

Neoadjuvant intraperitoneal chemotherapy for advanced stage gastric cancer (Review)

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Abstract. Gastric cancer remains one of the most lethal malignancies especially when diagnosed in advanced stages of the disease; most often patients diagnosed later during the progression of their disease will present a certain degree of peritoneal contamination such as positive peritoneal cytology or peritoneal metastatic nodules. In such cases most often they then progress to peritoneal carcinomatosis and succumb to the disease within one year. In order to increase the lifespan in such cases multiple therapeutic strategies have been proposed such as radical surgery and intraperitoneal heated chemotherapy or direct intraperitoneal chemotherapy followed by radical surgery. To date, the benefits of intraperitoneal heated chemotherapy at the time of resection have been widely investigated; however the method is still associated with increased rates of perioperative complications. Therefore, attention was focused on investigating the benefits of such procedures as neoadjuvant therapies followed by radical surgery. The aim of the present review was to examine the most efficient therapeutic strategies in advanced-stage gastric cancer such as neoadjuvant laparoscopic heated intraperitoneal chemotherapy, perioperative heated intraperitoneal chemotherapy and neoadjuvant systemic and peritoneal chemotherapy.

Contents

1. Introduction
2. Methods
3. Principle of neoadjuvant HIPEC
4. Effectiveness of HIPEC in the neoadjuvant setting of peritoneal carcinomatosis from gastric cancer
5. Conclusions

1. Introduction

Gastric cancer represents one of the most lethal digestive malignancies affecting people worldwide especially in cases diagnosed in advanced stages of the disease; the overall estimated 5-year survival rate is 25% while in cases presenting advanced-stage disease this value significantly decreases to <5% (1-3). As numerous other malignancies, gastric cancer may spread via multiple pathways such as the hematogenous one leading to the apparition of distant, visceral metastases, the lymphatic one leading to the development of lymph node metastases and the peritoneal one leading to the development of peritoneal carcinomatosis (1). This latter pathway of spread is caused by the exfoliation of malignant cells from the gastric serosa and further implantation of these cells at the level of the peritoneal cavity. In time these cells will proliferate and will progress to the development of peritoneal carcinomatosis nodules; it is estimated that up to 45% of patients present synchronous peritoneal nodules at the time of the initial diagnosis, while a similar proportion will develop such lesions at a certain stage of the disease even if radical surgery has been performed at the time of the initial diagnosis (1-3). Once peritoneal nodules of carcinomatosis develop, multiple

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complications such as ascites, bowel occlusion, bowel perforation or nutritional deprivation may develop, leading to the apparition of intractable complications and finally patients succumb to the disease (1). Therefore, previous studies have considered peritoneal carcinomatosis as a locoregional disease and not a systemic one. However, the estimated survival rate of patients presenting peritoneal carcinomatosis from gastric origin is <6 months, this lifespan being minimally improved in cases submitted to systemic chemotherapy (4,5).

In this respect, aggressive surgical procedures such as intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy, neoadjuvant intraperitoneal and systemic therapy and cytoreductive surgery have been proposed (1,6-8). Hyperthermic intraperitoneal chemotherapy (HIPEC) has been demonstrated to play a significant role in the setting of advanced-stage gastric cancer as a prophylactic tool as well as in selected cases presenting peritoneal carcinomatosis (9-12). The method appears to be associated with several advantages such as direct delivery of high amounts of cytotoxic agents at the tumor level, use of heated agents which increase the antitumor effect and diminish systemic toxicity; all these advantages present significant interest especially in gastric cancer patients, in which disease recurs most frequently via the peritoneal route (13-15). However, the method has been demonstrated to be associated with significant rates of perioperative morbidity; therefore, attention was focused on identifying other therapeutic approaches which may maximize the effect of these procedures while also minimizing the risk of perioperative morbidity and mortality (1).

2. Methods

The present article is a literature review conducted on studies identified after searching the following keywords on Pubmed: 'neoadjuvant chemotherapy', 'advanced stage gastric cancer', 'peritoneal carcinomatosis from gastric cancer', 'hyperthermic chemotherapy'. Initially, 83 studies were identified from which studies in which the full text was not available, studies written in other languages other than English as well as case reports were excluded. Finally, 35 studies were identified, which were analyzed when writing the present review; the reviewed papers were published between 1995-2021.

3. Principle of neoadjuvant HIPEC

One of the most widely investigated therapeutic strategies is represented by using HIPEC as a neoadjuvant procedure, followed by interval debulking surgery. The method, performed in a laparoscopic manner appears to be associated with complete disappearance of the peritoneal metastases in up to 25% of cases and increased overall survival rates (13,16). Therefore, minimally invasive surgery in association with neoadjuvant HIPEC alone (in the absence of debulking surgery) appears to maximize the oncological benefits and to minimize the risks of perioperative morbidity. In addition, other authors have also examined the possibility of performing neoadjuvant HIPEC as prophylaxis of peritoneal carcinomatosis in patients with positive cytology; in this respect, in cases presenting serosal invasion, peritoneal cytology should be retrieved and whenever malignant cells are encountered, neoadjuvant HIPEC

followed by interval radical gastrectomy should be the option of choice (17,18). However, an interesting difference of opinion should be underlined between Eastern and Western countries; while in Asian trial studies published thus far the effectiveness of HIPEC was demonstrated in patients with serosal invasion as well as in those with peritoneal carcinomatosis, in Western countries it appears that the method proved to be particularly efficient only in cases with serosal invasion. The difference may be explained through the fact that there are significant differences between the two types of tumors in regard to tumor biology, genetics and type of treatment (19,20).

Another interesting concept is the one of preventive perioperative HIPEC in patients diagnosed with advanced stage gastric cancer; according to Sugarbaker (21), whenever a patient with advanced stage gastric cancer (with serosal invasion) is submitted to surgery an increased risk of intraoperative peritoneal contamination occurs via multiple mechanisms, therefore, surgical manipulation of the specimen, lymphatic transection during lymph node dissection as well as intraoperative venous hemorrhage may predispose to peritoneal seeding. Whenever a lymphatic is transected and its content is contaminated with malignant cells or a vein is sectioned and venous blood with possible tumor emboli reaches the peritoneal surface the risk of peritoneal contamination increases. Meanwhile, during the early postoperative period development of adherent syndromes and fibrin entrapment will fix the neoplastic cells at the level of the peritoneal surface and will further favor the development of peritoneal carcinomatosis. In this respect, Sugarbaker (21) proposed a prevention perioperative HIPEC protocol in all cases diagnosed with advanced stage gastric cancer.

4. Effectiveness of HIPEC in the neoadjuvant setting of peritoneal carcinomatosis from gastric cancer

The concept of neoadjuvant intraperitoneal chemotherapy has been initially taken into consideration in the absence of hyperthermia but in association with systemic chemotherapy. The method, also known as neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), has been demonstrated to combine the benefits of the two pathways of administration of the cytotoxic drugs; therefore, a higher amount of chemotherapeutic agents will be concentrated at the level of the peritoneal nodules, reaching these lesions via hematogenous flow and also, directly via the peritoneal pathway. According to Sugarbaker, the most appropriate candidates for this therapeutic strategy are patients younger than 65 years old, with a good general status (Eastern Clinical Oncology Group score of two or less), no hematogenous or lymphatic metastases, normal hematogenous, renal, cardiac and hepatic function, no other synchronous malignancies and confirmed peritoneal contamination by cytology or histology (21). The procedure can be applied for 4 to 6 cycles and is further followed by radical surgery in cases in which a positive response (defined by negative cytology and regression of the peritoneal lesions) is achieved (21).

The role of neoadjuvant HIPEC in peritoneal carcinomatosis from gastric cancer has been thoroughly investigated thus far. It appears that the method plays a crucial role in cases presenting extended peritoneal lesions from the time of the

initial diagnosis; therefore, performing two to five sequences of neoadjuvant HIPEC appears to significantly decrease the extent of the peritoneal lesions [quantified by the peritoneal carcinomatosis index (PCI)] and therefore to increase the rates of complete cytoreduction. One of the most eloquent studies which demonstrated the efficacy of neoadjuvant HIPEC in order to decrease the PCI and to increase the lifespan has been recently published by Yu *et al* (22); the study included 38 patients submitted to neoadjuvant systemic chemotherapy, HIPEC and debulking surgery (18 cases, conversion therapy group) and their outcomes were compared with the ones reported in the control group (20 patients submitted to chemotherapy and HIPEC solely). The authors reported a significant increase of the median overall survival in the conversion therapy group (21,1 months) when compared with the control group (in which the median overall survival rate was only 10,8 months ($P=0.002$)). In addition, the authors underlined the fact that cases in which the PCI decreased under a value of 6 at the time of the second laparoscopy reported a significantly improved outcome when compared with those in which this value was higher (22).

Data published to date, as well as the ongoing clinical trials at this time aim to demonstrate the effectiveness of neoadjuvant HIPEC alone or in association with neoadjuvant systemic chemotherapy in patients with positive cytology or limited peritoneal lesions (23). According to Beeharry *et al*, patients with positive cytology and in the absence of macroscopically visible peritoneal lesions during laparoscopy should be further submitted to neoadjuvant HIPEC while cases presenting macroscopically visible but limited lesions should be further submitted to NIPS (23). The same study group elaborated a protocol and a clinical trial in which they aimed to compare the efficacy of neoadjuvant laparoscopic HIPEC in association with neoadjuvant systemic chemotherapy followed by radical gastrectomy and HIPEC vs. radical gastrectomy followed by adjuvant chemotherapy in advanced stage gastric cancer. The multicentric phase III randomized controlled trial included 326 patients who were randomized to one of the two groups after laparoscopic exploration. Cases included in the first arm received one procedure of neoadjuvant laparoscopic HIPEC (60 min at 43°C with 80 mg/m² paclitaxel) followed by three cycles of neoadjuvant systemic chemotherapy with oxaliplatin, radical D2 gastrectomy with intraoperative HIPEC and another 5 cycles of oxaliplatin-based adjuvant chemotherapy. The control group was submitted to standard radical D2 gastrectomy followed by 8 cycles of adjuvant systemic chemotherapy with oxaliplatin. The aim of the study was to compare the long-term outcomes between the two arms, defined by the 5-year progression-free survival rate, the 5-year overall survival rate and the peritoneal metastasis rate as well as the short-term outcomes defined by the overall morbidity rate (24).

The efficacy and safety of neoadjuvant HIPEC in patients with positive peritoneal cytology as well as in cases with radiologically occult peritoneal carcinomatosis after neoadjuvant chemotherapy or even chemoradiotherapy has been demonstrated by Badgwell *et al* in 2017 (25). The study was conducted on 19 patients; peritoneal carcinomatosis being present at the time of the initial diagnosis in 13 cases and positive cytology in the remaining 6 cases. These cases were

submitted to 38 laparoscopic HIPEC procedures which were performed after a median number of 8 cycles of neoadjuvant systemic chemotherapy; among the 19 cases in 14 patients chemoradiotherapy was also performed before or between the cycles of HIPEC. The authors reported null mortality after HIPEC while the morbidity rate was 11%. In addition, 7 out of the 19 patients presented no intraoperative signs of peritoneal carcinomatosis and no imagistic signs of parenchymatous lesions at the end of the protocol were observed; negative cytology results. Therefore, they were proposed for radical surgery, and 5 of them were further submitted to radical gastrectomy; the number of HIPEC procedures performed in these cases ranging from 1 to 10 procedures (while the remaining two patients refused radical surgery). With regard to the long-term outcomes, the median overall survival after the first cycle of HIPEC was 20,3 months while the median overall survival after resection was 29 months. After a median follow up period of 18,9 months, 3 cases developed recurrent disease while the other 2 cases reported no signs of recurrence at 29 and 32 months, respectively (25).

Another interesting study from Yonemura *et al* was published in 2017; the study included 105 patients diagnosed with peritoneal carcinomatosis from gastric cancer. There were 53 cases who were submitted to 2 cycles of neoadjuvant HIPEC followed by interval debulking surgery and 52 cases submitted to 3 cycles of NIPS followed by debulking surgery. The authors demonstrated that in both groups the value of PCI significantly decreased after performing intraperitoneal chemotherapy while the overall rate of complete cytoreduction was 57,6% among the entire study group. In addition, the median survival rate was 19,2 months while the two-year survival rate was 41% (13).

This observation is particularly important due to the fact that, independent of the completeness of cytoreduction, the value of PCI appears to significantly influence the long-term outcomes (26-35). Therefore, in a study conducted by Glehen *et al* the authors demonstrated that none of the patients presenting a PCI >12 had survived at the three-year follow up after radical surgery and HIPEC even if complete cytoreduction had been achieved (8). In this respect, in the last decade it has been considered that debulking surgery and HIPEC should be considered as contraindications in patients presenting extended peritoneal lesions (21,30-35).

5. Conclusions

Neoadjuvant intraperitoneal chemotherapy delivered as HIPEC or in association with NIPS appears to provide promising results in the setting of advanced stage gastric cancer with positive cytology as well as in highly selected cases presenting peritoneal metastases. These methods have been demonstrated to be efficient in decreasing the peritoneal contamination and increasing the chances of achieving radical resections at the time of curative surgery. However, more prospective studies are still required in order to determine the best candidates for such procedures.

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Authors' contributions

NB, IB and MD contributed to the conception and design of the present study. CD, BS, FG, IB consulted relevant references and performed the literature data collection. IB and CS wrote the first draft of the manuscript. NB and IC revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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