15 Hyperthermic Intraperitoneal Chemotherapy in Gastric Cancer: Indications and Technical Notes

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Abstract

Synchronous and metachronous peritoneal carcinomatosis (PC) is the most important issue in gastric cancer (GC) recurrence. Progress in the therapeutic challenge posed by PC has been made through a new treatment consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), developed over the last two decades. This chapter provides a review of the literature and recent results. Current indications for HIPEC in GC are: for curative purposes in addition to CRS in the treatment of PC; as palliative treatment for otherwise untreatable ascites; and as adjuvant treatment in the absence of PC for tumors infiltrating the serosal layer. There is abundant evidence that a multimodality approach offers survival benefits over surgery alone. In selected patients and in experienced centers, HIPEC after radical CRS can prolong survival and reduce peritoneal recurrences. The early identification of GC patients at high risk for peritoneal disease is a task for the future.

Keywords

Gastric cancer • Peritoneal carcinomatosis • Cytoreductive surgery • Hyperthermic intraperitoneal chemotherapy • HIPEC • Surgical resection • Surgical cytoreduction • Hyperthermia • Induced • Micrometastasis • Molecular biology • RT-PCR • Randomized controlled trials

15.1 Rationale

The loco-regional progression of gastric cancer (GC) frequently results in peritoneal carcinomatosis (PC), with random distribution on the peritoneal surface. The molecular mechanisms by which GC gives rise to PC remain to be clarified but may include chemokines. These small secretory proteins control the migration and activation of leukocytes and other cell types through interactions with a group of transmembrane receptors. Expression of the chemokine receptors CXCR4/CXCL12 has been shown to play a role in the development of PC from GC, as evidenced in a xenograft animal model in which treatment with a CXCR4 antagonist suppressed the PC development. Moreover, CXCR4 expression on the primary tumors of patients with advanced GC was shown to significantly correlate with the occur-

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rence of PC, strongly suggesting that CXCR4-expressing GC cells are preferentially attracted to the peritoneum, where the receptor's ligand, CXCL12, is abundantly produced. Growth factors such as vascular endothelial growth factor (VEGF) and VEGF-C are thought to be associated with the development of peritoneal metastasis. Furthermore, the relevance of interactions between VEGF, CXCR4, and CXCL12 in the development of peritoneal metastasis was recently demonstrated [1]. These results provide very interesting diagnostic and therapeutic perspectives for GC-related PC.

At surgical exploration, from 15 to ≥ 50% of patients present with PC, especially when there is serosal involvement by the tumor [2, 3]. The prognosis of these patients is very poor, as median survival is less than 6 months [4, 5]. PC developing from GC is likewise associated with a poor prognosis, with median survival ranging from 1–1.6 to 3.1–9 months [6]. The risk of peritoneal recurrence is particularly high in patients with diffuse Lauren's type tumors and serosal infiltration [7]. **[CE]**

Even after curative resection of GC, there is a major problem with PC recurrence. Two Italian studies, with 441 and 200 GC patients, showed peritoneal recurrence in 17 and 32.9% at the median follow-up of 48 and 42.3 months, respectively [7, 8]. A Korean study of 500 GC patients who underwent standardized radical surgery found that, within 5 years after gastrectomy, PC is the most frequent form (51.7%) of recurrence [9]. A prospective randomized controlled trial (RCT) in Japan involving 530 patients treated with curative gastrectomy also found peritoneal recurrence as the most frequent event (15.8%) at 3 years follow-up [10].

Conventional surgery is not adequate for PC; instead, current treatments are systemic chemotherapy and palliative therapy, albeit with no hope of cure. Synchronous and metachronous PC is therefore the most important issue in GC recurrence and metastasis. Over the last two decades, a new therapeutic strategy, consisting of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), has been developed. This multimodal approach takes advantage of surgery to reduce the visible tumor burden and of regional hyperthermic chemotherapy to eradicate microscopic peritoneal implants.

The well-codified surgical procedures that comprise CRS depend on the extent of peritoneal disease [2, 11]. The aim of CRS is complete macroscopic cytoreduction as a pre-condition for HIPEC. Residual disease is classified intraoperatively using the completeness of cytoreduction (CC) score. The efficacy of intraperitoneal chemotherapy reaches its highest degree in the absence of visible residual disease (CC-0) or in the presence of neoplastic residuals ≤ 2.5 mm (CC-1). The main theoretical advantage of intraperitoneal chemotherapy is that it allows the direct administration of a high local concentration of potentially effective drugs while incurring minimal systemic exposure and toxicity. Experimental studies have demonstrated that hyperthermia (42–43°C) may have an important therapeutic effect on tumor tissue when applied alone [12]; moreover, hyperthermia synergistically enhances the chemosensitivity of neoplastic cells to antimitotic agents and allows deeper penetration of drugs into tumor tissue [13].

Nowadays, HIPEC can be considered the standard treatment for peritoneal mesothelioma, pseudomyxoma peritonei, and—when a complete CRS is possible—for PC arising from colorectal cancer [5, 14]. For GC, the results are more controversial and HIPEC has yet to be adopted as standard therapy.

15.2 Indications

Current indications for HIPEC in GC patients are the following: (1) for curative purposes in addition to CRS in the treatment of PC; (2) as palliative treatment for otherwise untreatable ascites; and (3) in the absence of PC, as adjuvant treatment for tumors infiltrating the serosal layer.

15.2.1 HIPEC in the Treatment of PC

Since the first report concerning the possibility of treating PC with HIPEC and the following papers from Sugarbaker et al in the 1980s [15,16] many studies have been carried out examining cytoreduction associated with HIPEC in the treatment of PC. Series of CRS and HIPEC for GC-related PC evaluated in the late 1990s [17] reported overall medi-

an survivals between 6.6 and 27.7 months, with great improvement (up to 43 months) in patients treated by radical CRS.

In 49 consecutive patients with PC from advanced GC submitted to CRS and HIPEC, Glehen reported an overall median survival of 10.3 months; median survival was of 21.3 months for 25 of the 49 patients who received CC-0 and CC-1 surgery vs. 6.1 months for patients with residual nodules > 5 mm in diameter ($p < 0.001$) [18].

Very interesting results were recently obtained in a multi-institutional study [14] consisting of 159 patients with PC from GC (44% synchronous) among 1290 patients treated by CRS plus HIPEC for PC of nongynecologic malignancies. The overall median survival was 9.2 months and the 1-, 3-, and 5-year survival rates were 43, 18, and 13%, respectively. Median survival for the 85 CC-0 patients was 15 months with 1-, 3-, and 5-year survival rates of 61, 30, and 23%, respectively. The 37 CC-1 patients and 30 CC-2 patients had a median survival of 4 months and none of them was alive at 2 years [14]. The only independent prognostic indicator at multivariate analysis was the completeness of CRS, as confirmed by Yonemura et al. [19]. In a recent study, median survival was 43.4 months for CC-0/CC-1 patients vs. 9.5 and 7.5 months in CC-2 and CC-3 patients, respectively [20]. These results emphasize the fact that HIPEC, for this indication, should not be recommended in patients in whom complete CRS cannot be achieved.

In conclusion, CRS + HIPEC in the treatment of PC arising from GC is an aggressive combined therapy still under investigation. Notwithstanding, several studies carried out in Europe and Asia show the possibility of 5-year survival rates of ~25% 5— until recently, an unexpected outcome.

15.2.2 HIPEC as Palliative Treatment for Neoplastic Ascites

For patients who are not candidates for CRS and who present with neoplastic therapy-resistant ascites, HIPEC is indicated as a palliative treatment. The clinical management of malignant ascites using a myriad of conventional treatment modalities has been inconsistent, temporary at best, and generally unsatisfactory. Palliative HIPEC provides definitive treatment of neoplastic ascites with resulting improvements in the quality of life of these patients. Abdominal sclerosis and the induction of dense adhesions are probably the major factor influencing the technique's efficacy. The use of video laparoscopic surgery approaches has resulted in low morbidity and mortality and limited surgical trauma, allowing possible treatment of the entire peritoneal surface. In addition, laparoscopic viscerolysis is a low-risk procedure. A complete and definitive disappearance of the ascites was observed in 94% of these patients [21, 22].

15.2.3 HIPEC in the Adjuvant Setting for Advanced GC Without PC

Perhaps the most promising indication for HIPEC is as adjuvant treatment. Peritoneal recurrence develops in 60% of patients with pT3 or pT4 tumors after curative resection [23]. In serosa-invading tumors, invisible implants are already present in the peritoneal cavity at the time of curative surgery, and the peritoneum is the only site of first recurrence in 40–60% of patients [5]. Therefore, peritoneal dissemination alone usually results in the death of 20–40% of patients with GC [24].

Cytological examination of peritoneal washings at the time of primary tumor resection is frequently positive. Free peritoneal cells are associated with an average survival of 4 months vs. 21 months for patients with negative cytology [23, 25]. The majority of patients with positive cytology on peritoneal lavage develop PC, although it also occurs in patients with negative cytological results. These observations indicate that conventional cytology lacks sensitivity for the detection of residual cancer cells and the prediction of peritoneal spread. Many recent reports have emphasized the clinical significance of molecular diagnosis using reverse transcriptase-polymerase chain reaction (RT-PCR) analysis for more sensitive detection of GC cells in peritoneal lavage. Fujiwara analyzed the survival of 123 patients with serosa-invading GC. The prognosis of the 29 patients with positive cytology in the peritoneal lavage was very poor, and most of them died within 1 year after surgery. Among the 93 patients with negative cytology (CY0), 49 had a positive genetic diagnosis and a significantly poor-

er prognosis than those with negative genetic results. More than half of the patients with positive PCR and CY0 developed peritoneal recurrence after surgery, while almost all patients with negative PCR and CY0 had no peritoneal recurrence after surgery [26]. These results have been confirmed by many authors (e.g., [24]), who concluded that molecular diagnosis based on peritoneal lavage fluid is useful to predict peritoneal recurrence for patients with serosal invasion of GC [27].

Four prospective RCTs from Japan and Korea evaluated adjuvant HIPEC after potentially curative GC resection. The first found no significant difference between the two groups of patients, presumedly because of the small number enrolled [28], but the other three studies reported positive responses: In Fujimoto's 141 patients, HIPEC significantly reduced the incidence of peritoneal recurrence ($p < 0.001$) and improved the survival rate ($p = 0.03$) without adverse postoperative events [29]. Yonemura randomized 139 patients in three arms, surgery alone, surgery plus HIPEC, and intraperitoneal chemotherapy without hyperthermia. The 5-year survival was 61% in the HIPEC group compared to 43 and 42% in the other two groups [30]. Zhang confirmed a reduction in recurrence and an improvement in survival, both statistically significant, for patients treated with surgery plus HIPEC [31].

In 2001, the results of a controlled study of 103 patients with serosal-involving GC who underwent surgical resection alone or surgical resection plus HIPEC were published. The 5-year survival rate was significantly higher in the experimental group when patients with distant metastases were excluded ($p = 0.0379$). The most common recurrence pattern was loco-regional in the HIPEC group and peritoneal in the control group [32].

Yan systematically reviewed 13 RCTs and the ten of acceptable quality were subsequently meta-analyzed. Overall, 1648 patients with resectable advanced GC, with macroscopic serosal invasion but without distant metastases or PC, were randomly assigned to receive surgery combined with intraperitoneal chemotherapy or surgery without intraperitoneal chemotherapy. Meta-analysis established that, compared with current standard treatments, HIPEC is associated with significant improvement in the survival of patients with advanced GC ($p = 0.002$). However, the authors pointed out the need for a well-designed prospective multi-institutional RCT [33].

On the basis of the reported results and rationale, a cooperative European multicentric randomized study to determine the role of HIPEC in the prevention of peritoneal dissemination after curative GC resection in patients at high risk for peritoneal recurrence has been proposed. Its aim is to evaluate the added value of HIPEC to D2 gastric resection plus systemic therapy with respect to the survival of patients with serosal-infiltrating GC or/and free cancer cells in peritoneal washing [34].

15.3.3 Principles of Technique and Complications

HIPEC associated with surgery can be performed using either the closed or the open technique. In the closed version, after cytoreduction, gastrectomy, and anastomoses are completed, the drains are positioned and the abdominal wall is closed. HIPEC is thus initiated with the abdominal cavity closed. The position of the operating bed is changed every 15 min to facilitate circulation of the perfusate into the abdomen. In the open version, at the end of the CRS, the abdominal wall is suspended by a retractor, such as the Thompson (Thompson Surgical Instruments, Traverse City, MI, USA) or the Flexitrac (Medicon Instrumente, Tuttlingen, Germany), with stitches or clamps on the skin. The abdominal cavity is covered by a plastic sheet, thereby creating an artificially closed area. The surgeon inserts his or her hand through an incision in the sheet, and mixes the solution in order to obtain more homogeneous spreading of the perfusate in the abdomen.

With both techniques, in-flow and out-flow abdominal drains are inserted and connected to an external circuit including the pumping system and the heat exchanger. Performer-LRT (Rand, Mirandola, Italy) and Exiper (Menfis bioMedica, Bologna, Italy) are examples of modern HIPEC-dedicated devices providing an integrated system that monitors temperature, pressure, and flow. The chemotherapeutic agents are added into the circuit as soon as the abdominal temperature reaches 41.5–42.5°C. Lavage with 5% dextrose through the

drains during the early postoperative period is suggested. The purpose is to prevent free cells from embedding in the fibrin, the so-called cathedrals of cancer, resulting in disease recurrence. Postoperative lavage must be performed every hour until a clear liquid is obtained and then continued every 2 h thereafter for the first 12 h postoperatively [11].

Postoperative mortality after CRS and HIPEC is 2–4%; morbidity is relatively high (25–41%) but comparable to that following major gastrointestinal surgery. The morbidity rates seem to be related to the extension of CRS rather than to the HIPEC itself. The anastomosis following total or subtotal gastrectomy in combination with CRS and HIPEC is relatively safe. In a series of 49 patients submitted to HIPEC for PC of gastric origin, 13 underwent subtotal and 26 total gastrectomy. Major complications occurred in 13 patients but no leakage at the esophago- or gastro-jejunostomy was observed [18]. Piso analyzed 37 patients who underwent gastric resection with curative intent for PC. No leakages occurred at the site of the esophageal or gastric anastomosis/suture [35].

15.4 Conclusions and Perspectives

Neither surgery alone nor systemic chemotherapy is adequate treatment for PC whereas a multimodality approach clearly offers survival benefits over the former. In selected patients and in experienced centers, HIPEC after radical CRS can prolong survival and reduce peritoneal recurrences. The surgical technique of peritonectomy is complex and has a long learning curve. To date, complete cytoreduction and HIPEC has yielded unexpected results, with 5-year survival rates of 19–25% [14, 20]. The use of HIPEC in the adjuvant setting in patients with GC infiltrating the serosal layer looks very promising, but needs to be confirmed, perhaps by the forthcoming European trial [34]. Pre-operative laparoscopy with cytology is mandatory for peritoneal staging and further therapeutic choices. The introduction into clinical practice of genetic diagnostic techniques for peritoneal lavage from patients with GC will soon increase the number of candidates for more aggressive treatments, including HIPEC [26]. In the near future, CXCR4 expression in biopsy specimens and CXCL12 levels in peritoneal washing may serve as useful molecular markers, identifying a subset of GC patients at very high risk of peritoneal recurrence. Furthermore, by targeting CXCL12, a therapy including CXCR4 antagonists may become part of the multi-modal treatment of PC [1].

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