Review Article

Intraperitoneal chemotherapy for locally advanced gastric cancer to prevent and treat peritoneal carcinomatosis

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Abstract: Gastric cancer (GC) is one of the leading causes of cancer death in both sexes in the world. The overall survival (OS) of GC patients is still unsatisfactory. The peritoneal dissemination is the most common type of recurrence in advanced GC. The rationale for administering chemotherapeutic drugs directly into peritoneal cavity is supported by the relative transport barrier that is formed by the tissue surrounding the peritoneal space. Intraperitoneal (IP) chemotherapy with taxanes is safe and feasible. Further randomized phase III clinical trials are needed to validate IP chemotherapy with taxanes for peritoneal carcinomatosis (PC) from GC. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) used as prophylaxis against peritoneal recurrence in patients with high risk GC is safe, significantly improves the survival and reduces the risk of peritoneal recurrence. A drug delivery system with anticancer drugs seem to be have a pharmacokinetic advantage but further randomized clinical trials are needed to validate its effect.

Keywords: Intraperitoneal chemotherapy (IP chemotherapy); hyperthermia; taxanes; S-1; drug delivery system; cytoreductive surgery (CRS); gastric cancer (GC)

Received: 12 July 2016; Accepted: 14 July 2016; Published: 09 August 2016.
doi: 10.21037/tgh.2016.07.04
View this article at: http://dx.doi.org/10.21037/tgh.2016.07.04

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer death in both sexes in the world, accounting for 8.8% of the cancer death every year (1). D2 lymphadenectomy have been accepted as the standard surgery for locally advanced GC both in East Asia and in the West (2-5). Although overall survival (OS) of GC patients is improved with the implementation of D2 lymphadenectomy and the development of chemotherapy as well as new targeted drugs in the past years (6-8), the long-term survival rates of these patients are still unsatisfactory. Since the peritoneal carcinomatosis (PC) occurs synchronous with primary GC on about 14–43% of patients and accounts for 35% of all synchronous metastasis (9), the peritoneal recurrence is seen in 10–54% of all patients with GC after a curative surgery (6,10).

The peritoneal dissemination is the most common type of recurrence in advanced GC. Yoo *et al.* (11) analyzed the data from 2,328 patients who underwent curative resection for GC, the mean time to recurrence was 21.8 months and peritoneal recurrence was the most frequent (45.9%). Serosal invasion and lymph node metastasis were risk factor for all recurrence patterns. In addition, independent risk factors involved in each recurrence pattern included younger age, infiltrative or diffuse type, undifferentiated tumor and total gastrectomy. The main mechanism of the peritoneal recurrence is though to be via the exfoliation of free cancer cells (FCCs) from tumor in the gastric serosa. Therefore the risk factors that predispose to peritoneal recurrence/metastasis in GC include advanced T stage (especially serosal involvement), positive cytology in the peritoneal lavage fluid, lymph nodes involvement, and signet ring cell and diffuse-mixed histology.

The frequency of recurrence thus increases once the tumor cells penetrate the serosa. Bando *et al.* (12) reported that the overall cumulative survival curves according to peritoneal lavage cytological findings in patients with GC. The rate of 5-year survival rate was significantly worse for cytologically positive patients with positive findings than for those with a negative examination. However, this type of recurrence also occurs in patients without serosal invasion. Huang *et al.* (13) reported that a total of 685 patients with non-serosa-invasive GC who underwent curative D2 resection. The overall incidence of peritoneal metastasis was 20% (137/685). Tumor infiltrating growth pattern (INF), together with Borrmann type and TNM node stage, are important factors associated with peritoneal metastasis in non-serosa-invasive GC. Marutsuka and colleagues (14) investigated the mechanisms of peritoneal metastasis after operation for non-serosa-invasive GC with an ultra-rapid detection system for intraperitoneal (IP) FCCs. The method enabled to complete the detection of cancer cells within approximately 70 min. Both the carcinoembryonic antigen (CEA) and cytokeratin 20 (CK20) in IP lavage after lymph node dissection were identified in three (14.3%), four (26.7%) and six (46.2%) patients with submucosal, muscularis propria and subserosal tumors, respectively. Lymph node metastasis was the independent predictor of the existence of IP FCCs. The ultra-rapid quantitative RT-PCR demonstrated that FCCs from lavage reduced after six to eight and disappeared after seventh to ninth wash. The result indicated that lymph node dissection opened lymphatic channels and spread viable cancer cells into the peritoneal cavity and the routine wash of the peritoneal cavity can not eliminate the FCCs.

The rationale for administering chemotherapeutic drugs directly into peritoneal cavity is supported by the relative transport barrier that is formed by the tissue surrounding the peritoneal space. The peritoneal-plasma barrier (PPB) consists of a monolayer of mesothelial tissue, which account for a total thickness of 90 μm. The connective tissue layers include interstitial cells and a matrix of collagen, hyaluron, and proteoglycans (15). The PPB, which retards the clearance of high molecular weight chemotherapy from the peritoneal cavity, results in a large exposure of small cancer nodules on abdominal and pelvic surfaces.

IP chemotherapy with taxanes combined with S-1

Tegafur-gimeuracil-oxo (S-1), an oral fluoropyrimidine, has shown its potential to treat IP micrometastasis in phase III adjuvant trial, ACTS-GC, where the incidence of PC has declined condsideably after curative surgery for stage II/III GC through administration of S-1, compared with treatment of surgery alone (16). Mori *et al.* (17) assessed the pharmacokinetics and effect on survival time in an animal model. Pharmacokinetics were investigated by measuring intratumor, peritoneal lining, and blood concentrations after the administration of S-1 and fluorouracil (5-FU) and maintenance of high 5-FU concentrations in the peritoneal tumors (5.5 times) was confirmed in S-1 group. The inhibitory effect of S-1 on peritoneal dissemination was evaluated by killing mice at the start of administration, and 1 and 3 weeks after the start of administration, and examining them for the presence of peritoneal dissemination under a fluorescence stereomicroscope. The survival time was prolonged without any decrease in oral food intake or body weight. Taxanes are hydrophobic, high-weight molecular materials, IP administered taxanes are gradually drained from the peritoneum through lymphatic stomata that open directly into the pleural space (18). The area under the curve ratio of the intra-abdominal space to the plasma after IP administration of the drug are about 1,000 for PTX, 207–552 for DOC (19,20).

There are two types of IP chemotherapy with taxanes for GC: neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) and sequential perioperative IP chemotherapy (SPIC) (21). Yonemura *et al.* (22) performed NIPS with IP DOC and CDDP combined with S-1 in 96 patients. After two cycles of NIPS, 82 patients underwent cytoreductive surgery (CRS) (gastrectomy with D2 dissection and peritonectomy). Complete cytoreduction was achieved in 58 patients. The MST and 1-year OS of patients who underwent CRS was 14.4 mo and 61%, respectively. The MST of patients who underwent complete cytoreduction and those who did not undergo CRS were 21.1 and 9 mo, respectively. Kitayama *et al.* (23) reported 64 GC patients with peritoneal chemotherapy who had malignant ascites with IP and IV PTX combined with S-1. CRS without peritonectomy was performed in 34 patients. The MST of these patients and 1-year OS were 26.4 mo and 82%, respectively. Those of 30 patients who did not undergo gastrectomy were 12.1 mo and 26%, respectively. In the past years, there about six phase I and six phase II studies on IP chemotherapy with taxanes in Japan (21). Dose-limiting toxicities of these phase I studies included grade 3 febrile neutropenia, leucopenia, abdominal pain, and diarrhea. The overall response rate (ORR) among

those phase II studies ranged from 55–71%. The MSTs and 1-year OS were 14.4–24.6 mo and 67–78%, respectively. Phase III trial (the PHOENX-GC trial, UMIN000005930) compared S-1 in combination with IV and IP PTX (IP) to S-1 with IV CDDP (SP) in 180 GC patients with P1. This study began in 2011, and the final analysis was reported by Ishigami as Poster Discussion Session during ASCO 2016. The middle survival time (MSTs) of patients in IP and SP group were 17.7 and 15.2 mo, respectively, P=0.081. The ORR were 53% and 60%, respectively, P=1.0. The negative result of this phase III trial indicated that IP hyperthermia in combination with IP taxanes may obtain better ORR compared IP taxanes alone.

Hyperthermic intraperitoneal chemotherapy (HIPEC) for prevention of peritoneal recurrence

Hyperthermia has become the fifth method of therapy after surgery, chemotherapy, radiation and biological therapy, and plays an important role in multidiscipline therapy for cancer. This is associated with the better understanding of several biological parameters such as radiosensitization, chemosensitization, direct cytotoxicity, thermotolerance, and stepdown heating, as well as complete changes in micromilieu, especially involving the microvasculature (24-26). For the first time we observed that hyperthermia at 43 ℃ for 60 min upregulated E-cadherin and gamma-catenin expression but downregulated beta-catenin expression on colon carcinoma cells *in vitro*, alpha-catenin expression is not affected by hyperthermia (27). However, the pathways between apoptosis and hyperthermia which is one of the inducers remain unclear. From another animal experience we identified that hyperthermia in combination with radio- and chemotherapy can achieve a better effect and enhance changes in apoptosis-related genes such as *P53*, *Bcl-2* and *Bax* though its definite mechanism is still unknown (28). Hyperthermia causes an important augmentation of cell kill by certain drugs; consequently it may markedly increase regional cytotoxicity of the chemotherapeutic agents. Tumor growth time with IP chemotherapy alone *vs.* heated IP chemotherapy at 41.5 ℃, tumor growth is delayed in heated IP chemotherapy (26). Heat increases the penetration of IP chemotherapy into tissues such as omentum, bladder, bowel, spleen and abdominal wall (29). When IP administrated with mitomycin C (MMC) combined with hyperthermia, the area under the curve ratio of IP concentration over plasma concentration time of heated IP MMC is approximately 30.

Ninety patients were divided into two groups, all of which underwent radical D2 lymph node dissection, Patients in group A received HIPEC after surgery, whereas those in group B underwent surgery without HIPEC. The 5-year survival rate was 66.7% in group A and 60% in group B. No significant differences were observed between the two groups (P>0.05). For the stage IIIB cases, the 5-year survival rate was 40.9% in group A and 27.3% in group B. The difference were significant (P<0.05). Therefore surgical resection combined with HIPEC may prolong survival of the patients with stage IIIB GC (30). A meta-analysis demonstrated that HIPEC may improve the OS for patients who receive resection for advanced GC potentially, and help to prevent peritoneal local recurrence among patients with serosal invasion in GC (31). The GASTRICHIP study (32) is going to evaluate the effects of HIPEC with oxaliplatin on patients with GC involving the serosa and/or lymph node involvement and/or with positive cytology at peritoneal washing.

IP interstital chemotherapy

The interstitial chemotherapy is also called slow-release chemotherapy. It is a drug delivery system with some carriers such as lipid-, liposomes-, actived carbon particles- and silica gel-based formulation (33). IP chemotherapy with MMC bound to actived carbon particles has been used for prophylaxis and treatment of PC in Japan (34). An animal experiment has been carried and gained a satisfactory result, the small cancer foci were detected in the peritoneal cavity on only two of eight mice in MMC bound actived carbon particles (MMC-CH) group (33). We conducted a pharmacokinetic study to investigate the advantage of this method. A nude mouse model with transplanted human GC was established. The mice were given MMC by i.v. or IP injections, or given IP MMC bound to actived carbon particles. Pharmacokinetic assays were carried out at different time points in seven mice per each time point, to compare the MMC concentration revealed by the above mentioned methods. As a result, high concentration of MMC in peritoneal exudate, omentum and lymph nodes maintained longer than 24 hrs and a significantly lower MMC serum concentration can be achieved by administration of IP administration of MMC-CH (35). The following clinical practice of IP chemotherapy with MMC-CH gained positive result, a significantly higher postoperative recurrence-free time of 3-year was observed in MMC-CH group (76.27%) as compared with the control

group (22.83%), P<0.05 (33). Our another study and study from Zhao also indicated the effect on prophylaxis for postoperative PC for patients with GC (36,37).

Sinofuan is L-polylactic acid based sustained-released fluorouracil. The animal experiment showed that sinofuan implanted to abdominal cavity of rats leads to mild hematologic toxicity and no liver and kidney dysfunction and have a good effect and safety in the treatment of the mice clearing H22 ascites tumors (38,39). A total of 124 patients with locally advanced GC undergoing radical operation in our hospital were analyzed retrospectively. All patients were divided into two groups according to whether intra-operative sinofuan was implanted or not. The treatment group (n=64) was implanted with sinofuan in abdominal cavity after radical resection. The 3-year survival rate was higher in treatment group (64.3% *vs.* 42.4%, P=0.018) (40).

In conclusion, IP chemotherapy with taxanes for PC from GC is safe and feasible. Although several phase II clinical studies have shown promising results, further randomized phase III clinical trials are needed to validate IP chemotherapy with taxanes for PC from GC. Adjuvant HIPEC used as prophylaxis against peritoneal recurrence in patients with high risk GC (serosal invasion or nodal metastasis) is safe, significantly improves the survival and reduces the risk of peritoneal recurrence. A drug delivery system with anticancer drugs seem to be have a pharmacokinetic advantage but further randomized clinical trials are needed to validate its effect on gastric PC.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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doi: 10.21037/tgh.2016.07.04
Cite this article as: Liang H. Intraperitoneal chemotherapy for locally advanced gastric cancer to prevent and treat peritoneal carcinomatosis. Transl Gastroenterol Hepatol 2016;1:62.

