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Hyperthermic intraperitoneal chemotherapy and colorectal cancer: From physiology to surgery

Ammerata G *et al.* HIPEC and CRC

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Abstract

The pursuit of this study is to collect principal reviews and systematic reviews about hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) used in colorectal cancer (CRC). We focused on principal biological aspects of CRC, hyperthermia effects and surgical procedures. We searched on PubMed, (MEDLINE) the principal reviews and systematic reviews from 2010 to 2021 regarding the bimodal treatment (CRS + HIPEC) against local and advanced CRC. In literature, from several studies, it seems that the efficacy of bimodal treatment with an accurate CRS can extend overall survival. Despite these studies, there are no still any straight guidelines more detailed and scheduled about the use of combined treatment in patients with CRC. Even if the concept still not very clear and shared, after a careful evaluation of the published data, and after some technical and pathophysiological descriptions, we concluded that it is possible to grow the overall survival, quality of life and to reduce the tumor relapse in patients affected by locally advanced (pT4) CRC with peritoneal metastases.

Key Words: Hyperthermic intraperitoneal chemotherapy; Colorectal cancer; Peritoneum; Cytoreductive surgery

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Core Tip: The purpose of this review is to summarize the most relevant evidences on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer and to specify the main properties of HIPEC and its application.

INTRODUCTION

The synergistic anti-tumor effects of heat and intraperitoneal chemotherapy, have been known to be effective since decades and is now well known as hyperthermic intraperitoneal chemotherapy (HIPEC); this strategy is based, firstly, on hyperthermia, secondly, high intraperitoneal concentration of chemotherapy (IP).

Originally, hyperthermia was introduced by Spratt *et al*^[1] who demonstrated the benefit of heated IP perfusion in canine models; furthermore, the first prototype IP therapy filtration system was designed and tested by Palta *et al*^[2].

HIPEC is based on the physiological effect of the "peritoneal-plasma barrier": while peritoneal surface malignancies (PSM) cannot be effectively reached by intravenous chemotherapy^[3], these tumors can benefit from intraperitoneal administration of high-dose cytotoxic drugs in direct contact with tumor cells, combining the effect of hyperthermia and minimizing the systemic toxic effects of drug reabsorption.

The first treatment of HIPEC was described in 1979 for the treatment of recurrent peritoneal pseudomyxoma (PMP) after previous cytoreductive surgery (CRS)^[4]; subsequently, Sugarbaker *et al*^[5,6], compared the use of 5-fluorouracil IP with systemic therapy for colorectal cancer (CRC) and appendiceal cancer to show the benefits of IP chemotherapy^[7-10]. During the years, HIPEC was become a new option of care for different tumors with peritoneal metastases (PMs): CRC, appendiceal cancer, ovarian cancer (OC), gastric cancer (GC) and peritoneal mesothelioma^[11,12].

Later, HIPEC was also performed in the treatment of PSM from GC and OC: in 1988 Fujimoto *et al*^[9], reported the effects of HIPEC on patients with PMs from GC and in 1996 Yonemura *et al*^[13], showed a 5 year survival of 11% in a cohort of 83 patients undergone to CRS and HIPEC from GC; moreover in 1989 HIPEC was used for peritoneal lesions from OC^[14].

Since the 1990s, CRS combined with HIPEC has been a treatment option for PSM; today, CRS and HIPEC represent the standard of care for PMP and peritoneal mesothelioma^[15]. In particular, regarding the combination of CRS plus HIPEC in CRC, there were several clinical trials about this specific combined treatment; nevertheless,

this option of treatment remains a debated topic. Ceelen^[16], firstly, described the efficacy of CRS + HIPEC in peritoneal carcinomatosis arising from CRC. Later, numerous studies have been conducted until nowadays, reaching a better use of the bimodal treatment. For instance, Birgisson *et al*^[17] studied the use of the peritoneal cancer index (PCI) like prognostic factor in patients affected by PMs from CRC and treated with CRS + HIPEC.

Rosa *et al*^[18], showed the clinical outcomes in 67 patients affected by CRC, focusing on the complete cytoreduction of PMs and calculating the median overall and disease-free survival.

Moreover, Elias *et al*^[19] showed the results of HIPEC plus second look surgery in selected patients, increasing their 5 year-overall survival to 90%.

However, despite several studies on this topic, there is still no consensus on the indication of CRS combined with HIPEC in CRC.

The purpose of this review is to summarize the most relevant evidences on the use of HIPEC in CRC and to specify the main properties of HIPEC and its application.

MATERIAL AND METHODS

In this narrative review, we have searched the key-words on PubMed, free online biomedical database, developed by the National Center for Biotechnology Information at the National Library of Medicine (NL: “Colo-rectal Tumor” and “HIPEC”, “Colo-rectal Cancer” and “HIPEC”, “HIPEC”, “Hyperthermic Intraperitoneal Chemotherapy”, “Hyperthermia and HSPs”, “Hyperthermia and Tumor”, “Hyperthermia and Cancer” (Figure 1). We have collected the reviews and systematic reviews from 2010 to 2021 and we have analyzed the principal clinical studies about the management of PMs arising from CRC (Table 1; Figure 2). This current work, has focused the attention on HIPEC, from its first uses to now, looking at principal uses in different tumors like gastric, ovarian and colo-rectal. Moreover, the review explains in details the biologic HIPEC effects on tumoral cells and the latest clinical trials regarding locally advanced colo-rectal cancer tumors describing CRS technique step by step.

HIPEC AND CRC

CRC is a big killer, representing the third most commonly diagnosed malignancy worldwide; it represents ⁴ the third most common cancer in men (746000 cases; 10 % of the total) and the second in women (614000 cases; 9.2 % of the total)^[20]. Surgery represents the elective therapy for resectable CRC (to gain $r = 0$); instead chemotherapy, radiotherapy or the combination of both have indication for neoadjuvant and adjuvant purposes^[21].

CRC most frequently metastasizes to the liver and peritoneum. PMs from CRC are tumoral deposits on the peritoneal surface, originating from the primitive cancer. PMs originated from CRC can cause several and severe complications like: bowel and ureteral obstruction, malignant ascites^[22-24].

There are a variety of chemohyperthermia protocols in the literature, but in general they consist of intraperitoneal infusion of different drugs at a particular range of temperature and pressure for a definite time at the end of surgery to eradicate the residual microscopic tumor tissue^[25,26].

Today, HIPEC after CRS is still considered an investigational treatment for CRC-originated PMs, but its role is not yet defined.

HIPEC AND PHYSIOLOGICAL MECHANISM

HIPEC for PMs from CRC, has some technical specific parameters like temperature, drugs and pressure.

Mitomycin-C (MMC) is administered as monotherapy in a large majority of protocols^[11,27-29] or in combination with cisplatin^[30-34]. The second most commonly used drug in monotherapy is oxaliplatin or also in combination with irinotecan. MMC gives higher efficacy as a single agent administered at a dose of 35 mg/m²^[35-40], although the dose of MMC can be modified from 10 to 40 mg/m²^[41].

Establishing the drug dose is the cornerstone for even distribution of chemotherapy; some institutions use an approach called body surface area-based and others use a

concentration-based approach. These approaches have some limitations such as gender and the presence of malignant ascites, but both attempt to find a conventional dose^[42].

High temperature is a key issue; there are three temperature ranges that classify the type of hyperthermia: fever hyperthermia (39-40 °C), mild hyperthermia (heat shock temperature 41-43 °C), and thermal ablation (cytotoxic temperature, > 43 °C).

Focusing attention on biological aspects, it is necessary to discuss about hyperthermia effects on tumor tissue. Hyperthermia has an important role in different paths like apoptosis regulation, neoangiogenesis and immune status of the tumor. For example, hyperthermia induces DNA damage response by activating single strand break, double strand break, histone H2AX with phosphorylated C-terminal serines (γ -H2AX) foci formation and ataxia-telangiectasia mutated protein phosphorylation, and by decreasing DNA replication and repair.

Indirectly hyperthermia activates DNA damage response and induces tumor suppressor alternative reading frame by starting reactive oxygen species (ROS) production, cell cycle arrest, cell cycle checkpoint arrest, cell death; in addition hyperthermia decelerates DNA replication.

Hyperthermia can also damage cancer stem cells exceeding conventional therapeutic regimens, so it is used in combination with chemotherapy or radiation to results in non-reversible damage to tumor cellular DNA^[43].

Specifically, fever range hyperthermia can alter cell membrane fluidity and stability, changing cell shape and affecting intracellular sodium-calcium levels^[44]; moreover, it recruits heat shock proteins (HSPs) and endoplasmic reticulum (ER) stress (type II) at the same time^[45].

ER stress and ROS (type I) activate immunogenic cell death (ICD) and promote, through specific signals “eat me” and “enabler”, the recruitment of immune cells. Definitely hyperthermia can be considered an inducer of ICD and a powerful change of tumor microenvironment (TME)^[46-48].

A range of heat shock temperature recruits different molecules like L-selectin, P-selectin, intracellular cell adhesion molecule-1 in the vessel wall, and causes the

production of pro-inflammatory cytokines and chemokines [interleukin (IL)-1 β , IL-6, IL-8, IL-10 and C-C class chemokines 22]^[49-52]. These cytokines “storm” facilitates the infiltration of lymphocytes in TME and provides to trigger an immune cascade against solid tumor.

Many HSPs¹⁶ are expressed on the surface of different types of solid and haematological tumors, a high concentration of mHSPs, is associated with tumor progression and resistance to anti-tumour therapies, but under stress (for example anoxia and hyperthermia) HSPs can modify their relationship with tumor. Hyperthermia, in this sense, becomes an inducer of HSPs, it rapidly regulates different heat shock factors in tumor cells and activates HSPs, and in particular leads HSPs’ translocation to nucleus and their synthesis by an autocrine loop^[53].

HSPs constitute a large family of proteins, acting as molecular chaperones; they reside in three intracellular compartments such as cytosol, nucleus and plasma membrane or in the extracellular space. For example, Hsp 70, localized¹⁹ on the plasma membrane of tumor cell in CRC^[54], facilitates cross-presentation² of antigenic peptides via major histocompatibility complex class I molecules and determines the consecutive induction² of a CD8+ T cell-mediated immune response. Regarding to CD8+ T cells differentiation and function of cytotoxicity are both temperature sensitive, in fact hyperthermia can promote² antigen-specific naïve CD8+ T cell differentiation and can increase cytotoxic potential of T cells and memory stem T cell generation. Moreover, chaperones of Hsp 70 family, can activate the proliferation of natural killer cells even without immunogenic peptides^[55].

There is no univocal standard on the temperature to be used during HIPEC: a range from 38.5 °C to 44 °C is reported in the abdomen with an average value that is usually considered close to 42 °C. However, it is essential that the temperature does not exceed thermal ablation to avoid systemic toxic effects.

CRS: STEP BY STEP

CRS has a curative intent and consists of a complex series of steps, which aim is to achieve a radical visceral and parietal peritonectomy to eliminate the macroscopic visible tumor nodules, leaving a most microscopic residual tumor tissue. It is important to consider cancer histopathology, radiological imaging, and PCI to plan the best surgery^[56-58].

The patient is in lithotomic position, supine with legs extended and laid on St. Mark's holders and arms beneath the torso.

The tools used in CRS are based on electrosurgery and electro-evaporation, specifically it is usual to use ball-tipped electrosurgical handpiece to minimize blood lost.

The median incision is from xiphi-sternal junction to pubis; at this point, if tumor nodules are visible, the surgeon can start with parietal peritonectomy or rather separating parietal peritoneum from the inferior surface of the anterior abdominal wall. The dissection of visceral peritoneum starts generally from bottom to top.

Omentectomy is often necessary and sometimes mandatory in order to better explore the peritoneal cavity.

CRS continues with dissection of the left hypochondrium: We start by dissecting the peritoneum behind the rectus muscle to the left diaphragmatic dome and mobilizing the left colic flexure, thus exposing the diaphragm with its vessels and exposing the spleen, which can be removed, if it is infiltrated by neoplastic tissue.

The approach to the right side is mirrored by the contralateral; it is essential to totally mobilize the liver from its peritoneal attachment, particularly the right and left triangular ligament, the falciform ligament, and the teres hepatic ligament; sometimes the Glisson's capsule must be fulgurated if cancerous deposits are present.

As for the small intestine and its mesentery, it is important to free them and completely inspect them because if they are involved by the tumor, the surgeon will remove the affected part. The colon is another elective situs of peritoneal carcinomatosis, particularly the fusion layer between parietal and visceral peritoneum of the right colon. Sometimes it is necessary to proceed to partial or total colectomy.

The pelvic peritonectomy is another important step in CRS. Two anatomic structures represent the polar star in this part of pelvic dissection: posteriorly the ureters and anteriorly the muscular portion of bladder.⁵ The right and left ureters are identified and preserved, in the woman the ovarian vessels are ligated at the lower pole of the kidney, otherwise in men, the testicular vessels are avoided from the surgical field. After these procedures, it is usual to execute in woman hysterectomy with colic resection and in men an anterior resection of rectum. If there were some visceral resection, the surgeon will restore intestinal functions with anastomoses or stomas^[59].

PROTOCOLS OF HIPEC FOR CRC

Nowadays there are two attitudes to execute HIPEC: In closed or in open abdominal cavity (also defined coliseum technique)^[60,61]

Close technique implies the insertion of two inflow drains under the left and right diaphragmatic cupola and an outflow drain in the pouch of Douglas. Temperature probes are also inserted within the abdominal cavity (behind the liver pedicle and near the first jejunal loop). Other temperature probes are set up outside the abdominal cavity on the inflow and outflow drains and inside the bladder within a Foley catheter. As a final step there is a closure of laparotomy incision and the inflow and outflow drains are connected to a closed sterile circuit. Also, in this case there are no specific evidences that suggest which technique is better than other, probably closed technique reduces risks of exposure of drugs to the personnel^[62].

The intraperitoneal chemotherapy after cytoreductive surgery trial compared the benefit of HIPEC with early, post-operative, normothermic IP chemotherapy (EPIC) in patients affected by colo-rectal cancer and undergone optimal CRS.

Enrolment began in March 2013 with completion date of March 2018 at Memorial Sloan Kattering Cancer Center and were given MMC in HIPEC and floxuridine in IPEC.

The outcome measure¹ of the study is disease-free survival, within 3 years, though secondary measures monitor surgical and chemotherapy -related toxicities up to 60 days post-operative^[63].

The PRODIGE7 study, a randomized, multicentre, phase III trial at the Institut di Cancer Val d' Aurelle (Monpellier, France), started to evaluate the benefit of HIPEC to complete CRS.¹⁴

The recruitment of 270 patients with CRC and limited peritoneal dissemination was completed in 2013. Patients, undergone to CRS, were randomized intraoperatively to receive HIPEC or saline lavage only.¹ In this study, oxaliplatin (460 mg/m²) in 2 L/m² of dextrose 5% over 30 min at a temperature of 42 °C was used. One hour before the HIPEC, 20 mg/m² of leucovorin and 400 mg/m² of 5-fluorouracil were given intravenously in HIPEC-arm^[64].

CAIRO-6 study, similarly to the previous study, focused on the role of perioperative systemic therapy on survival in patients undergoing CRS and HIPEC for CRC. This phase II/III study randomized patients to undergo neoadjuvant therapy intravenously with 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) or capecitabine, oxaliplatin (CAPOX) with bevacizumab followed by CRS and HIPEC, then adjuvant systemic therapy with FOLFOX and CAPOX^[65].¹⁰

The control arm is represented by CRS and HIPEC only. Both the studies confirm the importance of full CRS in patients that received systemic chemotherapy.

The ProphyloCHIP-PRODIGE 15 (France) study started the recruitment of 150 patients in 2010. This is a multicentre, randomized, phase III study, it's due to demonstrate the role of HIPEC as a prophylactic measure in initial treatment and in the adjuvant setting in patients with high risk of developing colo-rectal peritoneal metastases^[66].

The COLOPEC (Netherlands) study, enrolled 204 patients, aged from 18 to 75 years, between 2014 and 2017. The patients had CRC in T₄ N₀₋₂ M₀ stage, moreover, the treatment consisted of injection intravenously of fluorouracil (400 mg/m²) and¹⁷

leucovarín (20 mg/m^2), then, during the surgery, the use of oxaliplatin (460 mg/m^2) for 30 min. COLOPEC demonstrated an absolute risk reduction of 15% in PMs^[67].

CONCLUSION

In CRCs, PMs are underestimated and they are correlated with a poor prognosis. Despite the fact that the secondary localizations of tumor are visible in the chest or in the liver, during the execution of full-body computed tomography scan for tumor staging, PMs cannot be identified easily. Moreover, a failed treatment of PMs determines a median survival of 5 mo; on the contrary, a palliative systematic therapy increases the median survival from 5 to 15 mo. Unfortunately, the survival remains worse in respect to non-peritoneal metastases.

Furthermore, CRC affects in higher percentage the young ages, so it becomes necessary to discuss about a protocol of treatment to prevent the principal complications (malignant ascites and obstruction) of colorectal tumors, eliminate macroscopic malignancies on peritoneal surface and increase the median survival.

As far as possible collect the principal studies regarding CRS plus HIPEC in CRC, it is still no very clear and shared the indications and technique used in PMs arising from CRC.

However, looking at the clinical trials and physiologic principles, CRS (open or laparoscopic) plus HIPEC can be a valid treatment especially in young patients (< 50 years), affected by locally advanced (pT4) CRC with PMs. In this way, it is possible to grow the overall survival, quality of life and reduce the tumor relapse.

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