Hyperthermic Intraperitoneal Chemotherapy

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With increasing awareness amongst physicians and improved radiological imaging techniques, the peritoneal cavity is increasingly recognized as an important metastatic site in various malignancies. Prognosis of these patients is usually poor as traditional treatment including surgical resection or systemic treatment is relatively ineffective. Intraperitoneal delivery of chemotherapeutic agents is thought to be an attractive alternative as this results in high tumor tissue concentrations with limited systemic exposure. The addition of hyperthermia aims to potentiate the anti-tumor effects of chemotherapy, resulting in the concept of heated intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal metastases as it was developed about 3 decades ago. With increasing experience, HIPEC has become a safe and accepted treatment offered in many centers around the world. However, standardization of the technique has been poor and results from clinical trials have been equivocal.

Keywords: peritoneal ; HIPEC ; intraperitoneal ; drug transport

1. Introduction

Peritoneal metastases (PM) are a common manifestation of abdominal malignancies, most frequently occurring in patients with upper gastrointestinal, colorectal, and ovarian cancer [1][2][3]. Although less often, primary solid tumors outside the peritoneal cavity such as malignant melanoma, lung cancer, and lobular breast cancer may also metastasize to the peritoneum [4][5]. An increased awareness amongst physicians as well as the improvement of radiological techniques such as diffusion-weighted MRI have resulted in an increasing incidence of PM being reported in population-based studies in recent years. When taking all the origins together, PM pose a significant burden on current oncological care.

For long, it has been recognized that systemic treatment of PM appears to be less effective as compared to lung or liver metastases [6]. Poor vascularization of the peritoneal cavity may play a role, but the exact mechanisms underlying this phenomenon remain to be elucidated. As anticancer drugs are usually administered systemically exposing healthy tissue, their therapeutic index is limited. Some of these shortcomings can be addressed by local or locoregional delivery of chemotherapy. During this mode of anticancer therapy, drug is administered either through a feeding artery, or into an anatomical cavity. Locoregional drug delivery allows to administer a higher dose with less systemic toxicity. Examples include hepatic artery infusion and instillation in the peritoneum (intraperitoneal, IP), bladder (intravesical), brain ventricles (intrathecal), and chest cavity (intrapleural).

Intraperitoneal chemotherapy takes advantage of the large surface area of the peritoneum (approximately 2 m^2) to enable mass transfer either from the peritoneal cavity to the systemic circulation (drug therapy), or vice versa (dialysis). The origins of the peritoneal route of drug delivery can be traced back to the eighteenth century: in 1744, the English surgeon Christopher Warrick, instilled a mixture of ‘Bristol water’ and Bordeaux wine in the peritoneal cavity of a patient with intractable ascites, apparently with great success [7]. There was some enthusiasm during the first half of the twentieth century for IP administration of radioactive gold (^{198}Au) in the adjuvant and palliative treatment of ovarian cancer, but significant morbidity was observed [8]. Also, intraperitoneal radioactive chromic phosphate (^{32}P) administration was attempted for ovarian cancer, but this led to significant complications and resulted in inhomogeneous drug distribution [9].

The interest in intraperitoneal drug delivery (IPDD) was rekindled with the publications of Dedrick in the 1970s. He proposed a theoretical framework for IPDD based on the pharmacokinetic (PK) advantage that results from the fact that systemic drug clearance is much faster compared to peritoneal clearance. As a result, IP drug can be administered at a higher dose with low systemic exposure and toxicity [10]. Of note, Dedrick was also one of the first authors to emphasize that despite the obvious PK advantage of IPDD, the resulting tissue penetration depth is very limited [11].

The use of hyperthermia to treat cancerous growths dates from several millennia ago and continues to find applications in modern medicine. The concept of combining IPDD with hyperthermia as a hyperthermic IP chemoperfusion (HIPEC) was

first studied in an animal model in 1974 by Euler [12]. The first clinical use of HIPEC was reported in 1980 by Spratt et al., who performed hyperthermic chemoperfusion with thiotepa in a patient with pseudomyxoma peritonei (PMP) [13].

In the following decades, HIPEC was introduced in the treatment of peritoneal metastases from a variety of primary malignancies and in primary peritoneal malignancies including peritoneal mesothelioma. Long surrounded by skepticism, HIPEC is now offered at hundreds of treatment centers worldwide [14]. Nevertheless, the efficacy and safety of HIPEC remain debated and hamper the universal acceptance by the oncology community. Proponents will argue that the addition of HIPEC was recently shown to prolong survival in ovarian cancer in a randomized clinical trial (RCT) but criticism was undoubtedly fueled by negative results of RCTs in patients with colorectal cancer (CRC) PM [15].

2. Clinical Implementation of Hyperthermic Intraperitoneal Drug Delivery

The basic setup used for HIPEC treatment consists of one or more inflow- and outflow tubes and temperature probes, one or more roller pumps, and a heating element. Several HIPEC devices are commercially available. There is considerable heterogeneity in the procedural parameters that are used to administer HIPEC: drug type and dose regimen, carrier solution, target temperature, treatment duration, and delivery technique all vary substantially according to local preference [16]. As a result, many different HIPEC-regimens are currently used and standardization is sparse, hampering pooling of outcome data [17].

2.1. Choice and Combination of Chemotherapy

Ideally, chemotherapy drugs for HIPEC should have the following properties: a favorable pharmacokinetic profile, no cell cycle specificity, and absence of local peritoneal toxicity. Unfortunately, all chemotherapeutics currently administered during HIPEC are used off label. In colorectal cancer, debate persists on the use of oxaliplatin versus mitomycin C for HIPEC. Results from retrospective studies are difficult to interpret due to differences in clinical and treatment parameters [18]. A prospective randomized trial in appendiceal cancer showed that compared to mitomycin C, the use of oxaliplatin for HIPEC was associated with a better safety and quality of life profile [19][20]. However, oxaliplatin as a HIPEC agent failed in recent randomized trials in colorectal cancer. Possibly, additional factors such as choice of carrier solution, target temperature, and treatment duration are important determinants of the efficacy of oxaliplatin, as recently demonstrated in organoid models [21][22].

Although it seems intuitively appealing to combine drugs for HIPEC, several caveats should be taken into consideration. First, unsuspected chemical or physical incompatibilities may exist that preclude the administration of two or more drugs IP in the same solution. Second, when toxicity occurs, it will be problematic to find out which agent is responsible for which observed toxicity. Third, prospective clinical trials do not support the use of multi-agent HIPEC regimens. Quénet and coworkers showed that, compared to HIPEC with oxaliplatin alone, the addition of irinotecan significantly increased the complication rate, but did not benefit recurrence-free or overall survival [23].

2.2. Open Versus Closed Abdomen Perfusion

Chemoperfusion with the skin and/or fascial layer closed theoretically prevents contamination of the OR environment and heat loss and may enhance convection driven tumor chemotherapy penetration due to increased IP pressure. The open technique (‘coliseum’), on the other hand, allows to manually stir the abdominal contents in order to ensure homogeneous drug and temperature distribution. Prospective comparative studies are lacking, but retrospective data suggest that both techniques are comparable in terms of intraoperative hemodynamics and postoperative morbidity [24][25]. Recent developments include the use of CO_2 recirculation and laparoscopy assisted HIPEC [26][27].

3. Clinical Results of HIPEC

The results of the most important randomized clinical trials that have investigated HIPEC are summarized in **Table 1**.

Table 1. Overview of randomized trials comparing surgery combined with HIPEC versus surgery alone

Tumor	Study, Year	Inclusion	Primary Endpoint	Treatment and N Randomized	Results	95% CI of Effect and *P* Value
Colorectal cancer	Verwaal [28] (2003, updated 2008)	Histologically proven PM, age <71 yrs, no distant metastasis	Disease specific survival	Chemotherapy alone (5-FU-LV) *N* = 51 CRS and HIPEC (MMC, 90 min) *N* = 54	12.6 m 22.2 m	*P* = 0.028
	Prodige 7 (2021) [15]	Histologically proven PM, PCI ≤25	Overall survival	CRS *N* = 132 CRS and HIPEC (OX, 30 min) *N* = 133	41.2 m 41.7 m	HR 0.63–1.58, *P* = 0.99
	COLOPEC (2019) [29]	Clinical or pathological $T_4N_{0–2}M_0$-or perforated colon cancer	Peritoneal metastasis free survival at 18 months	Adjuvant HIPEC (OX, 30 min) and adjuvant chemotherapy *N* = 102 Adjuvant chemotherapy *N* = 102	80.9% 76.2%	*P* = 0.28
	PROPHYLOCHIP (2020) [30]	Synchronous and resected PM, resected ovarian metastases, perforated tumor	Disease free survival	Adjuvant chemotherapy and HIPEC (OX ± IRI, 30 min) *N* = 75 Adjuvant chemotherapy *N* = 75	44% 53%	HR 0.61–1.56, *P* = 0.82
	Rovers (2021) [31]	Histologically proven isolated resectable PM	% complete CRS/% Clavien-Dindo ≥ grade 3 morbidity	Perioperative chemotherapy and CRS-HIPEC (MMC, 90 min or OX, 30 min) *N* = 40 CRS and HIPEC alone *N* = 40	89%/22% 86%/33%	RR 0.88-1.23, *P* = 0.74/0.31–1.37, *P* = 0.25
Ovarian cancer	Spiliotis (2015) [32]	Recurrent EOC	Overall survival	CRS and HIPEC (CIS or DOX with PTX or MMC, 60 min) *N* = 60 CRS alone *N* = 60	26.7 m 13.4 m	*P* = 0.006
	OVHIPEC (2018) [33]	EOC with at least stable disease after three cycles of carboplatin–PTX	Recurrence free survival	Interval CRS and HIPEC (CIS, 90 min) *N* = 122 Interval CRS alone *N* = 123	14.2 m 10.7 m	HR 0.50–0.87, *P* = 0.003
	Zivanovic (2021) [34]	Recurrent EOC	Proportion free of progression at 24 months ('pick the winner')	CRS and HIPEC (Carboplatin, 90 min) followed by 5 cycles of Carboplatin based IV chemotherapy *N* = 49 CRS alone followed by 6 cycles of Carboplatin based IV chemotherapy *N* = 49	16.3% 24.5%	Not applicable (no winner determined)

4. Conclusions

There are sound theoretical arguments that favor the incorporation of HIPEC in a multimodal strategy for patients with PM. Its current place remains, however, uncertain due to the significant variability in the drugs and methods used to deliver HIPEC. Also, results from clinical trials are inconsistent. Further development of HIPEC will require a better understanding of how surgery and HIPEC affect the tumor TME and peritoneal ecosystem. In addition, the role of treatment variables such as chemoperfusion temperature, HIPEC duration, and chemotherapeutic drug(s) need to be established. At the same time, efforts should be directed to the development of novel IP compounds and delivery systems, and to the expansion of the clinical evidence from randomized trials.

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