REVIEW

THE ROLE OF HIPEC IN PERITONEAL CARCINOMATOSIS DUE TO COLORECTAL CANCER – PROCEDURE, COMPLICATIONS, AND LITERATURE EVIDENCE

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Abstract

Cytoreductive surgery and HIPEC have become de pillars of treatment in advanced, metastatic colorectal cancer. This state of evolution of the disease was considered terminal just a few years ago. It has been demonstrated that by combining these therapies in selected patients one can increase survival time. Once this has been obtained to some length modern studies have been focused on the quality of life, safety, and how this time interval can be increased. We have reviewed the most important prospective, randomized clinical trials regarding HIPEC and peritoneal carcinomatosis. The technique, complications, principles of action, and evolution through time of HIPEC have been addressed and covered. Special consideration had been given to the correlation between the carcinomatosis index and HIPEC. HIPEC with maximal cytoreduction can be considered a curative procedure only in strictly selected patients diagnosed with colorectal cancer and peritoneal carcinomatosis. Although it has been present in the medical field for almost 30 years, it is not wide-spread due to the high costs of implementation and the requirement of highly specialized surgical and medical teams. As technology evolves, the costs can be decreased and HIPEC should be largely available in oncological centers since the foundation of implementation is solid and the fact that clear benefits although small have been demonstrated. Taking into account all of the above, HIPEC should not be considered a standard treatment at present and should only be performed in experienced centers. The correct selection of patients is critical to the success of this procedure. Maximum cytoreduction should only be performed if the carcinomatosis index allows.

Keywords*: HIPEC, colorectal cancer, carcinomatosis*

Introduction

Historically, systemic chemotherapy has little effect on malignant pathologies when they diffuse to the peritoneum. This reduced effect is due to the weak blood supply of the peritoneum which does not allow the chemotherapeutic to penetrate the tumors. Debulking surgery can be a solution but inevitably there will be a residual macroscopic or microscopic disease with a major impact on survival. Surgery also interrupts the tumor mass facilitating the dissemination of cells into the peritoneum. Postoperative adhesions

also provide an excellent, nutrient-rich environment that allows tumor cells to develop.

In 1955, Weissberger introduced the concept of intraperitoneal chemotherapy. In 1978, Dedrick studied the degree of penetration of molecules into the tissue. He identified for some a penetration of 1-3cm. For these reasons it has been postulated that tumor deposits should not be greater than 2,5 cm after resection. Intraperitoneal chemotherapy does not find its usefulness unless optimal cytoreduction has been performed [1, 2].

The chemotherapeutic agents must meet several physical criteria: they must have a high molecular weight, be hydrophiles, and be ionized. These characteristics allow the peritoneum-blood barrier to repel them thus obtaining high intraperitoneal concentrations and low systemic toxicity [3, 4].

The small amounts of chemotherapeutic that reach the systemic circulation have a short validity and are rapidly inactivated by hepatic metabolism or renal elimination. The concentration of chemotherapeutic at the peritoneal level is measured by the under-curve area (AUC). The AUC ratio between the intraperitoneal and plasma concentration of chemotherapeutic expresses how long the chemotherapeutic remained in the peritoneal cavity as well as the amount that diffused into the plasma. A large difference in this ratio must be maintained to achieve a high intraperitoneal concentration with low systemic toxicity [5].

Intraperitoneal chemotherapy with hyperthermia (HIPEC) and cytoreduction surgery (CR) was first explored in the 1980s and at present, 30 years later it has become the pillar of treatment for carefully selected oncological patients with peritoneal metastasis [6].

Although HIPEC has proven effective in advanced ovarian cancer, its role is also explored in patients with digestive tract tumors (stomach, colon, rectum) [7]. Up to 15% of these patients have peritoneal determinations at the time of diagnosis [7].

An important role in predicting the impact of HIPEC is related to surgery and maximum cytoreduction. The first studies on the role of HIPEC were conducted in 1970 on animals when it was shown that in the peritoneum there were concentrations from 2x to 8x higher of the chemotherapeutic agent than those obtained by systemic chemotherapy. During the same period, the role of temperature on malignant cells was studied and it was demonstrated that temperatures of 42-43C were sufficient to eradicate malignant cells in vivo [8].

Despite some proven benefits for HIPEC, the necessary management and logistics have limited use in current practice. HIPEC is administered at the time of cytoreduction surgery when the free movement in the abdomen of the fluid is not limited by any adhesions that may form in the postoperative period. The surgeon can also control the duration and distribution of fluid by following the protocols in force. Our study aimed to explore the literature and discuss the use of HIPEC in more selective surroundings such as colorectal cancer with peritoneal metastasis.

Materials and Method

A literature review was conducted. The period researched spanned until 01.10.2020 with the topics HIPEC in colorectal cancer. The abstracts and the full texts of all relevant articles were examined. To conduct the search, we used the following words: “intraperitoneal chemotherapy” AND “carcinomatosis in colorectal cancer” AND “HIPEC”. The variables taken into consideration and discussed were: demographic information, chemotherapeutic agents used in HIPEC and intravenous, tumor stage, tumor load, overall survival, and disease-free survival.

The PubMed database was considered. The articles were manually evaluated using the P.I.C.O.S concept defined as Patient, Intervention, Comparator, Outcome, Study to construct the inquiries as to ensure clinical potency. After the articles were identified they were appraised using the PRISMA checklist.

A number of 63 articles were identified. From these 9 were excluded due to fact that they were duplicates and 54 articles were left for analysis. Another 10 articles were excluded because the full text could not be accessed. From the remaining 44 articles, another 5 were eliminated as they were not written in English. After analysis of the 39 articles, 3 were excluded since the subject studied did not correspond with our aim of the review. Finally, 34 articles were used for detailed discussion in the main text.

Discussion

Principle and technique

Intraperitoneal chemotherapy does not find its usefulness unless it has been performed in the framework of maximum cytoreduction surgery. The procedure is performed through an average xipho-pubic incision. At the beginning of the procedure, the index of peritoneal carcinomatosis should be calculated by dividing the abdominal cavity into 13 different regions. The surgeon will assign a tumor load score depending on the tumor volume for each of these regions [9].

Subsequently, surgical removal of tumor masses will be carried out. After completing the intervention and obtaining the maximum cytoreduction with tumor residue below 1 cm the intervention is continued with intraperitoneal chemotherapy the aim is to remove the microscopic residual disease by obtaining high concentrations of chemotherapeutic at the local level. The effectiveness of the chemotherapeutic agent can be increased with the aid of hyperthermia [10].

For tumors of the digestive tract (colorectal or appendix), mitomycin or oxaliplatin is recommended while for gastric cancer and tumors of the gynecological sphere cisplatin should be used [11].

The chemotherapeutic is administered by pressure pumping with the help of 2 silicone tubes placed intraperitoneally after closing the median wound (Figure 1). The peritoneal cavity is preheated with a saline solution at a temperature of 42-43°C and then the chemotherapeutic infusion is performed for 30-90 minutes. The liquid used is subsequently discharged at the end of the procedure (Figure 1). An important problem is the intensity of the exposure of malignant cells to the chemotherapeutic and how this exposure can be homogenous for the entire peritoneal surface.

In general, chemotherapeutic agents are administered according to the body surface in the quantity: mg/m^2. During HIPEC the entire peritoneal cavity should be in contact with the therapeutic agent. This can be achieved by using a substance carrier. In general, 2 liters are recommended but it is also important the type of substance used as it can influence the cytotoxicity of the chemotherapeutic agent. Isotonic substances are preferred-physiological serum (Figure 1).

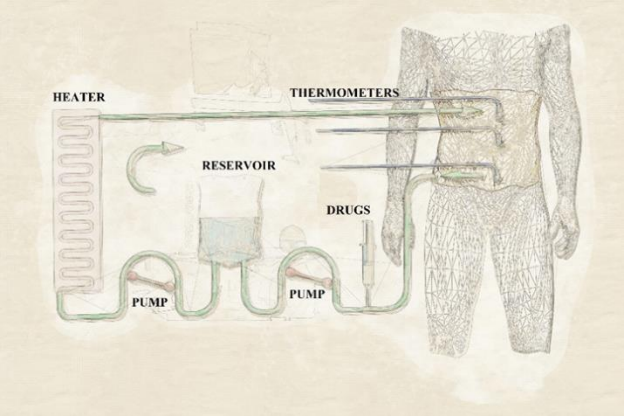

Figure 1 – HIPEC mechanics and assembly

Is HIPEC an option in the treatment of peritoneal carcinomatosis due to colorectal cancer after optimal cytoreduction?

In addition to lymphatic and hematogenous spread, colon cancers can produce transcolonic dissemination in the peritoneal cavity, resulting in peritoneal carcinomatosis. Peritoneal carcinomatosis has a poor prognosis compared to metastatic disease in visceral organs [12, 13]. Once the tumor has spread to the peritoneum frequently their microscopic metastasis in other organs. Until recently, most oncologists saw peritoneal carcinomatosis as a terminal condition, and the only treatment available was palliative through systemic chemotherapy. However, in about 25 percent of cases, the peritoneal cavity appears to be the 3rd site of the onset of metastatic disease for tumors of the lungs and liver. This has led to the assumption that, in some cases, peritoneal carcinomatosis may be the first place of dissemination and is therefore not necessarily indicative of a generalized disease [14, 15].

However, this concept is not supported by clinical trials. Jayne et al. demonstrated on a number of 2095 patients with colorectal cancer that 364 of them were diagnosed with peritoneal carcinomatosis but only 44 (2%) have been identified with exclusive secondary metastasis at the level of the peritoneum [15].

Published randomized trials

To date, 4 randomized trials have been performed to investigate the role of surgical cytoreduction with or without HIPEC for patients

with peritoneal secondary determinations in colorectal cancer but none of these produced definite results. Only two demonstrated moderate improvements in patients with HIPEC and cytoreduction compared to the control group [16-18].

In the first study, 105 patients diagnosed with, peritoneal carcinomatosis with primary colorectal tumor (n=87) or appendix (n=18) were randomized into an arm with maximum cytoreduction and HIPEC with mitomycin followed by systemic chemotherapy (fluorouracil and leucovorin) and an arm with systemic chemotherapy (fluorouracil and leucovorin) and palliative surgery. Despite the high postoperative mortality (8%), DFS (disease-free survival) in the HIPEC group was significantly higher (22 months vs. 13months). After an average follow-up of 8 years, 45% of patients with intraperitoneal chemotherapy and maximum cytoreduction were still alive. The use of systemic oxaliplatin or irinotecan in the control arm seems to erase the difference in the benefit of survival since recent data indicate an increased survival in these 20-month regimens.

The second study, in which randomized patients were assigned in two arms: maximum cytoreduction vs. systemic chemotherapy (fluorouracil) gathered only 35 patients out of 90 planned (30 with colorectal cancer and 5 with appendix cancer) [18]. Although the survival of 2 patients with HIPEC and cytoreduction was 60% higher (much higher than the fluorouracil/leucovorin regime) this difference was not statistically significant.

Another study used oxaliplatin in the control arm to evaluate the efficacy. This study encountered recruitment issues and as such, only 48 patients were registered. Patients who were defined preoperatively with resectable tumors colorectal tumors and peritoneal metastasis were subsequently randomized to the group with maximum cytoreduction and intraperitoneal chemotherapy (fluorouracil – 550 mg/m^2) daily for 6 consecutive days and a monthly repeat of cycles or they were distributed in the group with systemic chemotherapy – oxaliplatin and fluorouracil administration every two weeks-both treatments were continued for 6 months. OS (overall survival) at 6 years was significantly better in the surgical arm (54% vs 38%) and after 5 years 8 of the surgically treated patients survived compared to the control group in which the only one survived. The small-batch of patients, however, limits the impact of the conclusions.

The PRODIGE-7 is the most recent study, multicentric, in which 265 patients with stage IV colorectal cancer and peritoneal carcinomatosis index <25 were randomly distributed in an arm with maximum cytoreduction and HIPEC and a maximum cytoreduction group without HIPEC. Approximately 96% of patients received neoadjuvant or adjuvant or combined systemic chemotherapy for 6 months. In a preliminary report presented in 2018 after a median follow-up of 64months, HIPEC did not improve overall survival (41.7 months vs. 41.2 months, 5-year survival of 39% vs. 37%) but doubled postoperative morbidity at 60 days (24% vs 14%). Patients with carcinomatosis index between 0-10 or over did not benefit from HIPEC while patients with carcinomatosis index between 11 and 15 had benefited in OS. Although these data indicate quite clearly a lack of benefit of HIPEC in advanced colorectal cancers. Randomized studies are needed to assess the usefulness of maximum cytoreduction compared to systemic chemotherapy-preferably to achieve a stratification according to the peritoneal carcinomatosis index.

Taking into account all of the above-HIPEC should not be considered a standard treatment for advanced colorectal tumors with peritoneal carcinomatosis at present time and should only be performed in experienced centers due to the increased morbidity. The correct selection of patients is critical to the success of this procedure. Maximum cytoreduction should only be performed if the carcinomatosis index allows [18-20]. Cytoreduction should not be attempted if tumor load is high. If one cannot ensure the optimal reduction below 1 cm this procedure only increases the mortality and morbidity with no overall survival benefit. Taking into account all of the above-HIPEC should not be considered a standard treatment at present and should only be performed in experienced centers. The correct selection of patients is critical to the success of this procedure. Maximum cytoreduction should only be performed if the carcinomatosis index allows [21-23].

Complications in HIPEC

Risk factors

A direct proportionality was demonstrated between the peritoneal carcinomatosis index and perioperative morbidity/mortality. The reasons are related to the frequent multi-visceral dissection and resection, increased blood loss, and prolonged surgery time [24, 25].

Because the carcinomatosis index is calculated by the operating team at the time of the intervention it is slightly subjective. The surgical team's experience is decisive to reduce mortality and morbidity. Sarcopenia and low body mass index are associated with increased morbidity and mortality [26]. The value of the ASA score and duration of a surgery over 10 hours also increase the number and severity of the complications [27].

There are a number of factors that are directly related to the experience of the center that performs this procedure, so over time, the tertiary treatment centers have demonstrated that as the number of cases has increased, the rate of complications has decreased. An example is demonstrated by Glehen et al. who published a multicentric analysis in which he demonstrated that the hospital's experience is decisive in determining the rate of complications [14, 24].

Hematological complications

These complications are largely related to the chemotherapeutic agent used and the intraperitoneal concentration. Mitomycin is associated with neutropenia and can thus produce an increase in mortality of up to 66% [28, 29].

Gastroenterological complications

HIPEC and maximal cytoreduction are commonly practiced for tumors that originate in the digestive tract and frequently involve multivisceral resections and sometimes multiple digestive anastomoses. All this surgical stress to which HIPEC is added and the hyperthermia disturb the physiological healing process of the anastomoses. Thus, the percentage of fistulas can reach percentages of up to 19% of the patients [30, 31].

Other common complications are postoperative peritoneal abscesses, biliary fistula, lymphopenia, and gastric stasis. Objective risk factors of digestive complications are difficult to identify due to the high complexity of the surgery. They are generally related to the amount of blood lost, the duration of the surgery, and the number of anastomoses [32].

Pulmonary complications

Are frequently encountered in abdominal surgery and represents one of the main causes of prolonged hospitalizations. The presence of metastases at the diaphragmatic level and resections at this level frequently involve postoperative pulmonary complications such as pleurisy [33]. Secondary cases of pneumonia due to mechanical ventilation and Mendelson syndrome are encountered are in up to 10% of patients undergoing the HIPEC procedure [34].

Conclusion

In conclusion, the role of HIPEC in peritoneal carcinomatosis due to advanced colorectal cancers is unclear. The principle of using intraperitoneal chemotherapy to achieve locally higher concentrations than in the blood is good, but the problem resides in the lack of published high quality, high volume, multicenter, prospective, randomized trials that sustain this premises. In highly selected patients in tertiary centers where optimal cytoreduction was obtained with macroscopic tumoral residue below 1 cm, HIPEC has demonstrated a small increase in overall survival but we must take into account the increased morbidity of the procedure. This technique needs to be followed in the future but for now, palpable results are lack, thus it has not yet achieved wide acceptance.

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