Optimal drugs for HIPEC in different tumors

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Summary

Although there is adequate evidence to support treatment of primary and secondary peritoneal surface malignancies with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC), the latter procedure is still far from standardized and optimization of its aspects may be warranted. Significant variations remain in HIPEC procedures and include also the drug choice. In this manuscript the characteristics of the optimal HIPEC drug will be discussed. Subsequently, the drug choice for HIPEC treatment of different peritoneal surface malignancies will be briefly analyzed. Prospective randomized trials are warranted to determine which drug is the most effective for HIPEC in each type of peritoneal surface malignancy. In the future, it would be of major significance when the choice of the most optimal drug in HIPEC may be tailored to the patient’s individual tumor by adequate drug sensitivity testing of the tumor cells.

Key words: drug choice, HIPEC, peritoneal carcinomatosis, peritoneal surface malignancy, pharmacodynamics, pharmacokinetic

Introduction

During the last decades, cytoreductive surgery and HIPEC have become an established treatment modality for primary and secondary peritoneal surface malignancy. Randomized trials have demonstrated the benefit of this approach above conventional systemic chemotherapy (with or without surgery) in peritoneal carcinomatosis from gastric [1], colorectal [2] and ovarian cancer [3]. Further, there are large series that suggest a beneficial effect of cytoreductive surgery and HIPEC in pseudomyxoma peritonei [4,5] and malignant peritoneal mesothelioma [6]. Although there is adequate evidence to support treatment of peritoneal surface malignancies with cytoreductive surgery and HIPEC, the latter procedure is still far from standardized and optimization of its aspects may be warranted. Significant variations remain in HIPEC procedures and include the technique (open or closed abdomen), the duration, the administered drugs, their dose, the timing of drug delivery, the volume of the perfusate, the kind of carrier solution, the intra-abdominal temperature, the flow rate and other parameters. In this manuscript, the characteristics of the optimal HIPEC drug will be discussed. Subsequently, the drug choice for HIPEC treatment of different peritoneal surface malignancies will be briefly analyzed.

Drug characteristics

The choice of the chemotherapeutic drug that is to be delivered intraperitoneally is very important and certain aspects have to be taken into account [7]. The agent should lack severe local toxicity after intraperitoneal administration. Drugs that have to be metabolized systemically (usually in the liver) into their active form are inappropriate for intraperitoneal use. In HIPEC procedures,
a direct cytotoxic agent is needed. Antimetabolites, for example 5-fluorouracil, are not considered suitable for this application because the exposure duration is too short to be effective. Obviously, the drug should have a well established activity against the malignancy being treated. The response on previously (intravenously) administered drug regimens should be considered in the assessment of the sensitivity of the tumor that is to be expected for a certain drug. Although the higher local drug concentrations achieved by its intraperitoneal administration may overcome relative drug resistance, clinically observed resistance to an intravenously administered drug is usually a reason to choose another drug in HIPEC. Further, it is of utmost importance that the drug demonstrates a pharmacokinetic advantage after intraperitoneal administration with high locoregional drug exposure and limited systemic toxicity, while a synergistic effect with heat is preferred.

**Pharmacokinetic advantage**

Because the intraperitoneal route of delivering chemotherapy is logistically less convenient and technologically more challenging than conventional intravenous chemotherapy, the case has to be made for the pharmacokinetic advantage of intraperitoneal chemotherapy [7,8]. Following intraperitoneal delivery, high regional concentrations can be achieved, while systemic drug levels are low. The concentration differential arises because of the relatively slow rate of movement of the drug from the peritoneal cavity into the plasma (peritoneal clearance). This pharmacokinetic process is based on the characteristics of the 'peritoneal-plasma barrier', which maintains the continuous high ratio of chemotherapeutic drug concentration between peritoneal cavity and plasma [9,10]. For drugs that are to be delivered intraperitoneally, experimental or clinical evidence should be available suggesting that for the certain drug a concentration or exposure-dependent cytotoxicity exists. Otherwise, when low target drug levels are equally effective, conventional systemic chemotherapy, which is a less complex treatment modality, may be sufficient. Agents with a large molecular weight have more favorable pharmacokinetics because of limited and delayed absorption from the peritoneal cavity. Since drainage through the visceral peritoneum is into the portal vein system and the first-pass effect from the liver decreases the systemic drug exposure, drugs highly metabolized in the liver to non-toxic metabolites will provide further pharmacokinetic advantage. Additionally, rapid renal clearance of the drug may decrease systemic drug exposure. Variables that also have an impact on the pharmacokinetics of a certain drug include its dose, the perfusate volume, the duration of the procedure and the type of carrier solution and the intra-abdominal pressure [7,8].

The pharmacokinetic advantage of intraperitoneal drug administration is expressed by the maximal intraperitoneal drug concentration to the maximal plasma drug concentration ratio, or rather, the area under the concentration-time curve (AUC) gradient of the drugs from the peritoneal cavity to peripheral blood [7]. The intraperitoneal to plasma drug AUC ratio varies for the different drugs from 12 to more than 1000 [11].

**Systemic toxicity**

Although, as stressed above, only a relatively small amount of the drug will reach the systemic compartment, systemic toxicity, most frequently bone marrow depression, may occur. Hence, a drug with a mild systemic toxicity profile is warranted. The amount of the drug in the systemic compartment and subsequently the systemic toxicity depend mainly on the pharmacokinetic profile of the drug and the dose that is administered. In most centers the drug dose is based on calculated body surface area, since it is an accurate predictor of drug metabolism and consequently of systemic toxicity [8].

**Pharmacodynamics**

Although the pharmacokinetic advantage is essential, pharmacodynamics is also of major importance. Whereas pharmacokinetics explores what the body does to the chemotherapeutic drug, pharmacodynamics explores what the body does with the body. High intraperitoneal drug concentration and exposure are the two main factors affecting the treatment of free intraperitoneal tumor cells. However, these favorable pharmacokinetic parameters may not correlate with the drug amount in tumor deposits. For invasive peritoneal tumor deposits, it is more important to achieve satisfactory local tissue penetration and concentration of the drug rather than high intraperitoneal fluid drug concentrations only [12].

A major problem in intraperitoneal chemotherapy is the limited tissue penetration by the therapeutic agent. Unfortunately, for many agents
it is difficult to accurately measure tissue penetration depth and tissue concentration after intraperitoneal administration and, when possible, there is a large inter-individual variation. The penetration depth of drugs that are intraperitoneally delivered is estimated to be 2 to 5 mm at maximum [13-18]. This underlines the need for optimal cytoreductive surgery to precede intraperitoneal delivery of drugs. Besides the drug characteristics and pharmacokinetic variables, their penetration depth is determined by factors such as cellular adhesion capacity and packing density of tumor cells, vascularility and interstitial fluid pressure [8].

**Bidirectional intraoperative chemotherapy**

HIPEC may be combined simultaneously with intravenous chemotherapy to optimize treatment efficacy in residual tumor after cytoreductive surgery. In this bidirectional intraoperative chemotherapy, the intraperitoneally delivered cytotoxic agent penetrates the residual tumor nodules from the site of the peritoneal surface, while intravenous drug administration provides drug distribution by capillary blood flow into the tumor deposits [7,8]. The drug which is intravenously administered as a normothermic solution becomes subject to the effect of hyperthermia in the subperitoneal compartment which enhances its efficacy, as described below [8]. While ifosfamide is not suitable for intraperitoneal use due to the need for activation in the liver, it is a very attractive agent for intravenous administration during HIPEC because of the remarkable thermal enhancement of its efficacy [11].

**Hyperthermia**

Although a temperature of more than 41°C itself induces selective cytotoxicity of malignant cells, existence of the synergistic effect of the drug with hyperthermia is preferred for HIPEC [7]. Hyperthermia enhances chemotherapy efficacy in a number of ways [19]. The combination of heat and neoplastic drugs frequently results in increased cytotoxicity over that predicted for an additive effect. The synergism between both kinds of treatment is dependent on several factors including increased drug uptake in malignant cells, which is due to increased membrane permeability and improved membrane transport. There is also evidence that heat may alter cellular metabolism and change drug pharmacokinetics and excretion, both of which can increase the cytotoxicity of certain chemotherapeutic agents. Additional factors include increased drug penetration in tissue, temperature-dependent increases in drug action and inhibition of repair mechanisms. In many cases, this enhancement of activity and penetration depth of drugs has already been observed above 39-40°C. *In vivo* studies on different agents indicate that the drug of choice at physiological temperatures may not be the drug of choice at elevated temperatures [20]. A theoretical prerequisite for HIPEC is the heat stability of the drug that is to be administered, but fortunately nearly all drugs remain stable under these moderate hyperthermic conditions.

**Drugs used in HIPEC for different tumors**

The properties and experimental data of cytotoxic drugs that are used in HIPEC have been discussed extensively elsewhere [8,11]. Extrapolation of experimental results to clinical practice should be done very carefully, because of the differences between the conditions on the laboratory bench and those in the human body. In the clinical setting, circumstances are much more complicated and drug activity is moderated by many physiological factors. On the other hand, the possibility of creating standardized conditions may be of great help for interpretation of treatment efficacy since great inter-individual differences may encumber this process. One should be aware of the fact that results of *in vitro* and *in vivo* experimental studies often differ, with factors such as tumor physiology, microcirculation, pH and hypoxia playing a vital role in the activity of drugs and their interaction with hyperthermia. In addition, the use of different cell lines and treatment protocols further confuses interpretation of these studies. Furthermore, experimental studies provide indicative information that may be very valuable since it is practically impossible to study each treatment parameter in comparative clinical studies.

**Colorectal and appendiceal carcinoma**

In most centers, mitomycin C has been used for HIPEC in patients with peritoneal carcinomatosis from colorectal or appendiceal origin [21]. Mitomycin C is an alkylating antibiotic which is effective against gastrointestinal cancers. It has a considerably favorable pharmacokinetic profile (intraperitoneal to plasma drug AUC ratio: 13-80)
Optimal drugs for HIPEC

and a tumor penetration depth of 2-5 mm, while in vitro and in vivo studies have demonstrated significant thermal enhancement [11]. In general, although there is a remarkable difference in drug dosimetry, clinical studies have demonstrated improved outcome and acceptable toxicity [8].

The use of oxaliplatin in HIPEC for colorectal and appendiceal carcinomatosis has been pioneered by Elias and Sideris [22]. High dose of oxaliplatin (460 mg/m²) in a short (30 min) HIPEC procedure has been shown to be well tolerated. Oxaliplatin has a proven activity in these malignancies, while the relatively low AUC ratio of 16 is compensated by the rapid absorption of the drug into the tumor nodule [23]. In this treatment protocol, 5-fluorouracil and leucovorin are simultaneously administered intravenously to enhance the activity of oxaliplatin and to achieve bidirectional intraoperative chemotherapy. After the very promising initial report [24], non-randomized comparative studies have been recently published. In one study [25] that compared data from two centers, no clear benefit in outcome for HIPEC with oxaliplatin or mitomycin C could be demonstrated in patients with peritoneal carcinomatosis from colorectal cancer. In a multicenter comparative study [26], data suggested that mitomycin C might be a better agent for HIPEC than oxaliplatin in colorectal cancer patients with favorable histology and low burden of disease. In patients with higher tumor burden before cytoreductive surgery, unfavorable histology and/or severe symptomatology a non-significant better overall survival was found after HIPEC with oxaliplatin. The authors concluded that prospective studies which stratify patients by their initial tumor burden, histology and severity of symptoms and randomize them to HIPEC with mitomycin C versus oxaliplatin are warranted.

Irinotecan has also been used in HIPEC for colorectal carcinomatosis. Its high activity against gastrointestinal cancer, its high molecular weight and the fact that dose intensification leads to an increased efficacy make irinotecan a promising drug for intraperitoneal chemotherapy [8,11,27,28]. Irinotecan itself has little, if any, cytotoxic activity and can exert only its antitumor activity through its metabolite SN-38. This metabolization takes place mainly in the liver, making irinotecan, theoretically, not a candidate for intraperitoneal use. However, high intraperitoneal SN-38 concentrations suggest that metabolization to its active metabolite does not only occur in the liver [8]. Contradicting results regarding synergism between irinotecan and heat have been reported in experimental studies [11]. In a French study [29], the addition of irinotecan to oxaliplatin in HIPEC for colorectal peritoneal carcinomatosis was associated with increased morbidity and did not result in increased survival. In a retrospective analysis [30], bidirectional oxaliplatin-based and bidirectional irinotecan-based HIPEC had similar morbidity and toxicity rates in patients with peritoneal metastases from appendiceal and colorectal cancer, but oxaliplatin-based HIPEC was associated with a trend towards improved survival.

Melphalan is due to its favorable pharmacokinetic profile and tissue distributions combined with its remarkable synergistic effect with heat and cytotoxicity against a wide range of malignancies, including colorectal and appendiceal malignancies, an excellent salvage drug for HIPEC protocols [8,11].

In conclusion, the most optimal drug for HIPEC for colorectal or appendiceal peritoneal carcinomatosis has yet to be defined, but both mitomycin C and oxaliplatin appeared to be highly effective drugs in this setting.

Pseudomyxoma peritonei

Mitomycin C is also for this indication the most frequently used drug in HIPEC [4]. Besides its above mentioned favorable characteristics, it is of importance that cell death occurs regardless of tumor cell proliferative activity, indicating that mitomycin C is also effective against tumors with a low mitotic rate such as pseudomyxoma peritonei [11]. To the author’s knowledge, there are no studies that compare the efficacy of different drugs in HIPEC for pseudomyxoma peritonei.

Gastric cancer

In HIPEC for gastric cancer, either as adjuvant treatment for advanced locoregional disease or as treatment of peritoneal carcinomatosis, mitomycin C and cisplatin are the most frequently used drugs [31,32]. They are used either as a single agent or in combination. The pharmacological profile of mitomycin C has already been discussed. cisplatin is an attractive drug for HIPEC in gastric cancer, despite its moderate pharmacokinetic profile (AUC ratio: 12-22), because of its highly cytotoxic effect against gastric cancer, its significant concentration dependent cytotoxicity, its thermal enhancement and its tumor penetra-
Optimal drugs for HIPEC

Ovarian cancer

Various drugs have been used for HIPEC in ovarian cancer [33]. Most experience is obtained with platinum-derivatives and taxanes, previously shown to be highly effective in systemic chemotherapy for ovarian cancer. Because of their most excellent pharmacokinetic profiles, mainly due to their high molecular weight, both paclitaxel and docetaxel are attractive agents for intraperitoneal use [11,34-37]. The platinum compounds cisplatin and carboplatin do not have such an advantageous pharmacokinetic profile, but multiple studies have demonstrated that they exhibit an evident synergistic effect with moderate hyperthermia [11,38]. Data regarding thermal enhancement of paclitaxel and docetaxel is inconclusive; no effect or, a relatively limited increase of their cytotoxicity, has been observed in several available in vitro studies [37,39] as well as a not yet published in vitro study at the Medical School of Crete. Despite their limited thermal enhancement, pharmacokinetics and cytotoxicity are so favorable that they may also be considered attractive agents for HIPEC. Alternatively, taxanes may be used intraoperatively for intraperitoneal administration under normothermic instead of hyperthermic conditions, thus avoiding eventual adverse effects of heat. The intraperitoneal use of taxanes may especially be indicated in a platinum-resistant disease. Despite their superior pharmacokinetics, drugs such as mitoxantrone, mitomycin C and doxorubicin, have not been as widely used as platinum-derivatives because of their lower cytotoxic effect on ovarian cancer cells [11]. It has yet to be determined which drug is the most effective for each treatment indication in ovarian cancer. In one non-randomized study on HIPEC during secondary surgery [40], no difference in outcome between the use of carboplatin or paclitaxel had been observed.

Malignant peritoneal mesothelioma

Mitomycin C, cisplatin, doxorubicin and docetaxel, as a single drug or in combination with other drugs, have been used in HIPEC for malignant peritoneal mesothelioma [6]. Most frequently, a combination of cisplatin, doxorubicin and mitomycin C is chosen as a drug regimen. Besides doxorubicin, the other drugs have been discussed above. Due to its highly favorable pharmacokinetic profile as a result of its high molecular weight, its sequestration in tumor nodule, the absence of dose-limiting toxicity when used intraperitoneally and its thermal enhancement, doxorubicin is considered an interesting drug for HIPEC [8,11]. Levels of doxorubicin in tumor nodules cannot be predicted by measuring drug concentrations in peritoneal fluid and plasma because sequestration of doxorubicin occurs in tumor tissue, regardless of the underlying pathology or subtype. This sequestration phenomenon, of which the exact underlying mechanism is unknown, may result in improved efficacy of intraperitoneally administered doxorubicin [8]. Due to its rarity and heterogeneity, there are no data available to support a certain drug or drug combination for HIPEC in malignant peritoneal mesothelioma. Recently, a phase II study of intraperitoneal administration of pemetrexed in malignant peritoneal mesothelioma patients has been reported [41]. Since pemetrexed is a highly effective drug in intravenous treatment of malignant pleural mesothelioma, it may be an attractive agent for intraperitoneal chemotherapy for malignant peritoneal mesothelioma.

Patient tailored HIPEC

The efficacy of HIPEC drug protocols is governed not only by the above-mentioned pharmacokinetic and pharmacodynamic variables of the specific drug. Ultimately, individual drug sensitivity of a tumor may be equally important. There is evidence supporting a heterogeneous response of cytotoxic drugs in peritoneal carcinomatosis samples in a variety of tumors [42]. Hence, drug selection based on in vitro drug sensitivity testing may result in improved clinical outcome after HIPEC. Most recently, low expression of Bloom syndrome protein in colorectal cancer cell lines was associated with high sensitivity to heated intraperitoneally administered mitomycin C and in peritoneal metastases of colorectal cancer patients with improved survival [43]. To date, however, there are no prospective data supporting an improved clinical outcome from drug selection based on in vitro drug sensitivity testing.

Conclusions

As HIPEC treatment has not yet been standardized, the drugs and their doses that are used in
Optimal drugs for HIPEC

HIPEC vary widely among centers. The theoretical characteristics of the optimal drug for HIPEC are available, but appropriate prospective comparative clinical studies to determine the most optimal drug or drug combination for HIPEC in different tumor types are lacking. Retrospective analyses are available only for peritoneal carcinomatosis of colorectal and appendiceal origin, which support the use of either mitomycin C or oxaliplatin in HIPEC. Cytoreductive surgery and HIPEC has been successful for many tumor types, but might have been even more effective with the optimal drug or drug combination. Prospective randomized trials are warranted to determine which drug is the most effective for HIPEC in each type of peritoneal surface malignancy. In the future, it would be of major significance when the choice of the most optimal drug in HIPEC may be tailored to the patient’s individual tumor by adequate drug sensitivity testing of the tumor cells.

References

Optimal drugs for HIPEC


