed in either group. Remote results analysis showed a tendency toward a more frequent disease progression in the control group than in the IHCP group: 10 patients (34.5%) v 8 patients (20.5%), respectively (p = 0.28), in particular, trending toward a more frequent development of peritoneal dissemination: 27.6% v 12.8%, respectively (p = 0.21). The difference in the frequency of peritoneal dissemination appeared to be statistically unreliable (p > 0.05) and this may be due to the small number of observations in the groups. At the same time peritoneal dissemination also appeared to develop earlier in patients without IHCP: 10.6 ± 0.98 months v 6.9 ± 1.12 months in the IHCP group (p = 0.02). In contrast, we noted survival improvement in the IHCP-treated group.

Survival analysis: The follow-up period varied from 1 to 34 months. Overall 1-year survival (Kaplan-Meier) for the IHCP group was 0.952 ± 0.0465 [95% CI 0.866 – 1]; that for the control group was 0.667 ± 0.1111 [95% CI 0.481 – 0.924] [log-rank: chi2 on 1df = 4.9, p = 0.0312].

Discussion

Our trial results are in agreement with studies conducted by researchers in Europe and Asia that have shown a positive effect of IHCP on reducing peritoneal dissemination rates [8,9,11-13].

However, there are also reports about a lack of IHCP efficacy in managing peritoneal dissemination. Thus, according to a non-randomised study undertaken in the Medical University of Yokohama, Japan, there was a decrease in the frequency of peritoneal relapse: 50% in the IHCP group against 67.7% in the control group, with p > 0.05 [15]. The perfusate used in this trial comprised 150mg of cisplatin plus 15mg of MMC plus 150mg of etoposide administered at 42-43°C for 40 minutes. This study showed some decrease in the five-year survival rate (49% in the IHCP group v 56% in the control group) and an increase in the number of complications, including respiratory (73% v 19%, p < 0.0001) and renal failures (7% v 0%, p < 0.03). Based on these findings, it was concluded that IHCP was ineffective as a prevention method. A similar conclusion about IHCP inefficiency was drawn by Samel et al [14]. Their study comprised nine patients treated with cisplatin and MMC as IHCP agents. They reported a 66% postoperative morbidity that included kidney failure, pancreatitis and anastomotic failure. Furthermore, the disease progressed into carcinomatosis in 55% of cases and led to the death of these patients. These researchers concluded that the IHCP application results in an increase in postoperative complications and appears to be incapable of preventing or delaying disease recurrence in patients with advanced stomach cancer.

It is notable that all of the above-referenced studies [14,15], both testifying to the efficacy of IHCP or to lack of it, employed MMC or a combination of MMC and cisplatin in IHCP solutions.

As cisplatin is known to be fairly toxic irrespective of methods of administration, we opted for a combination of a reduced dosage of cisplatin to mitigate its side-effects and an increased dosage of doxorubicin to retain synergy of these two

drugs. Even so, we observed that the number of complications in the IHCP group exceeded that in the control group: 15.4% against 6.9%, respectively, although this difference appears statistically unreliable with $p > 0.05$. However, it should be noted that the complications observed in the IHCP group were mainly postoperative pneumonias which in itself is not attributable to the IHCP effect. Thus, in our estimate such an approach does not affect chemotherapy tolerance, nor does it compromise the treatment effect.

Given the difference of views on the efficacy of IHCP in treating radically operated gastric cancer patients, there is a need for further studies to evaluate the effect of IHCP with regard to peritoneal dissemination.

Conclusions

Based on the results of our trial study and the above cited studies, we can draw the following conclusions:

1. IHCP appears to be helpful in decreasing peritoneal dissemination;
2. IHCP has a potential for improving the survival rate among gastric cancer patients;
3. Further prospective studies based on a larger cohort of patients are needed to fully assess the potentialities of IHCP as a preventive treatment of gastric cancer associated with a high risk of peritoneal dissemination. ■

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