The Rationale of Hyperthermic Intraperitoneal Chemotherapy Treatment

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Peritoneal metastases (PM) are observed in approximately 8% of patients diagnosed with colorectal cancer, either synchronously or metachronously during follow-up. PM often manifests as the sole site of metastasis. PM is associated with a poor prognosis and typically shows resistance to systemic chemotherapy. Consequently, there has been a search for alternative treatment strategies. For intraperitoneal (IP) therapy to exhibit promise, it either needed to be combined with the removal of larger tumor nodules during cytoreductive surgery or administered as repeated intermittent treatments over an extended duration to affect macroscopic tumor nodules. Cytoreductive surgery, with hyperthermic intraperitoneal chemotherapy (HIPEC) treatment as an adjunct, emerged as a solution for the former situation.

Keywords: colorectal cancer ; peritoneal metastases ; locoregional therapy

1. Introduction

Colorectal cancer is one of the most common types of cancer, with a global incidence of 1.9 million cases per year and a worldwide death rate of 935,000 [1]. About 8% of individuals develop peritoneal metastases (PM), occurring either at presentation or during follow-up [2][3]. Peritoneal metastases present unique challenges as this metastatic site was historically associated with short survival [4], severe symptoms [5], limited extension of survival [6], and a response rate not exceeding 30% after systemic chemotherapy [7]. These factors led to a search for more effective treatments. The term cytoreductive surgery (CRS) was initially introduced in the treatment of testicular [1] and ovarian [2] tumors, based on the assumption that reducing the tumor volume enhances the effectiveness of further treatment [3][4][5]. Later, this concept was applied to the treatment of low-grade mucinous tumors originating from the colon or appendix [6]. In a specific study, complete tumor removal was followed by the intraperitoneal infusion of chemotherapy using 5-fluorouracil and mitomycin C. Five out of seven patients experienced remission following this treatment, motivating the team to further explore the combination of CRS and locoregional chemotherapy. Meanwhile, other tumor types were treated with heated chemotherapy, leveraging a pharmacokinetic advantage and the selective sensitivity of tumor cells to thermal damage, while safeguarding normal tissue through an intact cooling blood flow [7][8]. Furthermore, in vitro studies suggested the selectively increased antitumor action of chemotherapeutic compounds using hyperthermia [9].

2. Patient Selection and Work-Up

Peritoneal metastases (PM) from colorectal cancer (CRC) occur in 8–10% of cases as either metachronous or synchronous lesions [2]. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) presents a potential cure in specific patients, boasting a 5-year survival rate of 40–50% [10][11]. However, due to the elevated risk of postoperative morbidity associated with the procedure, only patients with a good performance status, age below 80 years, limited liver metastases, and favorable molecular biological characteristics may be considered for CRS-HIPEC. The extent of the disease is assessed using the peritoneal cancer index (PCI), typically evaluated intraoperatively during open exploration. The PCI score stands as one of the most acknowledged and independent prognostic factors for PM from CRC. A PCI score of 20 or less correlates with improved survival outcomes [12]. Selected patients with colorectal PM can undergo a potentially curative procedure, with survival heavily reliant on the PCI score and completeness of cytoreduction score (CCS) [13][14]. Therefore, a comprehensive diagnostic work-up plays a fundamental role in detecting PM, determining its extent, assessing metastases to other solid organs (such as the liver, lungs, extraregional lymph nodes, pleura, and bones), staging the disease, and selecting appropriate treatment strategies to enhance prognosis. Precise patient selection remains crucial in achieving long-term survival outcomes with CRS-HIPEC. Computed tomography (CT) serves as the primary imaging modality in the standard pre-operative assessment for patients considered for CRS-HIPEC [15].

In clinical practice, magnetic resonance imaging (MRI) serves as a secondary modality, often employed for the investigation of liver metastases or in cases involving locally advanced tumors or solid organ metastases to determine the feasibility of radical resection. PET-CT is typically used in cases concerning suspicious lymph nodes or extra-abdominal disease. MRI outperforms CT and PET-CT in detecting small tumor lesions and liver metastases [16][17]. MRI demonstrates sensitivity of approximately 80% and specificity of 85% in detecting peritoneal lesions, while also offering an approximate prediction of PCI before surgery [18]. Dohan et al. investigated the combination of CT and MRI in preoperatively estimating PCI, finding that CT along with MRI provided greater accuracy in predicting surgical PCI compared to CT alone [19]. MRI's added value revealed increased sensitivity in detecting PM in regions such as the central quadrant, pelvis, and upper left quadrant [19].

3. Prognostic and Predictive Factors

Undoubtedly, a noninvasive preoperative modality with high sensitivity, specificity, and accuracy in detecting PM is crucial for the selection of eligible patients for CRS-HIPEC. An ongoing multicenter randomized controlled trial in Holland aims to investigate whether MRI can replace staging laparoscopy as the preoperative modality for patients with PM from CRC eligible for CRS-HIPEC [20]. Despite careful patient selection, the majority of patients with CRC-PM will eventually develop recurrent disease. Known prognostic factors other than the PCI score and CC score with a negative impact on overall survival are locoregional lymph node metastases, a low differentiation grade, and the presence of a signet ring cell histology [21]. The peritoneal surface disease severity score (PSDSS) and the colorectal peritoneal metastases prognostic surgical score (COMPASS) are validated prognostic nomograms used as a clinical scores for the prediction of patient survival after CRS-HIPEC [21][22]. These nomograms are based on the age, PCI score, loco-regional lymph node status, and presence of signet ring cells. However, these nomograms do not consider the information from molecular markers. Nonetheless, other than clinical factors, there is also a need for a better understanding of molecular factors in relation to tumor biology in the selection process for CRS-HIPEC. In recent years, the classification of molecular markers has gained increased awareness in order to create a more personalized therapy in mCRC. Well-known predictive markers are the mutation status of the oncogenes KRAS, NRAS, and HRAS. Mutations in these oncogenes result in the constitutive activation of the Ras-Raf-MAPK pathway with the dysregulation of the cellular proliferation of epidermal growth factor receptor (EGFR). KRAS mutations are found in 40–46% and BRAF mutations in 5–11% of all mCRC cases [23][24]. It is well known that mutations in these genes have no beneficial response rate to anti-EGFR monoclonal antibody therapy [23]. Mutations in KRAS and BRAF are shown to have a negative impact on survival after CRS-HIPEC, independently of anti-EGFR antibody therapy [25]. Mutations in the mismatch repair (MMR) system, known as defective mismatch repair (dMMR), occur in 10–20% of all sporadic CRC cases [26].

4. The Rationale of HIPEC Treatment—Pharmacokinetics and Hyperthermia

4.1. Pharmakokinetics

As previously highlighted, the pharmacokinetic advantage of achieving higher intraperitoneal concentrations has been well demonstrated in various studies. One method to assess this advantage is by calculating the intraperitoneal to systemic exposure ratio, determined by dividing the area under the concentration curve (AUC) intraperitoneally by the AUC in plasma. Depending on the drug and perfusion time, this AUC peritoneum/AUC plasma ratio can range widely, from 8 to 1000 [27]. However, it is crucial to note that this ratio alone does not fully represent the chemotherapy uptake in peritoneal nodules. Several drug-related factors significantly contribute to determining how much of the compound is transported into the tumor nodule, aside from the concentration gradient created by this ratio [28].

The passage of a drug into the tumor nodule occurs through two mechanisms—convection and diffusion. Convection relies on the pressure disparity between the fluid-filled cavity and the stromal tissue pressure. The drug's velocity is invariably slower than the carrier fluid in which it is dissolved, forming the basis of the retardation coefficient. Hyperthermia, such as that used in HIPEC, and elevating intraabdominal pressure, as in PIPAC, are approaches employed to influence this pressure differential. On the other hand, diffusion relies on the concentration gradient. Theoretically, drugs with a high AUC peritoneum/AUC plasma ratio can enhance diffusion into the tumor nodule. However, several crucial stromal properties can impact diffusion. These include the viscoelasticity or stiffness of the tumor nodule, as well as the density and geometric arrangement of fibers. For more comprehensive details of these factors [28].

4.2. Hyperthermia

Certainly, hyperthermia possesses dual effects on malignant cells. While it is recognized for its potential lethality to cancer cells [29], hyperthermia can act as a double-edged sword. It triggers the induction of heat shock proteins that, under certain circumstances, may exert anti-apoptotic and proliferative effects on tumor cells [30][31]. The clinical significance of these effects remains uncertain.

Nevertheless, extensive research has investigated the synergy between hyperthermia and the enhanced uptake of chemotherapeutic drugs [9][32][33][34][35]. Platinum compounds have consistently demonstrated a synergy with hyperthermia, whereas mitomycin C has shown conflicting results. Conversely, certain compounds like taxanes have shown no enhancement with hyperthermia. In a rat study, hyperthermia alone and mitomycin C alone impeded peritoneal metastatic growth, but their combination had a notably synergistic effect, surpassing the efficacy of either treatment alone [36]. Regarding clinical trials, there is a single randomized clinical trial evaluating the use of hyperthermia in gastric cancer [37]. In this trial, patients with gastric cancer and peritoneal metastases underwent gastrectomy alone (surgery alone arm), gastrectomy with normothermic intraperitoneal chemotherapy (NIPEC) at 37 degrees, or gastrectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) at 41–42 degrees. Certainly, in the mentioned study, the multivariable model demonstrated a hazard ratio of 1.77 (95% confidence interval 0.91–3.42, $p = 0.092$) for the use of hyperthermia. Although this result did not reach full statistical significance, it indicated an intriguing trend. This underscores the need for further research to delve deeper into the clinical utility of hyperthermia

5. Patterns of Recurrence

The risk for recurrence after CRS and HIPEC for CRPM is high, with 5-year progression-free survival expected to be less than 20% and median progression-free survival of 15 months in 660 patients treated in Netherlands [38]. Breuer et al. revealed that in 505 patients treated with CRS and HIPEC for CRPM and having a median PCI of 6, 71.5% developed recurrences, 28.3% developed isolated hematogenous metastases, 24.6% had isolated PM, and 13.9% had mixed peritoneal and hematogenous metastases [39]. Those with isolated or mixed peritoneal metastases had a shorter time to recurrence than those with isolated hematogenous metastases, with hepatic and pulmonary metastases the most common hematogenous metastatic sites. Braams et al. revealed that out of 132 patients having recurrent disease after CRS and HIPEC, 32 underwent resection of the metastases, of which 17 were locoregional and 14 distal; it was more likely that the metastasis was resectable if the interval between the index CRS and HIPEC and recurrence was prolonged [40]. The recurrence risk is dependent on several factors. Previously, it has mentioned the completeness of cytoreduction, with CCS = 0 being the only group that can expect a cure or long-term disease free survival. The PCI is also of importance as a high PCI score is associated with a greater risk of recurrence. In the PRODIGE 7, study those with PCI < 11 had 23% DFS after 3 years, compared with 4% for those with PCI 11–15 and 3% if PCI > 15. Other factors, such as advanced *n* stage [39], signet ring cell differentiation [21], BRAF mutation [24], and gains of chromosome 1p and 15q [41], also have negative effects on the prognosis.

6. Conclusions

The efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) in conjunction with cytoreductive surgery (CRS) for colorectal cancer-related peritoneal metastases has been debated, despite being a standard treatment option. While some studies have raised doubts about the significant contribution of HIPEC to treatment outcomes, CRS plus HIPEC remains a primary therapeutic approach for peritoneal spread from colorectal cancer. Recent research and emerging studies have emphasized the need for ongoing efforts to optimize the patient selection criteria and refine the administration of chemotherapy in HIPEC. This includes exploring modifications in the selection process or adjusting the dosage of chemotherapy agents used during HIPEC. The goal is to enhance the efficacy of the treatment by improving the patient selection parameters and refining the delivery of chemotherapy within the peritoneal cavity to achieve better tumor eradication and control.

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