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Review

Pharmacological considerations regarding intraoperative hyperthermic intraperitoneal chemotherapy for ovarian cancer

Eelco de Bree[1,*], Dimosthenis Michelakis[1], Hara Polioudaki[2], Elisabeth Anagnostopoulou[1], Panayiotis A. Theodoropoulos[2]

[1] *Department of Surgical Oncology, Medical School of Crete University Hospital, 71110 Heraklion, Greece*

[2] *Department of Biochemistry, Medical School of Crete, 71013 Heraklion, Greece*

*Correspondence: debree@edu.uoc.gr (Eelco de Bree)

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Since ovarian cancer is limited to the peritoneal cavity for a prolonged period during the disease course, intraperitoneal chemotherapy seems a rational treatment option for residual peritoneal disease after cytoreductive surgery. Intraperitoneal when compared with intravenous chemotherapy exhibits a clear pharmacokinetic benefit. Performing intraperitoneal chemotherapy under hyperthermic conditions, as in intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), may enhance its therapeutic efficacy. Herein, the pharmacological aspects of (hyperthermic) intraperitoneal chemotherapy are discussed, including pharmacokinetics, drug penetration depth into the tumour, drug characteristics, optimal drug choice and the role of hyperthermia. Further clinical pharmacological studies are needed to appraise the optimal drug regimen for HIPEC in patients with primary and recurrent ovarian cancer. Development of new drugs and drug formulations may further improve the efficacy of HIPEC in the future.

Keywords

Ovarian cancer; Intraperitoneal chemotherapy; HIPEC; Hyperthermia; Drug choice; Pharmacokinetics

1. Introduction

Traditionally, advanced ovarian cancer is treated with a combination of cytoreductive surgery (CRS) and systemic chemotherapy. Even after optimal CRS microscopic residual tumour remains in the peritoneal cavity, which is aimed to be eliminated by chemotherapy. In 1955 Weisberger [1] treated patients with ovarian cancer for the first time with intraperitoneal chemotherapy, using nitrogen mustard. Intraperitoneal when compared with intravenous chemotherapy exhibits a clear pharmacokinetic benefit. Performing intraperitoneal chemotherapy under hyperthermic conditions may enhance its therapeutic efficacy [2].

During the last decades, CRS and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been more frequently applied in primary and recurrent ovarian cancer with peritoneal metastases [3]. Comparative non-randomized studies, meta-analysis and more recently randomized studies have shown the effectiveness of this treatment modality in primary and recurrent ovarian cancer [3–5]. The final results of various randomized trials, either still ongoing or with already completed accrual, may help to assess the exact role of this encouraging therapeutic approach. These studies vary essentially in treatment indications (primary or recurrent, platinum-resistant or platinum-sensitive disease), inclusion criteria and timing of HIPEC (after primary, interval or secondary CRS).

Despite the fact that the efficacy of HIPEC appears evident, many treatment parameters as duration, drug regimen and intra-abdominal temperature vary significantly among studies and have not been standardized among centres. In this manuscript, the rationale and pharmacological considerations for HIPEC are discussed.

2. Rationale of intraperitoneal chemotherapy

Ovarian cancer remains limited to the peritoneal cavity for a prolonged period during the course of the disease. Hence, regional instead of systemic therapy seems to be a valid treatment option. Intraperitoneal chemotherapy is such a regional treatment modality. Due to the limited absorption by the seroperitoneal surface and the subsequent drug clearance during the first-pass effect through the liver, high intraperitoneal and simultaneously low systemic drug exposure can be accomplished, resulting respectively in potentially higher cytotoxic efficacy and limited systemic toxicity [2]. Since the penetration depth of intraperitoneal chemotherapy into peritoneal tumour deposits is limited, comprehensive cytoreductive surgery leaving no macroscopic or very small nodules behind is a prerequisite for effective treatment [2].

3. Pharmacological aspects of intraperitoneal chemotherapy

From the nineties until today, much experimental and pharmacokinetic research on intraperitoneal chemotherapy has been performed [6, 7]. Its most important benefit is the delivery of a higher drug dose regionally. This will result in a higher effectiveness of the agent when a dose-effect relation exists, which may defeat the issue of relative drug resistance of cancer cells [6, 7].

After intraperitoneal administration of the chemotherapeutic agent, high intraperitoneal concentrations can be obtained, while concentrations of the drug in the systemic circulation will stay low. This is essentially due to the limited absorption of the drug from the peritoneal cavity into the systemic blood circulation (peritoneal clearance). The so-called 'peritoneal-plasma barrier' is the cause of this pharmacokinetic benefit and consists of peritoneal mesothelium, subserosal interstitium and capillary walls [8, 9]. The latter seems to be the most significant feature in inhibiting the shift of high molecular weight drugs through this barrier from the peritoneal cavity into the systemic circulation. Subsequently, systemic drug exposure may be further reduced by metabolism of the drug in the liver after initially absorbed by the peritoneal surface (first-pass effect) and rapid renal clearance of the drug when in the systemic circulation. The area under the concentration-time curve (AUC) gradient of the drugs from the peritoneal cavity to plasma displays most sufficiently the pharmacokinetic benefit of intraperitoneal delivery of a specific drug. This ratio varies from a factor 10 to a factor 1000, depending mainly on the molecular weight, the hepatic metabolism and renal clearance of the drug [6, 7, 10]. Theoretically, other advantages of intraperitoneal chemotherapy may be that during the initial transport of the drug to the liver and its absorption by peritoneal lymphatics, respectively, concurrent hepatic micrometastases and lymph node metastases may be treated [11, 12].

It might be beneficial when the peritoneal tumour is penetrated by the chemotherapeutic agent not only from the site of the peritoneal cavity, but also from the underlying subperitoneal space [7, 9]. 'Bi-directional chemotherapy', in which simultaneously intraperitoneal and intravenous chemotherapy are administered, and the drug amount that is absorbed from the peritoneal cavity to the systemic compartment during intraperitoneal chemotherapy may result in increased drug concentrations in the subperitoneal space and consequently in the tumour nodules [2, 7, 10].

Whereas the pharmacokinetic advantage and high drug concentrations in the peritoneal fluid are essential, they may not correlate with the drug amount in the target tissue, the residual peritoneal metastases [7]. The limited penetration of the drug into peritoneal metastases is of major concern in intraperitoneal chemotherapy. Although exact data are scarce, the penetration depth is estimated to be maximal a few millimetres for some drugs, while for other drugs it may be in fact a few cellular layers only [13–19]. The issue of limited drug penetration emphasizes the prerequisite of performing optimal CRS before intraperitoneal chemotherapy. Drug penetration into tumour nodules is a complex mass transport process that comprises many factors not only concerning the drug, but also tumour tissue characteristics, such as cell density, interstitial fluid pressure, extracellular matrix, vascularity, and binding [10, 20–23]. Various mathematical models have been developed which can offer exceptional knowledge in this process of drug penetration into tumour tissue during intraperitoneal chemotherapy, facilitating attempts to improve the relatively limited penetration depth of intraperitoneally administered chemotherapeutic agents [20–23].

4. Intraoperative intraperitoneal chemotherapy

When compared to postoperative intraperitoneal chemotherapy, the intraoperative application of intraperitoneal chemotherapy has some benefits. Firstly, intraoperative intraperitoneal chemotherapy provides better exposure of the entire seroperitoneal surface to the drug [2]. In postoperative intraperitoneal chemotherapy, homogenous distribution of the drug solution in the peritoneal cavity may be hindered by multiple adhesions that appear after CRS. Furthermore, the lack of an interval between surgery and chemotherapy prohibits potential regrowth of residual tumour cells, which however may occur when intraperitoneal chemotherapy is applied many weeks after CRS. Moreover, the frequently appearing peritoneal access device-related complications with postoperative intraperitoneal chemotherapy are avoided with performing intraperitoneal chemotherapy intraoperatively. Additionally, intraperitoneal chemotherapy is better tolerated by the patient under general anaesthesia than when the patients is awake, as during postoperative application of intraperitoneal chemotherapy. A demerit of intraoperative when compared with postoperative intraperitoneal chemotherapy is that the treatment duration is substantially shorter and is applied only once immediately after CRS. Experimental studies, however, have shown that even short exposure of ovarian cancer cells to high drug concentrations is very effective in inducing extended cancer cell growth arrest and cancer cell death [24–28]. On the other hand, intraoperative does not as such prohibit the subsequent application of postoperative intraperitoneal chemotherapy. The apprehension that the combination of two major treatment modalities during one procedure, extensive surgery and intraoperative intraperitoneal chemotherapy, exhibits a risk of high cumulative morbidity and mortality does not appear valid. The morbidity and mortality are related to the surgical procedure, i.e., CRS, rather than the intraperitoneal chemotherapy and in expert centres comparable to that of any major abdominal surgery [29–31].

5. Hyperthermia

The concept of carrying out intraoperative intraperitoneal chemotherapy under hyperthermic conditions, as in HIPEC, is based on the fact that hyperthermia increases the cytotoxicity as well as the tissue penetration of many drugs [6, 7, 32–37]. Additionally, local hyperthermia itself has a direct cytotoxic effect [2]. Research data imply that malignant cells are selectively killed by heat at temperatures of 41–43 °C [38]. Despite the fact that the exact mechanisms of this cytotoxicity remain uncertain, it has been demonstrated that hyperthermia causes changes in the cell membrane and nucleus,

protein denaturation and alterations in calcium permeability [38]. Hypoxic malignant cells are much more sensitive to these effects of hyperthermia than regular cells. Moreover, hyperthermia may provoke immune responses against the malignant tumour cells [39]. There might be some uncertainty of the value of adding hyperthermia to intraoperative intraperitoneal chemotherapy since it has been proposed empirically, without data of clinical (randomized) studies of its efficacy and the optimal intra-abdominal temperature being available. According to the centre's protocol, the aimed intra-abdominal temperature of the heated drug solution during HIPEC is usually between 40 and 42 °C for 30 to 120 minutes. Local temperatures of 43 °C and higher may produce thermal injury to organs and other tissues [40].

Recently, however, some studies demonstrated that hyperthermia may have some adverse oncological effects [41]. Hyperthermia may initiate immunosuppressive effects and consequently disease progression [42], whereas the heat shock proteins that are systemically released in high concentrations in patients undergoing HIPEC may impair the efficacy of hyperthermia and chemotherapy [43–47] as well as result in decreased apoptosis and increased tumour cell proliferation, invasiveness and metastatic dissemination [46, 48]. Interleukin-6 release which is induced by hyperthermia can also promote tumour cell proliferation and survival, angiogenesis, and escape of immune surveillance in the tumour microenvironment [49]. Remarkably, in experimental studies [50–52], rats with peritoneal metastases from colorectal or ovarian cancer exhibited longer survival and less morbidity after normothermic when compared with hyperthermic intraperitoneal chemotherapy with mitomycin-C or cisplatin.

Moreover, some concern exists regarding the potential increase of morbidity by addition of hyperthermia to intraperitoneal chemotherapy, including impaired healing of intestinal anastomoses [53–55], increased bacterial translocation from the intestine [56] and a systemic inflammatory response with severe haemodynamic derangements [57, 58]. Finally, hyperthermia seems to cause increased absorption of the chemotherapeutic agent from the peritoneal cavity into the systemic circulation, which consequently may result in higher systemic toxicity [59].

6. Drugs

A proper choice of the drug that is to be used in intraperitoneal chemotherapy is of critical importance [6, 7, 10, 33]. The preferred drug for intraperitoneal use under normothermic or moderate hyperthermic conditions may not be the drug of choice for conventional systemic chemotherapy. The chemotherapeutic agent should have proven efficacy against the malignant disease that is encountered, i.e., ovarian cancer. The drug should have a favourable pharmacokinetic profile after intraperitoneal administration (a high intraperitoneal to plasma concentration or AUC ratio) and there should exist proof for concentration- or exposure-dependent cytotoxicity of the drug. When there is not such an evidence, traditional systemic drug administration may be favoured because its efficacy might then be equal, whereas the treatment is less complicated. Moreover, local toxicity of the drug should be minor or absent, while the drug of choice needs to be cytotoxic itself, not requiring metabolism to its active form in the liver. Due to the short duration of intraoperative intraperitoneal chemotherapy, the use of antimetabolites may not be preferable. Furthermore, drugs with better penetration and accumulation in the tumour nodule are considered to be favourable. When administered intraperitoneally under hyperthermic conditions, as in HIPEC, documented synergism of the chemotherapeutic agent with clinically applicable hyperthermia is compulsory. Various chemotherapeutic agents have been used for HIPEC in ovarian cancer (Table 1, Ref. [3, 6, 7]). However, cisplatin, carboplatin and paclitaxel, drugs that all have demonstrated their effectiveness in systemic chemotherapy for ovarian cancer, have been used most frequently [3, 33, 60, 61].

6.1 Cisplatin

Cisplatin has been widely administered for intraperitoneal chemotherapy in ovarian cancer, although its pharmacokinetic profile is less advantageous than that of other drugs. The reported mean intraperitoneal to plasma concentrations and AUC ratios range from 10 to 36 and 12 to 22, respectively [6, 7, 10, 33]. Due to its significantly increased cytoxicity at higher drug concentrations and its favourable penetration depth which is reported up to 3–5 mm, cisplatin is considered an attractive drug for intraperitoneal chemotherapy [6, 15, 18]. Whereas thermal enhancement of the cytotoxicity of cisplatin has been demonstrated in the past [6, 33, 35–37], making it an interesting agent for HIPEC, recent *in vitro* studies on gastrointestinal and ovarian cancer cell lines failed to demonstrate such an effect at clinically relevant elevated temperatures [62, 63].

Regarding its toxicity, the main concern is the occurrence of nephrotoxicity and acute renal failure [15, 64, 65]. Adequate hydration of the patient is warranted to reduce the incidence of acute kidney injury. Furthermore, intravenous administration of sodium thiosulfate, a chelator of cisplatin forming inactive compounds that are not toxic to the kidneys, during and after HIPEC may possibly reduce cisplatin-induced nephrotoxicity [66]. This strategy was used for ovarian cancer patients in the recent Dutch HIPEC trial [5]. Similarly, the preoperative administration of amifostine, a thiophosphate that is metabolized by alkaline phosphatase to a thiol product capable of binding metabolites of platinum and free radicals, has been proposed to potentially protect the kidneys during HIPEC with cisplatin. In a preclinical mouse model, amifostine failed to provide a nephroprotective effect during HIPEC with cisplatin [65], but in a small retrospective comparative study [67], the administration of amifostine reduced the incidence of severe renal insufficiency, although the total incidence of renal insufficiency was not altered. The major concern with the use of both sodium thiosulfate and amifostine is that their binding with cisplatin and its metabo-

Table 1. Main characteristics of drugs administered in intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer [3, 6, 7].

Drug	Molecular weight	AUC ratio	Thermal enhancement	Penetration depth
Alkylating agents				
Mitomycin C	334.3	13–80	+	2–5 mm
Melphalan	305.2	17–63	+	NA
Platinum compounds				
Cisplatin	300.1	12–22	+	1–5 mm
Carboplatin	371.3	15–20	+	0.5 mm
Topoisomerase inhibitors				
Doxorubicin	580.0	162–230	+	4–6 cell layers
Mitoxantrone	444.5	1100–1400	+	NA
Antimicrotubule agents				
Paclitaxel	853.9	550–2300	- / minimal	>80 cell layers
Docetaxel	861.9	150–3000	- / minimal	1.5 mm

AUC, area under concentration versus time curve; AUC ratio, peritoneal fluid AUC/systemic AUC; NA, no data available.

lites may simultaneously decrease the cytotoxic effect of cisplatin in the peritoneal metastases. In a recent study [68], administration of cilastatin, a selective inhibitor of renal dehydropeptidase I in the proximal renal tubule cells, appeared to have a nephroprotective effect in patients undergoing HIPEC with cisplatin. Cilastatin is not commercially available alone, but only in combination with imipenem as the antibiotic Primaxin®.

The cisplatin dose that is used in different centres varies from 50 to 120 mg/m^2. A dose of 100 mg/m^2 cisplatin was chosen in the Dutch randomized trial, which showed improved survival by the addition of HIPEC to interval CRS in patients with advanced primary ovarian cancer [5].

6.1.1 Carboplatin

Carboplatin, another platinum compound that has been effectively used in systemic chemotherapy for ovarian cancer, exhibits similar pharmacokinetics after intraperitoneal administration. The peritoneal to plasma AUC ratio is 15–20 in various pharmacokinetic studies [6, 7, 10, 33]. Although the toxicity profile of carboplatin is favourable compared to that of cisplatin, essentially because of lacking the risk of renal insufficiency, cisplatin has been used more frequently. The reasons for the less frequent use of carboplatin in clinical practice is that, when compared with cisplatin, the synergistic effect of carboplatin is noticed only at higher temperatures and the penetration into tumour nodules is much more limited [69, 70]. The doses that have been used in clinical studies differ from 300 to 1000 mg/m^2.

6.1.2 Paclitaxel

The taxane paclitaxel, an antimicrotubule agent, is one of the most effective drugs against ovarian cancer and has a highly favourable pharmacokinetic profile after intraperitoneal administration, with a peritoneal to plasma AUC ratio varying between 550 and 2300 in pharmacokinetic studies [6, 7, 71–73]. Its advantageous pharmacokinetics are mainly caused by its high molecular weight and hydrophobic properties which both hinder absorption from the peritoneal cavity into the systemic circulation. Since treatment response to paclitaxel seems to be dose-dependent for systemic chemotherapy, the high locoregional concentrations obtained during intraperitoneal chemotherapy are assumed to result in improved effectiveness [7]. Regarding its penetration into tumour nodules, an *in vitro* experimental study demonstrated a penetration depth of approximately 40 cell layers in 4 hours and over 80 cell layers after 24 hours [74], whereas in a clinical study a depth of only 0.5 mm was found [75]. The most commonly used dose is 175 mg/m^2, which is generally well tolerated [71–73, 76–78]. Its superior activity against ovarian cancer and its promising pharmacokinetic profile resulted also in its use as single agent for HIPEC in initiated randomized trials (NCT02681432, NCT04280185) [76].

Paclitaxel has also been used in combination with other drugs. In a randomized HIPEC trial, 175 mg/m^2 paclitaxel was used in combination with 100 mg/m^2 cisplatin in for platinum-sensitive ovarian cancer recurrence and in combination with 35 mg/m^2 doxorubicin for platinum-resistant recurrence, with acceptable toxicity [4]. In a multicentre Italian study, the HIPEC regimen for both primary and recurrent disease was a combination of 175 mg/m^2 paclitaxel with 100 mg/m^2 cisplatin, which was well tolerated also in this study [79].

The use of paclitaxel for HIPEC may not be appropriate because thermal enhancement seems to be limited, or even absent, in experimental studies [28, 41, 71]. Therefore, paclitaxel could be administered for normothermic intraoperative intraperitoneal chemotherapy, exploiting its well-known great effectiveness against ovarian cancer, proved in systemic chemotherapy and experimental studies, as well as its highly favourable profile reported in pharmacokinetic studies, while avoiding the potential oncological adverse effects and morbidity of additional hyperthermia [41]. Results of a small randomized trial (NCT02739698) comparing

hyperthermic with normothermic intraoperative intraperitoneal chemotherapy with paclitaxel after CRS for ovarian cancer are eagerly awaited [76].

6.1.3 Docetaxel

Docetaxel, another taxane which is also highly effective in the systemic chemotherapy of ovarian cancer, has been less often administered in intraperitoneal chemotherapy. Docetaxel may even be more effective in intraperitoneal chemotherapy, since in our recent experimental study with drug concentrations mimicking those of intraperitoneal chemotherapy, docetaxel was more cytotoxic than paclitaxel [41]. Pharmacokinetic studies demonstrated for docetaxel a promising profile comparable to that of paclitaxel, with a peritoneal to plasma AUC ratio of 150–3000 [6, 7, 71, 72, 80]. Similar to paclitaxel, thermal enhancement is limited or absent for docetaxel, while the depth of tumour penetration is appraised to be 1.5 mm [28, 41, 72, 72]. With the most common dose of 75–125 mg/m^2, its toxicity profile is generally well tolerated. Its favourable profile has led to its use as a single agent (75 mg/m^2) in an ongoing randomized trial (NCT03373058) [76].

6.1.4 Doxorubicin

The anthracycline doxorubicin, a topoisomerase inhibitor, has been used less frequently for intraperitoneal chemotherapy in ovarian cancer. Doxorubicin appears to be an interesting drug for intraperitoneal chemotherapy, as a result of its proven effectiveness against ovarian cancer, its concentration-related response and its advantageous pharmacokinetic profile (peritoneal to plasma AUC ratio: 162–230) [6, 7]. The penetration depth of doxorubicin after intraperitoneal administration has been found to be just 4–6 cell layers in a mouse ovarian cancer model [13], but in a clinical study, doxorubicin concentrations were higher in tumour tissue than in the peritoneal fluid [81]. The mechanism of such a sequestration phenomenon has not been elucidated. Its efficacy appears to be increased under hyperthermic conditions [37, 82, 83]. Doses of 15–35 mg/m^2 have been used. Its toxicity profile seems to be worse than of platinum compounds [84].

Pegylated liposomal doxorubicin has been administered in intraperitoneal chemotherapy, exhibiting an even more favourable pharmacokinetic profile (peritoneal to plasma AUC ratio: $\geq$1100) and increased uptake into peritoneal metastases [6, 7, 85, 86]. Hyperthermia increases the release of doxorubicin, tumour uptake of liposome-encapsulated doxorubicin into the tumour nodules, although not of free doxorubicin, and the drug's cytotoxicity [6, 87]. Doses that have been applied vary between 40 and 100 mg/m^2. The toxicity of intraperitoneally administered pegylated liposomal doxorubicin is tolerable. The systemic side effects are less than those observed with conventional doxorubicin.

6.1.5 Mitomycin C

Mitomycin C, an alkylating antibiotic, has been widely used in HIPEC for colorectal cancer and pseudomyxoma, mainly because of its well documented and substantial synergistic effect with hyperthermia [7, 37]. It has been used less frequently for ovarian cancer. Although its cytotoxic activity against ovarian cancer is less than for other, above mentioned, drugs, most probably the centre's expertise with this agent in other peritoneal malignancies, as in pseudomyxoma peritonei and peritoneal metastases from colorectal cancer, has been the reason for applying mitomycin C also in ovarian cancer [88]. Its intraperitoneal administration is associated with an advantageous pharmacokinetic profile (mean peritoneal to plasma AUC ratio: 13–80), while the penetration into tumour deposits has been appraised to be 2–5 mm in depth [7, 89]. Dosimetry varies from 12.5 to 15 mg/m^2 in a single dose to 35 mg/m^2 split in three sequential fractions (50%, 25% and 25% with 30-minute intervals) [10, 91]. The latter provides a more stable, high intraperitoneal concentration throughout the HIPEC-89procedure [49]. The adverse systemic effects are usually minor.

6.1.6 Melphalan

Melphalan is an efficacious alternative drug in HIPEC. This alkylating agent exhibits positive pharmacokinetics (peritoneal to plasma AUC ratio: 17–63), while its significant synergistic effect with hyperthermia is substantial [6, 7, 10, 37, 90]. It is mainly used as salvage treatment for recurrent peritoneal metastases in gastrointestinal as well as ovarian cancer [91, 92]. The usual dose is 50–70 mg/m^2, at which the adverse effects are acceptable.

6.2 Clinical HIPEC studies comparing drug regimens

Comparison between HIPEC drug regimens is very difficult since randomized trials, as in systemic chemotherapy, are lacking. The few reported comparative clinical studies on HIPEC for ovarian cancer are retrospective and limited in number of patients. In a South Korean study on CRS and HIPEC with carboplatin or paclitaxel for recurrent ovarian cancer [78], no substantial superiority of one of the drugs in clinical outcome was observed. Another, Spanish, comparative study could also not demonstrate a difference in the efficacy between the same drugs [79].

6.3 Patient-tailored drug choice

The above discussed specific drug pharmacokinetics and pharmacodynamics are not the only parameters for the prediction of potential effectiveness of specific HIPEC regimens. Eventually, sensitivity of an individual tumour to a specific drug is furthermore of high significance and a more individualised approach for drug selection may be beneficial. Heterogeneous responses to cytotoxic drugs in samples of peritoneal metastases in a variety of tumours, including ovarian cancer, have been demonstrated [92]. For individual patients, *in vitro* assessment of drug sensitivity has shown satisfactory correlation with clinical response after systemic chemotherapy for ovarian cancer [93]. Consequently, although doubted in a

small retrospective study [94], patient-tailored drug choice for HIPEC according to results of *in vitro* drug sensitivity testing for the individual tumour may result in optimisation of drug selection and consequently improved efficacy. In colorectal cancer, low expression of Bloom syndrome protein has been correlated with increased sensitivity to HIPEC with mitomycin C and better survival [95]. As yet, however, prospective studies on the clinical implication of a patient tailored drug choice based on *in vitro* testing of drug sensitivity have not been performed.

7. Future directions

7.1 New drug formulations

One of the main constraints of HIPEC is the short duration of treatment, although for example effective concentrations of paclitaxel and docetaxel are detectable in drain fluid for some days after the HIPEC procedure [73, 80]. Experimental data suggest that formulations with prolonged intraperitoneal release administered as thermosensitive hydrogels or gelatin microspheres result in sustained (up to 14 days) exposure of residual peritoneal disease, whereas they simultaneously may prohibit formation of adhesion postoperatively [96, 97]. Others have developed cisplatin-loaded polyarginine-hyaluronic acid nanoscale particles, which demonstrated increased anti-tumour efficacy when compared with free cisplatin after intraperitoneal administration in a rat model [98]. This development of new drug formulations may further improve the efficacy of HIPEC for peritoneal malignancies, such as advanced ovarian cancer, in the future.

7.2 Pressurized intraperitoneal aerosol chemotherapy

Especially when optimal CRS cannot be performed, in recurrent ovarian cancer and as palliative treatment, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin, another intraperitoneal chemotherapy modality, may be an alternative treatment option [99–101]. The novel concept of PIPAC uses the physical properties of gas and pressure to distribute the drug considerably homogeneous within the peritoneal cavity and to enhance drug uptake in the tissues. The penetration depth seems to be higher than in conventional intraperitoneal chemotherapy, while the technique is repeatable using minimal invasive access. Because of the high local bioavailability during PIPAC, the drug dose can be reduced resulting in low systemic toxicity.

The PIPAC-technique concerns a minimal invasive surgical procedure [99]. The abdomen is accessed with one 10–12 mm trocar for the nebuliser and one 5 mm trocar for visibility with a camera in the abdomen. The abdomen is insufflated with CO2 under standard pressure conditions (12 mmHg). Intraperitoneal chemotherapy containing oxaliplatin alone, for gastrointestinal malignancies, or cisplatin followed by doxorubicin injected in sequence, for gynaecological malignancies, is then applied as an aerosol using a standard high-pressure injector and using a procedure-specific nebuliser. After injection, the therapeutic capnoperitoneum is maintained for 30 min before the remaining aerosol is evacuated into a closed aerosol waste system through two microparticle filters in the wall outlet. With strict safety protocols, existing to avoid exposure of the personnel to chemotherapeutic aerosols, the risk of occupational exposure is very low [99].

Doses for the combined cisplatin (10.5 mg/m^2) and doxorubicin (2.1 mg/m^2) regimen were defined by a single dose-escalation study in patients with ovarian cancer [102]. While initially the dose for oxaliplatin (92 mg/m^2) had been empirically chosen as 20% of the dose for HIPEC, a most recent dose escalation study confirmed 90 mg/m^2 to be the optimal dose [103]. At higher concentrations of oxaliplatin the systemic absorption and consequently the toxicity increased significantly. Systemic uptake under PIPAC was minimal in various studies [99, 104]. In an experimental animal study [105], increased pressure during PIPAC resulted in higher tissue penetration depth of doxorubicin. Paclitaxel has been tested as an alternative drug in another animal model [106]. PIPAC with paclitaxel resulted in lower systemic drug exposure than with intravenous administration and higher tissue penetration depth than with HIPEC.

Clinical studies of PIPAC limited to ovarian cancer are sparse and mostly of retrospective nature. In the only prospective, phase 2, study [107], treatment with 3 courses of PIPAC was well tolerated and effective in 53 patients with recurrent ovarian cancer. Grade 3 toxicity was noted in 15% of the patients, of which half were surgery-related, while grade 4 toxicity and mortality were not observed. Sixty-two percent of the patients had an objective response and quality of life improved during therapy. However, the definite role of this novel therapy as an alternative to the existing treatment options has still to be established. It remains an experimental treatment modality and should not be performed outside the framework of prospective, controlled studies, as stressed by the AGO [108]. The results of ongoing randomized trials comparing systemic chemotherapy with PIPAC in platinum-resistant recurrent ovarian cancer are eagerly awaited [109, 110]. Moreover, selected patients with initially unresectable peritoneal metastases may be eligible to CRS and HIPEC after a good response to PIPAC [111].

7.3 Isolated abdominal perfusion

Another, recently recommenced, treatment concept for advanced abdominal malignancies, isolated abdominal perfusion chemotherapy, has been also used for inoperable platinum-resistant recurrences of ovarian cancer [112]. This intraoperative regional chemotherapy is based on the blockage of the blood circulation of the tumour area by means of inflatable balloon catheters in the aorta and the caval vein as well as tourniquets at the extremities, while perfusion of the isolated area is performed with an extracorporeal pump circuit [105]. High regional drug concentrations with concurrently low systemic toxicity can be obtained due to the vascular isolation of the target area and chemofiltration at the end of the procedure. Mitomycin C concentrations and AUCs

are, respectively, 10 and 4 times higher in the isolated abdominal than in the systemic blood compartment [113], while in an experimental study exposure to mitomycin C of abdominal tissues was 3 to 10 times higher with isolated abdominal perfusion as compared with intravenous chemotherapy [114]. In another pharmacokinetic study [115], the abdominal exposure (AUC) to gemcitabine was 5.5 to 200 times higher than the systemic exposure during isolated abdominal perfusion for advanced pancreatic cancer. As in HIPEC, the efficacy of the regional chemotherapy is assumed to be higher with increased drug exposure, which may overcome potentially also chemoresistance. Moreover, the perfusion circuit is not oxygenated and the resulting decrease in tissue oxygenation and pH enhances the cytotoxic effect of some drugs, like mitomycin C and doxorubicin [105]. Isolated abdominal perfusion chemotherapy is repeatable, associated with an acceptable morbidity and even well tolerated by elderly patients and by patients who have undergone prior chemotherapy and/or radiotherapy [113, 116, 117].

In a recent study [117], 107 patients with advanced abdominal platinum-resistant recurrence of ovarian cancer were treated with isolated abdominal perfusion with cisplatin, mitomycin C and doxorubicin. Complete and partial response rates were observed in 17% and 52%, respectively. In a pilot study [118], response to chemotherapeutic agents could be predicted by chemosensitivity and gene expression assays using circulating tumour cells from those patients in patients treated for recurrent ovarian cancer with isolated abdominal perfusion chemotherapy. Future studies may assess whether initially inoperable peritoneal lesions with significant tumour regression after isolated abdominal perfusion may become operable and subsequently be treated with CRS and HIPEC.

8. Conclusions

There is definitely a rationale for intraoperative intraperitoneal chemotherapy as treatment modality for advanced ovarian cancer, since it is confined to the abdominal cavity for a prolonged period. Intraperitoneally administered chemotherapy is associated with a highly favourable pharmacokinetic and pharmacodynamic profile. While the addition of hyperthermia, as in HIPEC, may have a direct cytotoxic effect and enhance the efficacy of many chemotherapeutic drugs, recently there has been concern regarding the potential adverse oncological effects of hyperthermia. Because of the limited penetration depth of intraperitoneally administered drugs, optimal CRS is a prerequisite.

While many parameters of treatment with HIPEC have not yet been standardized, optimal drug choice is essential. The drugs and their doses that are used in HIPEC for ovarian cancer vary among centres. Parameters as high activity against ovarian cancer, pharmacokinetic and pharmacodynamic profile, penetration depth, enhanced effect with hyperthermia and toxicity should be considered. The use of drugs with a more favourable pharmacokinetic and pharmacodynamic profile which however lack the benefit of thermal enhancement (i.e., paclitaxel, docetaxel) under normothermic conditions might be preferable over using drugs for HIPEC with increased cytotoxicity under hyperthermic conditions and a less advantageous pharmacokinetic and pharmacodynamic profile (i.e., cisplatin, carboplatin, mitomycin C, melphalan), avoiding the potential adverse effects of hyperthermia. Moreover, drugs with a higher tissue penetration depth may especially be preferred when CRS is less optimal, with larger residual tumour nodules left behind. Generally, the tissue penetration depth of drugs with a higher molecular weight may be less than that of smaller chemotherapeutic agents. Currently, cisplatin (100 mg/m^2) and paclitaxel (175 mg/m^2) are the most often used agents.

Unfortunately, there are no randomized clinical studies to define the most adequate drug or combination of drugs available. In two small retrospective comparative clinical studies on HIPEC for ovarian cancer, superiority of either carboplatin or paclitaxel could not demonstrate. Hence, at present there is no proof from clinical studies that a specific drug regimen is the most effective. Further clinical pharmacological studies are required to define the optimal drug regimen for HIPEC in patients with primary and recurrent ovarian cancer. In the future, it is likely that drug sensitivity testing and genetic profiling may provide data for a patient-tailored drug regimen in HIPEC. Moreover, the development and application of new drug formulations, and possibly the combination with alternative treatment modalities, may further improve the efficacy of HIPEC in ovarian cancer.

Author contributions

EB, DM, HP, EA and PAT reviewed and analysed literature data. EB wrote the manuscript with contribution of DM, HP, EA and PAT. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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