Review Article

A critical analysis of the cytoreductive surgery with hyperthermic intraperitoneal chemotherapy combo in the clinical management of advanced gastric cancer: an effective multimodality approach with scope for improvement

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Abstract: Peritoneal carcinomatosis (PC) is manifested in up to 40% of gastric cancer (GC) patients, after which their 5-year survival drops to less than 5%. The currently most acceptable treatment option for advanced GC (AGC) is systemic chemo and radio therapies with however generally very unsatisfying results and this led to a resurgence of interest in regional therapies like cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Small trials have indicated an association with prolonged survival when applying this technique to AGC manifesting with PC. High procedure-related morbidity and mortality associated with the CRS-HIPEC approach have however brought by a polemic on the merits of the latter: with the advent of regulatory approval of more effective as well as novel, more personalized treatment options in AGC, along with advances in tailoring investigational agents specifically for peritoneal delivery, there clearly is a need to outline the appropriate role of CRS-HIPEC in this disease. In a clear objective to improve the therapeutic efficiency of HIPEC, there have been immense developments in the technical aspects of this technology including the use of nanotechnology in more precise drug delivery systems (DDS) or choice of more efficient drugs such as gene-target technology, laparoscopy and so on. Henceforth, in this review, we will be highlighting the past and current status of the CRS + HIPEC procedure, shedding light on the pros and cons in order to boost up the efficiency of this multimodality approach.

Keywords: Hyperthermic intraperitoneal chemotherapy (HIPEC); cytoreductive surgery (CRS); advanced gastric cancer (AGC); nanotechnology; morbidity

Received: 22 August 2016; Accepted: 22 August 2016; Published: 20 October 2016.
doi: 10.21037/tgh.2016.08.05
View this article at: http://dx.doi.org/10.21037/tgh.2016.08.05

Introduction

Gastric cancer (GC), the fourth most common diagnosed cancer worldwide, carries an incontrovertible mortality burden with a 5-year survival rate of approximately 25% for all stages (1,2). However, despite the tremendous advances made in the clinical management and diagnosis of GC, the clinical incidence of advanced GC (AGC) has not seen a remarkable decline (2).

Peritoneal carcinomatosis (PC) or peritoneal metastasis (PM) is manifested in up to 40% of GC patients with some

type of peritoneal spread during the course of their disease, after which their 5-year survival drops to less than 5% (3-5). PC occurs synchronous with the primary tumor in about 14–43% of patients with GC and accounts for 35% of all synchronous metastasis (6,7). Apart from the poor prognosis and outcome of patients with non-resectable GC, there is a high prevalence of around 30–50% of recurrence after curative surgery (8-11): even though only 10% to 25% of patients following a radical D2 gastrectomy with lymphadenectomy manifest locoregional recurrence (8,12,13), 10% to 46% of GC patients develop peritoneal recurrence after the surgery (8,12,14-19). While adjuvant chemotherapy (8,18), neoadjuvant chemotherapy (14,20) and adjuvant chemo-radiation (21) have all proven to marginally improve survival rates after curative surgery in GC, none of them have been shown to significantly decrease the rate of distant metastases, including peritoneal recurrence (21,22) or change the patterns of recurrence (23).

In general, literature and clinical experience demonstrates that GC patients with peritoneal involvement have a significantly reduced probability of tumor response to chemotherapy (15,24,25) with reported response rates of 14–25% (26-28). Nevertheless, the median survival with chemotherapy in patients with only PC from GC is 9.5–12 months (29,30). The relatively low response rate of systemic chemotherapy against peritoneal recurrence in AGC and the quest for a solution for longer term survival in GC with PC have led many to explore alternate methods of prevention and treatment of PC and the belief that PC is more locoregional than systemic involvement (31) has led to a resurgence of interest in regional therapies like cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

CRS and HIPEC have been associated with improved survival for patients with abdominal malignancies with peritoneal dissemination (32,33). However, CRS and HIPEC have also been criticized for perceived high rates of morbidity and mortality. In several large series of CRS and HIPEC for a variety of cancer types, the rates of grade III–IV morbidity range from 22–34% and mortality from 0.8–4.1% (34-38). The few existing large studies of HIPEC for GC suggest mortality rates may be around 3.6% and 6.5% in series involving 152 and 159 GC patients respectively (39,40): when compared to the morbidity in ovarian cancer (OC), the higher mortality observed with CRS and HIPEC for GC may be related to gastrectomy, while the lower mortality observed with CRS and HIPEC for OC may be due to fewer visceral resections on average than CRS and HIPEC for primary gastrointestinal cancers. Common major postoperative complications include neutropenia, digestive fistula, pneumonia, postoperative bleeding, intra-abdominal abscess, systemic sepsis, wound infection, and renal insufficiency.

There are a lot of studies whereby the benefits of CRS and HIPEC have been clearly been depicted and proven. Nevertheless, simultaneously there have been a lot of speculations about the risks involved in the clinical application of CRS + HIPEC: the polemic about the nature of this new multimodality practice needs to be addressed from various aspects namely the technicalities of the procedure, the basic requirements and overall status of the patients, the choice of chemotherapy regimen and the adaptation of new technologies in order to find out better solutions to this mixed blessing.

Henceforth, in this review, we will be highlighting the benefits and shortcomings of the CRS + HIPEC treatment plan in AGC patients while carefully scrutinizing and analyzing the various aspects of the procedure whereby better management and upgrading could eventually ameliorate the outcome while decreasing the morbidity and mortality rates involved with this treatment option.

HIPEC in the clinical management of AGC: the past and present

Weissberger first introduced the concept of intraperitoneal (IP) chemotherapy to treat peritoneal tumors as a localized disease in 1955. The concept of IP chemotherapy was brought forth in the American National Cancer Institute in 1970. In 1978, Dedrick (8) established the experimental model of the pharmacokinetics behind IP drug delivery and later in 1988, Fujimoto used hyperthermia can increase the efficacy of anticancer drugs. The combination of hyperthermia and IP perfusion chemotherapy during surgery started to get recognition in the treatment of GI cancers until in 2006 when IP chemotherapy for OC was listed as one of the major achievements of clinical oncology by ASCO.

HIPEC has three potential implications in the management of GC: first, as a prophylactic measure to prevent peritoneal recurrence after a curative gastrectomy in high risk patients; second, as a therapeutic measure in patients with established PC after CRS and; third, as a palliation in patients with intractable ascites due to extensive PC not suitable for CRS.

Currently, CRS with HIPEC is increasingly being

used as a curative treatment of pseudomyxoma peritonei, peritoneal mesothelioma and selected patients with colorectal PC (41-43).

CRS + HIPEC clinical experience: promising results

The GYMSSA study is a prospective randomized trial aiming to compare a promising new systemic chemotherapy regimen to CRS with HIPEC followed by systemic chemotherapy for patients with GC carcinomatosis (17): the systemic chemotherapy used in both arms was FOLFOXIRI [irinotecan, leucovorin, oxaliplatin, and 5-fluorouracil (5-FU)] whereby in the first treatment arm (SA), irinotecan 165 mg/m^2 administered for 90 min followed by leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 over 2 hours on day 1 with 3,200 mg/m^2 5-FU administered over 48 hours as a continuous infusion while patients in the second treatment arm (GYMS) underwent gastrectomy, metastasectomy of liver or lung if needed, CRS and HIPEC (oxaliplatin 460 mg/m^2 at 41 ℃ for 30 minutes) and then the patients were then started on FOLFOXIRI 8 weeks after surgery. The results showed that the median survival in the SA arm was 4.3 months and the GYMS arm 11.3 months with 4 of 9 patients living longer than 12 months.

Another interesting approach was a multimodal strategy with neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), CRS + HIPEC and post-operative intraperitoneal chemotherapy (EPIC) (21,22): The basic idea was reduce tumor burden before surgery and NIPS in patients with positive peritoneal cytology washings as a bidirectional chemotherapy attacking peritoneal disease from both the peritoneum and from subperitoneal blood vessels followed by CRS with HIPEC. The NIPS technique uses 60 mg/m^2 of oral S-1 for 21 days, followed by 1 week of rest. On days 1, 8, and 15, 30 mg/m^2 of taxotere and 30 mg/m^2 of CIS in 500 mL of normal saline are administered into the abdomen. All these approaches are currently being studied on large scale in different clinical trials around the world.

Initially, this regionally focused approach was built on the concept of maximizing drug delivery to the sites of tumor and metastases while simultaneously elongating the therapeutic window by reducing systemic toxicity. Indeed, in a large phase III clinical trial in colorectal cancer spread to the peritoneum, HIPEC and CRS extended median survival from 12.6 to 22.3 months (P=0.032) (17). Likewise, small trials have indicated an association with prolonged survival when applying this technique to AGC with PC (23-25).

In advanced cases PC of gastric origin is a condition with poor prognosis, with a mean survival range of 2.2–8.8 months and no 5-year survival probability (44). Neoadjuvant as well as adjuvant treatment showed a potential benefit in decreasing rates of PC (45). Initial studies showed that patients receiving chemotherapy intraperitoneally with mitomycin C (MMC), but also cisplatin and 5-FU had better OS after curative resection of locally advanced GC (46). After the first report by Fujimoto *et al.* (47) regarding HIPEC in patients with secondary PC, others have used that technique for PC originating from GC. In a study conducted on 107 patients treated with HIPEC, Yonemura *et al.* (48) showed that patients who underwent complete resection had better 5-year survival (13%) than those with residual disease (2%). The extent of radical resection was an independent prognostic factor (49,50). In a French multi-institutional study on 159 patients, the 5-year survival rate of subjects undergoing radical resection and HIPEC was 23% (42), a relatively satisfying result. However, it should be emphasized that only a small proportion of patients who underwent complete macroscopic CRS (R0 or R1) had a chance of survival in that study.

In a meta-analysis by Xu *et al.* (51), 7 out of 11 randomized clinical trials compared surgery with HIPEC *vs.* surgery alone: IP chemotherapy was superior after curative surgery *vs.* surgery alone, and the combination of HIPEC and activated carbon particles was significantly better than other drug combinations. The second meta-analysis conducted by Yan *et al.* (52), reviewed all clinical trials of IP chemotherapy: all data form 1,648 patients showed a significant difference in survival of patients treated with HIPEC, or HIPEC together with EPIC. A trend toward survival improvement was observed with HIPEC. No benefit was seen using EPIC or DIPEC. In our opinion, the addition of HIPEC may provide a survival benefit in patients at high risk of PC after gastrectomy, such as patients with diffuse-mixed type, serosal invasion, or positive peritoneal cytology. HIPEC is an effective treatment in patients with FCCs and cancer microfoci, but becomes less effective as the tumor size increases, and the disease is disseminated (45). A new trial is ongoing to prove the effectiveness of HIPEC during curative gastrectomy in case of positive peritoneal cytology (GASTRICHIP trial). This new perspective can probably assist wider usage of HIPEC to prevent further PC.

The earliest report of the use of HIPEC as an adjuvant

treatment to prevent peritoneal recurrence was by Koga *et al.* (53) from Yonago, Japan in 1988: they reported two studies, the first a historical study comparing 38 GC patients with serosal invasion who underwent curative surgery followed by HIPEC using MMC with a control group of 55 patients who underwent curative surgery without HIPEC. They found that the HIPEC group had a significantly improved 3-year survival (74% *vs.* 53%, P<0.04) with fewer peritoneal recurrences (36% *vs.* 50%) respectively. Subsequently, they performed a randomized study in which patients were chosen to undergo curative surgery with HIPEC or only surgery: here also, they found that patients who received HIPEC had a trend towards a better 30-month survival compared to the control group (83% *vs.* 67%) although this was not statistically significant.

Fujimoto *et al.* (54) reported a prospective study of 59 patients, 32 of whom had advanced GC without PC who underwent curative surgery. The 2-year survival of the 10 patients who received HIPEC was significantly higher than that of the 20 patients who did not (56.5% *vs.* 12.9%, P=0.01). While no patient in the former group developed peritoneal recurrence, eight patients in the latter group died due to peritoneal recurrence.

Yonago from Japan reported about a study on 82 patients who were randomized to receive HIPEC or no HIPEC after curative resection of GC (55). IFCCs were detected in 23% and 15% of the HIPEC and control group respectively. There was a non-significant trend towards improved 5-year survival (64% *vs.* 52%) and reduced death due to peritoneal recurrence (39% *vs.* 59%) in the intervention group compared to the control group.

There have been various randomized controlled trials comparing HIPEC *vs.* no HIPEC in patients with locally advanced GC who underwent a potentially curative resection (56-60). A majority of them were conducted in Asian countries and have been published in Japanese and Chinese languages. In a small study, Yonemura *et al.* (61) reported a 5-year survival of 42% in 15 patients with Cy+/P0 disease after gastrectomy + HIPEC. During the period 1992–2002, 128 GC patients with peritoneal dissemination underwent surgery in our hospital were included in an HIPEC experiment and the 5-year survival rates were 5.5% for patients in the resection group and 0% for patients in the non-resection group (P<0.001). In the patients who underwent resection, the survival difference between the resection alone and the resection with HIPEC groups was significant (P=0.025), and HIPEC was an independent prognostic factor by multivariate analysis (62). In another trial from our faculty, 118 advanced GC patients with serosal invasion were enrolled from 1998 to 2001 amongst whom 96 patients without macroscopic peritoneal metastases were selected for prophylactic study, including 42 cases with HIPEC and 54 cases without HIPEC as control while other 22 patients with macroscopic peritoneal metastases were selected for therapeutic study, including 10 cases with HIPEC and 12 without HIPEC. The postoperative survival rate and peritoneal recurrence were compared. For prophylactic study, the 1, 2 and 4 years survival rates were HIPEC 85.7%, 81.0% and 63.9%, non-HIPEC: 77.3%, 61.0% and 50.8%. The overall 1, 2, 4 years survival rates: HIPEC: 76.9%, 69.2% and 55.2% while for the non-HIPEC: 66.2%, 49.7% and 41.4%. The peritoneal recurrence was control *vs.* HIPEC group 34.7% *vs.* 10.3% (63).

CRS and HIPEC have been used in three situations in GC: besides its role as a definitive curative treatment in GC patients with established PM, it has been used as a prophylaxis against PC after curative surgery and also as a palliative treatment in advanced PM with intractable ascites. While prophylactic HIPEC has been shown to reduce peritoneal recurrence and improve survival in many randomized trials, palliative HIPEC can reduce the need for frequent paracentesis.

The GASTRICHIP study is a phase III randomized European multicentre study evaluating the role of HIPEC with oxaliplatin in patients with GC who have either serosal infiltration and/or lymph nodal involvement and/or positive peritoneal cytology treated by a curative gastrectomy (64). The primary aim of the study is the 5-year overall survival (OS) while the secondary outcome measures include the recurrence free survival, patterns of recurrence, quality of life and morbidity. Another trial is being conducted by the European Network of Excellence on GC. In this trial, patients with high risk GC will receive three cycles of neoadjuvant systemic chemotherapy followed by a D2 gastrectomy and then randomized to receive HIPEC or no HIPEC (65).

Currently, there are a series of phase II and III clinical trials going on around the world with the solemn objective of evaluating the role of HIPEC as a prophylactic approach in the management of GC patients with serosal invasion.

The benefits and advantages of CRS + HIPEC in clinical application

As a multimodality approach to control AGC with

serosal infiltration, CRS + HIPEC have shown better aptitude in the prophylactic clinical management of AGC with no macroscopic PC lesions or intractable ascites. The benefits of HIPEC in this matter can be further categorized as per the main components of this procedure, hence, continuous perfusion, chemotherapy and hyperthermia.

Mechanical erosion of free cancer cells (FCCs) in the peritoneal cavity

Kuramoto *et al.* (41) have shown the value of mechanical cleansing of the peritoneal space with a large volume of fluid whereby they have used extensive intraperitoneal lavage (EIPL) to improve the survival of GC patients with high risk for implantation of GC cells. Hence, based on their findings and the results of other studies (32,41) that have suggested the presence of FCCs in the peritoneal lavage after GC radical surgeries, the effect of continuous perfusion inducing continuous mechanical erosion in addition to the hyperthermia and cytotoxicity would play a pivotal role in the prevention of PC in GC.

Direct peritoneal chemotherapy

The direct drug delivery to the site of cancer cell population in the abdominal cavity increases the reaction rate and contact between the chemotherapy drugs and the cancer cells. As a result of the peritoneum-plasma barrier (PPB), the level of drugs in the abdominal cavity is 20 to 1,000 times higher than the level of plasma. Hence, the long span of contact and high concentration of the drug increase the efficiency of the chemotherapy drugs (42). However, in addition to the direct drug delivery system in open laparotomy, there have been advances in the minimally invasive surgical techniques, allowing for the introduction of the laparoscopic HIPEC therapy. In terms of efficacy, an animal study demonstrated increased drug perfusion with the laparoscopic technique (66,67).

Absorption by the peritoneum and circulatory system

The high concentration of drugs in the abdominal cavity is slowly absorbed by peritoneum and to the circulatory system by the portal vein and retroperitoneal lymphatic vessels, which is very consistent with GC route of metastasis, hence further influencing micro-metastases in the lymphatic system and liver (68).

Hyperthermia can inhibit the activity of DNA repair enzyme, suppressing the cell repair of the tumor cells post-chemotherapy

By inhibiting essential nuclear functions such as DNA replication, transcription and repair, hyperthermia can influence the inductive function of the nuclear matrix, hence selectively killing tumor cells while simultaneously enhancing the cytotoxicity of chemotherapeutic agents and improve the drug penetration. Thus, the multiple roles of HIPEC thermal effect is that the hyperthermia can inhibit cancer angiogenesis at the tissue level, the tumor cell degeneration and necrosis, the self-stabilization mechanism, activation of lysosomal, cytoplasm and nuclear destruction, hence inducing cell apoptosis, cancer cell membrane protein denaturation by interfering in DNA and RNA synthesis (69).

Research shows that normal cells can continue to bear up to 47 ℃ for 1 hour under high temperature conditions while malignant tumor cells can only tolerate a maximum of 43 ℃ for 1 hour, hence the respective critical temperatures whereby normal tissues and malignant tumor cells would incur irreversible damage. Hyperthermia mediates tumor cell apoptosis by altering and inhibiting DNA replication, transcription and repair essential guide function in the nuclear matrix (70).

Hyperthermia increases membrane permeability

Although IP delivery does cause local drug concentration, but the drug penetration to tumor tissue penetration is still limited while the warming effect causes changes in the structure of the cell membrane, hence increasing permeability of the membrane. Jacquet *et al.* (71) reported increased tissue penetration of doxorubicin when the cancer chemotherapy solution was administered intraperitoneally at 43 ℃. This increase in tissue concentration did not affect the pharmacokinetic advantages of the IP administration. The elevated interstitial fluid pressure in tumor nodules compared to normal tissue is an acknowledged phenomenon (72,73).

Thermodynamic effect can significantly enhance the response rate of target molecules and boost up cytotoxicity

The thermodynamic effect can accelerate the reaction and combination of chemotherapy and cancer cells, enhancing the pharmacokinetic properties and synergia of the drug, hereby improving the response rate of the target cells to the chemotherapy drugs. The combined application

of hyperthermia and chemotherapy has a significant synergistic effect (17-21). Hyperthermia can eliminate and inhibit the ability of some oncogenes in the target cells to control cellular uptake and drug excretion, hence decreasing drug excretion while increasing the cumulative drug concentration. All along with the inhibition of damage repair caused due to chemotherapy with the changes in the blood circulation in the tissues surrounding the target cancer cells, hyperthermia catalyses the process and enhances the effects of the IP chemotherapy. However, the level of hyperthermia must be matched to the IP cancer chemotherapy agent, for example with cisplatin, the higher the temperature, the greater the cytotoxicity (74).

Laparoscopic HIPEC

In the present medical environment where there is a constant quest for minimally invasive procedures, two recent cohorts of patients treated with laparoscopic CRS and HIPEC versus laparotomy presented no significant differences in postoperative morbidity and mortality between the two approaches, identifying laparoscopic HIPEC as a safe and efficient alternative (67,75,76).

In short, the inclusion of factors such as continuous perfusion, IP chemotherapy and hyperthermia to the surgical and systemic chemotherapeutic management of AGC patients can improve the thermodynamics and pharmacokinetic response of IP drugs, hence improving overall therapeutic response rate.

The current limitations and drawbacks of CRS + HIPEC in clinical application

Prophylactic HIPEC vs. curative HIPEC

Although the effectiveness of CRS + HIPEC has been proven both experimentally and clinically, there is still room for improvement. Firstly, a significant proportion of patients still develop recurrent disease (as mentioned before): even though in past literature, CRS + HIPEC has shown significant amelioration in the OS rate and progression-free survival (PFS) in AGC patients with serosal infiltration, there has however been a lot of reports about such patients relapsing with PC after the procedure. In studies carried out around the world, there has been a lot debate about the curative use of HIPEC in the management of PC. Hence, as far as the efficacy of this multi-modality treatment plan is concerned, it would be safer to affirm its role as a prophylactic approach in the management of AGC. There are currently a lot of studies, including two from our institute (62,63), that have evaluated the role of CRS + HIPEC in the prophylactic, curative and palliative management of AGC and the results of the most studies have given more credit to the prophylactic approach.

Laparoscopic HIPEC vs. open HIPEC

The main disadvantage of performing HIPEC by closed technique is the improper drug distribution and consequently pooling of drug in isolated areas contributing to focal hyperthermic injury. However, its advantage lies in minimal exposure of chemotherapy agents to theatre personnel and safe disposal of chemo agent back to the circuit in a closed system (76). The consensus statement issued by the Peritoneal Surface Oncology Group International after the summit in Milan in 2006 reached the conclusion that the best technique to deliver HIPEC is yet the open one, without sufficient evidence in the literature to prove the superiority of one technique over the other regarding outcome, morbidity, and personnel safety (77,78). A study by Facy *et al.*, conducted on a swine model, reported that increased intra-abdominal pressure when applying the closed HIPEC technique resulted in tachycardia, a decrease in blood pressure despite more aggressive fluid resuscitation, and an increase in ventilation pressure (79). Therefore, even though the requirement of minimally invasive procedure makes it more attractive to opt for laparoscopic maneuvers, but however the laparoscopic approach does not guarantee lower morbidity or any improvement in the complications of the procedure. Instead, the laparoscopic feature does not allow uniform distribution of the perfusate and temperature in the peritoneal cavity, which is indeed a prerequisite for this procedure.

HIPEC equipment

The HIPEC procedure is mainly based on perfusion, hyperthermia and chemotherapy. For the time being, the availability of proper and precise instrumentation allowing for constant flow with constant temperature without affecting the exposed anatomy of the surgical sight still is a major problem. Dedicated perfusion devices are not readily available in most hospitals. The basic requirements for continuous perfusion and stable temperature are

prerequisite for the success of the procedure. In earlier studies, there were reports of HIPEC equipment failing to demonstrate better control of fluid flow and temperature which in the end, added up to the morbidity related to the procedure itself. Hence, the lack of such FDA approved equipment on the medical market brings about a lot of speculations about the feasibility of this procedure, not to mention the cost affiliated with the latter.

Drug clearance and absorption

Regional chemotherapy, such as IP chemotherapy, has the pharmacokinetic advantage of an increased ratio of the peritoneal-to-plasma area under the curve (AUC) to the tumor-containing peritoneal cavity (80,81). Despite this pharmacokinetic advantage, the clinical use of IP therapy has been challenged by the premature clearance of a small molecular weight drug from the peritoneal cavity, a lack of target specificity, and poor drug penetration into the target tissues (82). The currently available drugs which are display acceptable synergy under hyperthermic conditions however have a lower peritoneal to plasma AUC value, meaning that they get cleared off the peritoneal cavity faster than they can actually influence the target sites. Hence, it is yet a priority to find new technologies or new pharmacokinetic strategies to improve drug retainment in the peritoneum, optimizing the reactions between the drugs and the target sites.

Incomplete cytoreduction

As promising as these results appear for a condition that is usually considered lethal, not all patients achieve these survival benefits. Even for patients in whom a complete cytoreduction is achieved, the risk of cancer recurrence can be quite high depending upon the primary cancer. Oftentimes the expectation from the time of surgery is that the CRS/HIPEC will be therapeutic, but not be curative. The current literature suggests that HIPEC in the setting of an incomplete cytoreduction does not offer any advantage in terms of OS (83). In light of this, Elias and Goéré have gone so far as to say that it is "unethical, dangerous, costly and finally reprehensible" to perform HIPEC in patients with an incomplete cytoreduction due to the added morbidity of the procedure (84).

Procedure related morbidity

The main toxicities reported from this multimodality approach are neutropenia, particularly in the early post-operative period, as well as GI toxicity, including leaks and fistulas. There are quite a number of studies reporting hardly any leaks or no severe GI toxicity while others, such as the GYMSSA trial, had a high (>20%) 90-day mortality rate with a limited number of patients receiving the planned adjuvant FOLFOXIRI chemotherapy. There was no detectable correlation identifiable between the type of IP chemotherapy administered and post-procedure complications. All studies do recommend for these procedures to be performed at high volume peritoneal surface malignancy centers. The most common complications include bleeding, wound infection, sepsis, abscess, anastomotic leakage, perforation, fistula formation, ileus, renal insufficiency, thromboembolic episodes, pleural effusion, and chemotherapy-related hematologic toxicity (85,86). Intraoperatively unrecognized small-bowel damage is a major cause of postoperative morbidity. Nevertheless, past literature has not been able to properly differentiate the morbidity to the surgical procedure itself and the HIPEC procedure. Hence, currently, there are a series of controlled clinical trials going around the world to validate the efficacy and risks associated with this procedure.

Hemodynamic parameters and related morbidity

Pascual-Ramírez *et al*. did not detect any difference in hemodynamic parameters during CRS and HIPEC when describing the closed technique in OC patients. Nevertheless, in the Pascual-Ramírez series there was not a rise in body temperature or a disturbance in renal function, consistent with the study by Schmidt *et al.* (65,87). A retrospective analysis of 78 patients undergoing CRS and HIPEC demonstrated a large intraoperative fluid turnover, increased airway pressure, and central venous pressure (due to the increased intra-abdominal pressure with the closed technique), while increased body temperature resulted in a mild metabolic acidosis (88). According to the findings of another prospective study of 60 patients, hemodynamic disturbances occurred during HIPEC administration, characterized by an increase in heart rate and cardiac output and a decreased systemic vascular resistance on account of increased body temperature and decreased effective circulating volume (89,90).

Choice of the drugs

The choice of the chemotherapeutic drug to be used during

HIPEC is very crucial. In short, the agent should not cause local toxicity and should not require metabolization into its active form (usually in the liver). It should also be directly cytotoxic, have well-established activity against the malignancy being treated, and demonstrate a pharmacokinetic advantage after IP administration, with high locoregional drug exposure and limited systemic toxicity. A synergistic effect with heat is preferred, because increased temperature can enhance the responsiveness of tumor cells to cytotoxic agents. More favorable pharmacokinetics and thermal enhancement can make a systemically less-effective drug highly advantageous for IP chemotherapy.

Post-operative quality of health

Recent systematic reviews (91,92) and a meta-analysis (90) of fifteen studies (1,583 patients), demonstrated that health-related quality of life declines immediately after. However, at 6–12 months after the procedure, health-related quality of life improves from its preoperative level. However, after 1 year, the postoperative scores on the Functional Assessment of Cancer Therapy and the European Organization for Research and Treatment of Cancer quality-of-life questionnaire were significantly improved for overall health status and emotional health. The indicated benefits could persist for up to 5 years. Evidence about health-related quality of life compared with reference populations is inconclusive.

Risk of medical personnel exposure

In a study by Villa *et al.* (91), air and surface contaminations and internal contamination of healthcare workers during open-abdomen HIPEC using oxaliplatin were evaluated: Platinum (Pt) was measured in urine of exposed workers and in multiple air and surface samples and the results showed that the air samples did not detect any oxaliplatin contamination, however, heavy contamination of the operating table, the floor at the surgeon's feet, and the surgeon's overshoes was observed. Hand contamination was observed in surgeons using double gloves for intra-abdominal chemotherapy administration, but not in those using three sets of gloves. Pt was not detected in urine samples obtained after HIPEC. The main risk of HIPEC is related to direct or indirect skin exposure and can be prevented by correct use of adapted protective equipment.

CRS + HIPEC: broader clinical acceptance prompts for better control and management

Based on the past literature proving the efficiency of CRS + HIPEC, there has been a lot of questions raised on the safety and feasibility of the procedure based on some unbiased reports. It is not to be denied that the prevailing rate of procedure related morbidity id alarming, but still better clinical management and close patient follow-up could be able to control the situation. In studies carried out in other parts of the world, or in our faculty itself, we haven't noticed an increased rate of procedure related morbidity in the small scale trials conducted. Yet it is to be emphasized that the personnel to be handling the whole process should be properly trained and bestows the proper expertise to carry out the experiment. From the surgical staff to the surgeons and anesthesiologists, all the members need to properly equipped and trained for the matter. The procedure related morbidity, on the other hand, not only relies on trained personnel, but also on good handling of the whole HIPEC unit. On basis of a complete cytoreduction, the proper and careful use of HIPEC should bring around pleasing results.

Regional chemotherapy, such as IP chemotherapy, has the pharmacokinetic advantage of an increased ratio of the peritoneal-to-plasma AUC to the tumor-containing peritoneal cavity. Despite this pharmacokinetic advantage, the clinical use of IP therapy has been challenged by the premature clearance of a small molecular weight drug from the peritoneal cavity, a lack of target specificity, and poor drug penetration. The combination of nanotechnology and regional chemotherapy, that is regional delivery of nanomedicine, may compensate for each other's limitations. This combination may potentially present several advantages. First, the regional delivery of a nanomedicine may have dual pharmacokinetic advantages and second, the application of hydrophobic, poorly water-soluble chemotherapeutic agents for regional delivery is associated with serious problems of poor absorption and low bioavailability. The advent of nanotechnology can improve the aqueous solubility of poorly soluble drugs and thus may introduce more candidate drugs for the application of regional chemotherapy (92). Third, the anticancer activity of some conventional drugs, such as 5-FU, gemcitabine, paclitaxel, and camptothecin, is primarily cell cycle-dependent, resulting in the requirement of prolonged exposure times (93). The sustained-release function of nanomedicines may overcome this inherent limitation.

Therefore, the use of proper advanced drug delivery systems (DDS) in the application of HIPEC might bring along a better control of the concentration, target range and duration of the whole process, hence prompting for more lucrative results.

Conclusions

In summary, 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. However, most of these RCTs have been conducted in Asian countries and the data from the western world is scarce. CRS + HIPEC have been considered to be the optimal treatment options for selected patients with GC with PC. Accumulating evidence suggests that the administration of IP chemotherapy for GC patients with PC may improve the patient survival. The pharmacokinetics of such treatment should be considered to optimize IP chemotherapy. In addition, newly emerging molecular-targeted therapies and research into new DDS, such as nanomedicine or controlled absorption/release methods, are essential to improve the effects of IP chemotherapy. This review summarizes the current status and future prospects of IP chemotherapy for the treatment of gastrointestinal cancer.

There are still some unresolved issues in the use of HIPEC as an adjuvant treatment in GC- choice of drug, dosage, duration of treatment etc., for which there is no consensus. Hence, the widespread acceptance and adoption of prophylactic HIPEC in advanced GC requires more concrete and evidence based answers to these questions.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2016.08.05
Cite this article as: Beeharry MK, Liu WT, Yao XX, Yan M, Zhu ZG. A critical analysis of the cytoreductive surgery with hyperthermic intraperitoneal chemotherapy combo in the clinical management of advanced gastric cancer: an effective multimodality approach with scope for improvement. Transl Gastroenterol Hepatol 2016;1:77.

