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CURRENT STATUS AND PROGRESS OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN GASTRIC CANCER: A LITERATURE REVIEW

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ABSTRACT

Patients with metachronous peritoneal metastasizing gastric cancer show poor prognosis. Despite potentially curative treatment, gastric cancer survival remains low, primarily due to metastasizing recurrence. To prolong the survival rate and reduce the recurrence rate after radical resection of gastric cancer has become a focal point in the diagnosis and treatment of gastric cancer. Hyperthermic intraperitoneal chemotherapy has a good effect on the prevention and treatment of postoperative recurrence of gastric cancer and advanced malignant ascites. We review the current status of HIPEC in gastric cancer in terms of mechanisms, drug selection, prophylactic and therapeutic HIPEC, and biomarkers related to prognosis.

KEYWORDS: Gastric cancer; Peritoneal metastases; Cytoreductive surgery; Hyperthermic intraperitoneal perfusion chemotherapy.

INTRODUCTION

Gastric cancer is the most common malignant tumor in the upper gastrointestinal tract. According to the most recent tumor epidemiological data in the world, its incidence ranks fifth among malignant tumors, and its mortality ranks third.[1] The median survival time for patients with radical treatment is approximately 50 months[2], and the main cause of treatment failure is peritoneal metastasis. The incidence of peritoneal metastases is as high as 70%, and the average survival time is only 4 months.[3] The poor prognosis of gastric cancer is closely related to the presence of distant metastases, and peritoneal metastases is one of the most common metastatic site.[4] In gastric cancer, there is a 10% - 20% probability of developing peritoneal metastasis; however, up to 50% - 60% of patients develop peritoneal metastasis after curative resection of advanced gastric cancer[5,6]; therefore, it is imperative for us to concentrate on how to reduce the incidence and improve the prognosis of such patients as much as possible. Since Spratt *et al.*[7] first introduced intraperitoneal hyperthermic perfusion chemotherapy (HIPEC) for the treatment of patients with peritoneal pseudomyxoma in 1980, HIPEC is a very effective treatment for peritoneal cancer and its accompanying malignant ascites, which is caused by peritoneal metastases from abdominal malignancies such as gastric, colorectal, ovarian, peritoneal pseudomyxoma, malignant peritoneal mesothelioma, pancreatic, cholangiocarcinoma, and liver cancer.[8] Several studies have reported the clinical utility of HIPEC technology in gastric cancer patients, but there is still some controversy regarding its use. This article summarizes the current status and progress of HIPEC in gastric cancer.

Mechanism & Classification of HIPEC

Due to insufficient blood supply to the peritoneal surface and the existence of the plasma-peritoneal barrier, intravenous chemotherapeutics have difficulty reaching the peritoneum, whereas HIPEC may be able to directly contact the tumor along with exerting antitumor effects through killing effects of hyperthermia, chemotherapy synergistic effects, and mechanical perfusion washout of the peritoneal cavity.

Tumor cells are more sensitive to hyperthermia than normal tissue cells. Irreversible damage can be caused if tumor cells are heated to 43°C for one hour, while normal tissues can tolerate 47°C for one hour. The thermal effects of HIPEC may damage peritoneal tumor cells by activating lysosomes, damaging the cytosol and nucleus, interfering with energy metabolism, damaging DNA repair. In addition, altered homeostasis of tumor cell membranes facilitates the entry of chemotherapeutic drugs into cancer tissues, increases the absorption of chemotherapeutic drugs by cancer cells, and limits the

absorption of chemotherapeutic drugs into the blood through the perineal region, thus maintaining high concentrations of the drugs in the abdominal cavity. The heat effect can also induce an antitumor effect in the autoimmune system by activating heat shock proteins. In addition, the large amount of circulating perfusion fluid in the peritoneal cavity of HIPEC can kill or wash away the detached tumor cells as time progresses.[9-12]

Closed HIPEC are more numerous and can be categorized into three types. First, there is intraoperative closed HIPEC (also called semi-open HIPEC)[13], in which perfusion tubes are placed during open surgery, and then the surgical incision is temporarily closed so that a confined space to administer thermal perfusion chemotherapy is formed, and finally the abdomen is reopened and the perfusion fluid is drained; second, there is postoperative closed HIPEC[14], in which four perfusion tubes are placed; third, there is internal closed HIPEC[15], which involves placing ultrasound-guided peritoneal punctures followed by continuous circulating perfusion that is connected to a thermal perfusion system. In contrast to open surgery, laparoscopic surgery has the advantages of easier handling, reduced heat loss, the ability to achieve and maintain target temperatures quickly, increased chemotherapeutic drug penetration of tissues, less exposure of medical personnel to chemotherapeutic drug inhalation, and a higher postoperative recovery. In addition, closed surgical methods also provide the advantage of fractionated dosing and multiple treatments. However, the biggest problem with the closed technique is the lack of uniform distribution of the perfusion solution. This may lead to the accumulation of heat and chemotherapeutic drugs, leaving some areas untreated. The most significant disadvantage of the closed technique is that it may result in the accumulation of heat and chemotherapeutic drugs, subsequently leaving some areas untreated[16], and that the associated costs for managing the damage caused are high and invasive.

Optimal drugs selection for HIPEC in the treatment of gastric cancer

Among the most widely used drugs for HIPEC treatment of gastric cancer are mitomycin-C (MMC) and cisplatin (CDDP), which are often administered as single agents or in combination.[17,18] Considering these results, the combination of 5-FU and nab-paclitaxel has also been reported. The study by Murata *et al.*[19] studied the safety and efficacy of a three-drug combination of 5 - Fu, CDDP, and MMC in patients with peritoneal metastases of gastric cancer treated with HIPEC. The results showed that the combination of MMC, CDDP, and 5 - Fu was safe and effective. Mitomycin C (MMC) is a broad-spectrum chemotherapeutic agent commonly used in the clinic for the treatment of gastrointestinal tumors, and it is often combined with different platinum drugs, 5-fluorouracil, in the postoperative intraperitoneal hyperthermic perfusion therapy of gastric cancer.[20] The mechanism of action of mitomycin C is primarily alkylation, which forms cross links with DNA double helix structures. It inhibits the replication of DNA and also causes DNA single strand breaks and has an inhibitory effect on RNA at high concentrations. CDDP is a non-specific, broad-spectrum antitumor drug with a large molecular weight, strong water solubility, and deep penetration, which can kill tumor cells at any stage and promote the apoptosis of tumor cells, but also stimulate pleural cell proliferation, fibrosis, and stop malignant effusion.[19] After cisplatin has been injected into the body cavity, the intraluminal concentration peak and the area of the concentration time curve were 12 and 20 times higher than those of plasma, respectively. 5-fluorouracil (5-FU) is a commonly used chemotherapeutic drug that acts as an antimetabolite after being converted inside of the cell into fluorouracil deoxynucleotides by blocking the deoxyribouridylate from internal thymidylate synthase to thymidylate, while affecting the synthesis of DNA, and is frequently used in intraperitoneal chemotherapy for gastric cancer.

Prophylactic HIPEC in gastric cancer

Prophylactic HIPEC is currently widely used after R_0 resection in patients with advanced gastric cancer who have risk factors without macroscopic peritoneal metastases.[21,22] In addition, there are risk factors such as the presence of local invasion beyond the serosal layer, the presence of enlarged lymph nodes, and the development of cancer nodules.[23,24] As early as 1988, Japanese researchers Koga *et al.*[25] used continuous hyperthermic peritoneal perfusion containing mitomycin C solution as a preventative treatment for gastric recurrence and found that the perfusion group was superior to the control group in 3-year survival rate and rate of no peritoneal metastasis, while both retrospective and prospective studies found that the incidence of anastomotic leakage and adhesive ileus was not increased in the perfusion group. Demonstrated its advantages in terms of safety and survival. In an RCT study by Hamazoe *et al.*[26], prophylactic HIPEC administered after curative surgery for gastric cancer patients with serosal invasion was effective in reducing the incidence of peritoneal metastasis, and the 5-year survival rate of the study group was higher than that of the control group (64.2% vs. 52.5%), and the mortality rate due to recurrence of peritoneal metastasis was lower than that of the no-perfusion group. Additionally, another study[27] showed that HIPEC was effective and safe in preventing recurrence of peritoneal metastases after gastric cancer surgery. Hirose *et al.*[28] compared the effects of multiple risk factors on the prognosis of advanced gastric cancer and the occurrence of peritoneal metastasis, and the results indicated that HIPEC was an independent prognostic factor in the preventive study, and its effect on preventing peritoneal metastasis may have a positive effect on long-term survival.

However, there are some studies that do not affirm the role of HIPEC in preventing peritoneal metastatic disease. The results of Kunisaki *et al.*[29] included 124 patients

with advanced gastric cancer who underwent prophylactic HIPEC, compared with 79 patients who did not undergo prophylactic HIPEC during the same period, showed that prophylactic HIPEC did not improve 5-year survival, did not effectively prevent peritoneal recurrence of gastric cancer, or affect patterns of recurrence and metastasis.

There are currently two clinical trials underway or licensed that provide additional evidence. The GASTRICHIP trial (NCT01882933)[30] is a randomized, multicenter, prospective phase III trial that involves gastric resection followed by D1-D2 lymphadenectomy combined with HIPEC (oxaliplatin) for patients with cytologically positive advanced gastric cancer. GASTRIPEC (NCT02158988) was an open label, randomized, multicenter trial that compared the efficacy of HIPEC with or without HIPEC in patients with peritoneal metastases of gastric cancer receiving chemotherapy, CRS, and adjuvant chemotherapy. As both studies have been running since 2014 and continue to accrue data, we anticipate that future data from randomization will shed light on the efficacy of HIPEC.

Therapeutic HIPEC in gastric cancer

Currently, the first choice for metastatic gastric cancer treatment is systemic chemotherapy[31], whereas conventional chemotherapy for gastric cancer patients with peritoneal metastasis is not ideal, as it is very difficult for chemotherapy agents to reach metastatic lesions within the peritoneal cavity due to the so-called "blood-peritoneal barrier". HIPEC has the advantage of creating a high concentration of drug accumulation in the peritoneal cavity, and the superimposed thermo-synergistic effect further enhances the efficacy and reduces the systemic reactions caused by intravenous chemotherapy.

Therapeutic HIPEC is mainly applied to gastric cancer patients with macroscopic peritoneal metastasis or accompanied with cancerous ascites, and its main purpose is to alleviate the symptoms of cancerous ascites in such patients, based on the combination of systemic chemotherapy or debulking surgery, etc., to maximize the survival time.[32] A prospective clinical study by *Glehen et al.*[33] showed that HIPEC combined with cytoreductive surgery (CRS) had a positive effect on peritoneal metastases caused by gastric cancer, and a better survival benefit was expected for patients with resectable gastric cancer whose systemic condition allowed, primary and peritoneal metastases were resectable. A French multicenter retrospective study[34] enrolled 159 patients who also underwent CRS combined with perioperative HIPEC, and the combination of both resulted in some degree of survival benefit, with a 5-year survival rate of 23%, in patients with estimated limited resectable peritoneal metastases from gastric cancer. Blum Murphy *et al.*[35] showed that laparoscopic HIPEC (mitomycin 30 mg, cisplatin 200 mg, and paclitaxel 60 mg / m2) for the treatment of peritoneal metastases from gastric cancer did not increase the incidence of treatment toxicity and complications within this safe dose, while the long-term survival situation still needs to be verified by subsequent follow-up. A meta-analysis[36], after including 11 RCTs over a period of 30 years and 21 non-RCTs, concluded that HIPEC could prolong the median survival of patients with gastric cancer with peritoneal metastases. A 2019 Pan-Asian and ESMO joint guideline on the treatment of metastatic gastric cancer[37] affirms the value of CRS + HIPEC in gastric cancer with peritoneal metastasis, although higher-level evidence is still pending from clinical studies.

At present, domestic and foreign scholars generally regard the rating of peritoneal cancer index (PCI) as a quantitative index to assess the degree of peritoneal metastasis[38,39], this method divides the peritoneum into 13 zones, scores the tumor size of each division, and the sum of the scores is the PCI index. Whereas the tumor residual score after CRS is currently commonly measured by the degree of cytoreduction (CCR)[40], 0 is no residual tumor, 1 is residual tumor diameter less than 2.5 mm, 2 is residual tumor diameter between 2.5 mm and 2.5 cm, and 3 is residual tumor diameter greater than 2.5 cm. Generally, it is believed that the CCR after cytoreductive surgery in patients with peritoneal metastases with PCI index less than 6 is expected to reach 0 or 1, and the prognosis can be significantly improved by HIPEC treatment. A Spanish multicenter study[41] that included 88 patients with gastric cancer with peritoneal metastases showed a survival benefit from treatment modalities of CRS combined with HIPEC in patients with PCI < 7. The study by Pamela *et al.*[42] showed that HIPEC combined with CRS was able to improve 5-year survival of patients without the risk of additional complications only when the prospective assessment of CCR was between 0 and 1.

Prognostic biomarkers

Zunino *et al.*[43] found that HIPEC can induce anti-cancer immune responses by increasing the exposure of heat shock protein 90 (HSP90), which means that patients who express high HSP90 levels after HIPEC treatment are likely to have a positive prognosis. Among patients with advanced gastric cancer treated with CRS and HIPEC, Zhang *et al.*[44] analyzed miRNA expression profiles and discovered that miRNA-218 was up-regulated to a significantly higher extent than 8 times following treatment. The expression of miRNA-218 was up-regulated in human gastric cancer cells (SGC7901). It was found that up-regulation of miRNA-218 significantly inhibited the growth of tumor cells. Therefore, the increased expression of miRNA-218 may be indicative of the long-term benefits of HIPEC. According to Grazioso *et al.*[45], the expression of tumor metastasis related genes in the mouse gastric cancer model was significantly downregulated after HIPEC treatment, including colorectal adenomatous polyposis (APC); Integrin gene 3 subunit (ITGB3); Chemokine stromal cell derived factor-1 receptor (CXCR4); Spleen

tyrosine kinase (SYK); Vascular endothelial growth factor receptor 3 / FMS related tyrosine kinase 4 (VEGFR3 / FLT4); Type IV collagen α 2 chain (COL4A2); C-terminal binding protein 1 (CTBP1). In conclusion, the results of the study showed that a reduction in the expression of the above gene could be indicative of a reduction in tumor metastasis among mice following HIPEC treatment. However, further clinical trials are required to support this conclusion. In a retrospective study, Kooten *et al*.[46] assessed the ability of C-reactive protein (CRP) to predict the development of short-term complications after CRS + HIPEC. Included 181 patients were divided into SAE ≥ 3 group (n = 50) and SAE < 3 group (n = 131) according to the classification standard of serious adverse events (SAE). CRP levels were compared between the two groups. The results showed that the level of CRP in patients with SAE ≥ 3 increased significantly from 2 to 5 days after operation (P values were 0.023, 0.001, 0.002 and 0.002 respectively), and the risk of CRP > 166mg / L on the 3rd day and CRP > 116mg / L on the 4th day was the highest. CRP levels continued to rise on the second day after operation, CRP > 166mg / L on the third day after operation or CRP > 116mg / L on the fourth day after operation, suggesting that there is a high risk of high-level SAE.

CONCLUSION

At present, a limited number of effective treatments are available for gastric cancer. HIPEC is one of the most effective ways to improve the treatment of gastric cancer patients. Clinical studies have demonstrated that HIPEC has a beneficial effect on patients with gastric cancer who have a high risk of peritoneal metastasis and who have simultaneously developed peritoneal metastases of gastric cancer (PCI < 7). Nevertheless, the success rate of HIPEC is not optimal in patients with advanced peritoneal metastases, metachronous peritoneal metastases, and inoperable advanced peritoneal metastases. However, in terms of basic research, we are not only lacking effective targets for improving the effectiveness of HIPEC, but also a lack of more accurate predictive biomarkers. There is no doubt that HIPEC will play a major role in the comprehensive treatment of gastric cancer patients. However, multicenter prospective clinical studies are required to assert the results of this review.

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