HIPEC Methodology and Regimens: The Need for an Expert Consensus

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ABSTRACT

Background. Hyperthermic intraperitoneal chemotherapy (HIPEC) is performed with a wide variation in methodology, drugs, and other elements vital to the procedure. Adoption of a limited number of regimens could increase the collective experience of peritoneal oncologists, make comparison between studies more meaningful, and lead to a greater acceptance of results from randomized trials. This study aimed to determine the possibility of standardizing HIPEC methodology and regimens and to identify the best method of performing such a standardization.

Methods. A critical review of preclinical and clinical studies evaluating the pharmacokinetic aspects of different HIPEC drugs and drug regimens, the impact of hyperthermia, and the efficacy of various HIPEC regimens as well as studies comparing different regimens was performed.

Results. The preclinical and clinical data were limited, and studies comparing different regimens were scarce. Many of the regimens were neither supported by preclinical rationale or data nor validated by a dose-escalating formal phase 1 trial. All the regimens were based on

pharmacokinetic data and did not take chemosensitivity of peritoneal metastases into account. Personalized medicine approaches such as patient-derived tumor organoids could offer a solution to this problem, although clinical validation is likely to be challenging.

Conclusions. Apart from randomized trials, more translational research and phases 1 and 2 studies are needed. While waiting for better preclinical and clinical evidence, the best way to minimize heterogeneity is by an expert consensus that aims to identify and define a limited number of regimens for each indication and primary site. The choice of regimen then can be tailored to the patient profile and its expected toxicity and the methodology according regional factors.

EVOLUTION OF INTRAPERITONEAL CHEMOTHERAPY AND CURRENT INDICATIONS FOR ITS USE

Intraperitoneal chemotherapy (IPC) was developed in the 1980s when the use of intravenous (systemic) chemotherapy treatment for peritoneal metastases (PMs) was producing dismal results, and regional chemotherapies with or without hyperthermia were being developed for different tumors.^{1,2} It was assumed that PMs are poorly vascularized compared with metastases at other sites due to drugs unable to reach the tumor site, leading to a comparatively poorer response to systemic chemotherapy (SC).³ Intraperitoneal chemotherapy would allow direct exposure of the tumor nodules to the

chemotherapeutic agent, and the two-compartment model of drug transport across the peritoneal membrane supported this therapeutic rationale.⁴⁻⁶

Research has demonstrated that the peritoneum is a well-vascularized structure and that the reason for a poor response is not only inability to deliver the drug to the tumor, but most likely also the inherent chemoresistance of the tumor cells resulting from an adverse molecular profile.^{7,8} Peritoneal metastases arising from low-grade appendiceal mucinous tumors are of the low-grade variety and therefore respond poorly to SC.⁹ In contrast to this, PMs in ovarian cancer have a high response rate (80%) to SC, with 10–15 % of patients experiencing a pathologic complete response.¹⁰⁻¹¹

Patients with extensive PMs are symptomatic more often than their counterparts with metastases at other sites.¹² The symptoms of PMs have a negative impact on quality of life and performance status, making it more difficult to administer aggressive systemic therapies. Improvement in imaging and identification of risk factors for the development of PMs have led to an increase in early diagnosis of PMs when they are likely to be more responsive to SC.¹³⁻¹⁵ This coupled with the development of more effective SC regimens during the last 30 years has led to an improvement in the outcomes with SC alone as well as the combination of surgery and SC.¹⁶⁻¹⁸

Despite the progress in systemic therapies, surgery remains the cornerstone of potentially curative treatment for patients with PMs irrespective of the primary tumor site. Regional chemotherapy or IPC has a role to play in addition to surgery and systemic chemotherapy.

MODES OF INTRAPERITONEAL DRUG DELIVERY

The three most common modes for administering IPC are instillation of multiple doses through an intraperitoneal catheter (port-directed IPC or normothermic IPC [NIPEC]), multiple applications of aerosolized chemotherapy with raised intraabdominal pressure (pressurized intraperitoneal chemotherapy [PIPAC]), and intraoperative application of chemotherapy agents during surgery using hyperthermia (hyperthermic intraperitoneal chemotherapy [HIPEC]), usually performed only once.¹⁹ The current indications for the use of IPC are summarized in Table 1.

IS INTRAPERITONEAL ADMINISTRATION OF CHEMOTHERAPEUTIC AGENTS A SOUND THERAPEUTIC RATIONALE?

Intraperitoneal chemotherapy entails off-label use of drugs meant for intravenous administration. The theoretical benefits apart from a direct exposure of tumor cells to the

drug are a prolonged retention of the drug in the peritoneal cavity, resulting in prolonged exposure of the peritoneal surfaces to the drug and a decreased systemic absorption resulting in reduced systemic toxicity.^{36,37} Thus, IPC allows higher drug doses to be administered without the resultant systemic toxicity.

Another possible mechanism often ignored is possible access of IPC to the peritoneal lymphatics, thus acting on translymphatic tumor spread.^{38,39}

For all three modes of intraperitoneal (IP) administration, despite uneven distribution of the chemotherapy solution in the peritoneal cavity, a therapeutic benefit has been observed.^{40,41} Access to the transperitoneal lymphatics enables the drug to reach all areas because these lymphatics are connected subperitoneally.

The depth of conventional IPC penetration usually is not more than 3 mm, but may reach 6 mm around the microinjection pump in PIPAC.^{42,43} Thus, it acts best in the presence of minimal or no residual disease. After complete cytoreductive surgery (CRS), IPC can address the free intraperitoneal cancer cells more effectively, reducing the implantation of these cells at the surgical site.

However, all three modes of IPC have shown benefits in the neoadjuvant/palliative setting also in the presence of gross disease, used either alone or in combination with SC.⁴⁴⁻⁴⁷ The IPC may be acting on the translymphatic spread or in combination with SC, which reduces the size of tumor nodules, facilitating destruction by IPC. This may be an important mechanism that can explain the differential response in different tumors. Translymphatic spread is seen in tumors such as peritoneal mesothelioma, pseudomyxoma peritonei, and epithelial ovarian cancer, and these tumors are the most responsive to IPC. In limited colorectal PM, it may be less effective given the different mechanism of spread, namely, transmesothelial, which is in contrast to the aforementioned translymphatic route.⁴⁸

Hyperthermia has many theoretical benefits. Heat itself is cytotoxic. It potentiates the cytotoxicity of the chemotherapeutic drugs, and in some instances helps in overcoming drug resistance.⁴⁹⁻⁵⁰ Despite clear demonstration of these benefits in preclinical models, the clinical benefit has not been validated in the treatment of PM. Because the hyperthermia clearly complicates the logistics of IPC, it needs further validation. Therefore, IPC should be regarded as an adjunct to surgery, SC, or both.

HIPEC

Hyperthermic intraperitoneal chemotherapy is the most controversial component of multi-modality treatment for PM. While evidence from randomized trials is accumulating in favor or disfavor of HIPEC, the procedure itself

TABLE 1 Current indications for different methods of intraperitoneal chemotherapy

Type of IPC	Primary tumor site	Level of evidence	GRADE of evidence ^a	Comment on the GRADE	Timing of IPC	Disease time point(s)
HIPEC	Colorectal	1 ^{20–22,51}	Low	One RCT was negative; one case-controlled study with many limitations showed a benefit of HIPEC over CRS alone.	With CRS	Metachronous/synchronous PM
	Stomach	3 ²³	Low	Based on the results of an observational study in which propensity score-matching was done for the confounding factors, the HR was >0.5 for CRS+HIPEC vs CRS alone. Hence the GRADE of evidence is “low.”	With CRS	Synchronous PM
	Ovary	1 ²⁴	Moderate	Based on the results of one randomized trial. The benefit in the primary end point (PFS) was less than the benefit in the secondary end point.	With CRS	Interval CRS
	Pseudomyxoma peritonei	3 ^{25–27}	Low	Based on the results of an observational study in which propensity score-matching was done for the confounding factors. The HR was >0.5 for CRS+HIPEC vs CRS alone. Hence the GRADE of evidence is “low.”	With CRS	–
	Peritoneal mesothelioma	4 ²⁸	Low	Although no study has evaluated the role of HIPEC in addition to CRS, the benefit of CRS-HIPEC over SC alone is fourfold when historical data is compared. Hence, the grade is low and not “very low” for this very rare disease	With CRS	–
NIPEC	Ovary	1 ^{29–32}	High	Based on the results of RCTs	Adjuvant therapy	Primary and interval CRS
	Stomach	4 ³³	Low	Based on the results of prospective and retrospective studies that do not have a comparator arm and do not evaluate the benefit of NIPEC alone	Neoadjuvant therapy	Synchronous PM
	Colorectal	1 ³⁴	Moderate	Based on the results of one RCT that due to poor accrual had to be closed prematurely	Adjuvant therapy	Metachronous/synchronous PM
PIPAC	Various primary tumors	4 ³⁵	Low	Based on the results of prospective and retrospective studies that do not have a comparator arm and do not evaluate the benefit of PIPAC alone	Neoadjuvant therapy for unresectable disease; palliation	Synchronous/metachronous PM

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IPC, intraperitoneal chemotherapy; RCT, randomized controlled trial; HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; PM, peritoneal metastases; HR, hazard ratio; NIPEC, normothermic intraperitoneal chemotherapy; PFS, progression-free survival; PIPAC, pressurized intraperitoneal aerosolized chemotherapy

^aThe GRADE method of rating evidence is summarized in Table 5.

continues to be performed with a wide variation in the methodology, drugs, and other elements vital to the procedure. The recently published PRODIGE 7 trial did not show a benefit of adding HIPEC to CRS for patients with colorectal PM.⁵¹ One of the many questions raised about the trial has focused on the choice of drug regimen, and it has been proposed that an alternative regimen could have

resulted in a positive outcome.⁵² This question is perhaps the most difficult to answer given the numerous regimens that have been used to perform HIPEC.

Having a limited number of regimens could increase the experience of the peritoneal oncology community, make comparison between studies more meaningful, and lead to a greater acceptance of the results from randomized trials.

We performed a review of literature reporting the preclinical and clinical data on HIPEC regimens as well as studies and trials comparing different HIPEC regimens to determine the possibility of standardizing HIPEC regimens. Our aim was also to determine what the basis of such standardization should be and the best method for identifying a limited number of regimens that could be adopted by peritoneal malignancy centers across the world.

METHODS

A review of Pubmed, Medline, and Embase library databases was performed using the terms “HIPEC regimen,” “HIPEC methodology,” “HIPEC drugs,” “peritoneal carcinomatosis,” and “peritoneal metastases.” The search aimed to identify preclinical studies that evaluate the pharmacokinetic aspects of different HIPEC drugs or drug regimens and those evaluating the impact of hyperthermia as well as the efficacy of different HIPEC regimens. For this study, clinical trials including phases 1 and 2 dose-finding studies and phases 2 and 3 randomized controlled trials, trials evaluating the efficacy of HIPEC, and trials comparing different drugs and drug regimens and HIPEC methodology were considered. Similarly, prospective and retrospective studies reporting on the same parameters (dose range, efficacy) and comparisons of different methodologies and regimens were considered. A critical appraisal of the available evidence was performed by the authors to identify the parameters pertaining to HIPEC methodology and regimens that need to be standardized as well as the best method of performing such a standardization.

RESULTS

This section, alongside the results of the literature search, describes the key technical aspects of performing HIPEC.

HIPEC Methodology and Clinicopharmacologic Variables

The HIPEC procedure involves the circulation of a heated chemotherapy solution in the peritoneal cavity for 30 to 120 min using a roller pump and heat exchanger (now custom-made machines). The abdomen is kept open, semi-open, or closed during the process. A number of clinical and pharmacologic variables influence the efficacy of the procedure. Unlike SC, with the drug administered in a closed compartment, because the peritoneal cavity represents a huge space with a very variable volume according to the sex and body habitus. HIPEC is performed after

CRS, which involves resection of varying amounts of the peritoneum and adjacent viscera. Thus, variations in the methodology are inevitable, and the impact of different variables is difficult to quantify and control.

Pharmacologic Factors The impact of pharmacologic factors on the efficacy of HIPEC includes pharmacokinetic variables such as the drug (combination), dosage, molecular weight, carrier solution and its volume, application time and intraabdominal pressure, and pharmacodynamic variables such as tumor nodule size, density, vascularity, interstitial fluid pressure, binding, and temperature.⁵³

Drug Dosing *Threshold and Peak Doses* Drug dosing is based on preclinical and clinical data. Two dose limits should be considered: the “threshold dose,” which is the minimum dose required to produce a therapeutic effect, and the “peak dose,” which is the maximum dose above which additional therapeutic benefit is not observed or unacceptable toxicity is observed.⁵⁴

The first method uses *in vitro* studies to determine the minimal toxic dose on cancer cell lines, and based on this, the IP dose is calculated. This is used as the threshold dose. The minimum or threshold dose of irinotecan is 50 mg/m², and the threshold dose of mitomycin C is 10 mg/m² (Table 2).^{55,56} For doxorubicin, the IP dose is much lower than the intravenous (IV) dose due to the risk of peritoneal sclerosis as doses exceed 15 mg/m².^{25,58} No threshold dose of this drug is known. Subsequently, dose escalation studies are performed to determine the peak dose.⁵⁹ The cell lines, however, have a major limitation of not capturing the tumor microenvironment, which has a major influence on the drug uptake and its efficacy.

The second method is to use the IV dose as a reference, and the baseline dose is a multiple of the IV dose. For oxaliplatin, the IV dose of 120 mg/m² was used as a reference standard to develop two different regimens. The peak dose was 460 mg/m² for a 30-min application and 200 mg/m² for a 2-h HIPEC.^{60,61} Similarly for cisplatin, 50 mg/m² was used as the minimum dose, and further increments of 50 % were tested for toxicity in two phase I trials. Notably, the dose-limiting toxicity was observed at different doses in the two trials, with each recommending a different ceiling dose.^{62,63} For gemcitabine, the IP dose required to achieve a target plasma level of the drug was used as a reference in one study, and the intravenous dose was used in other dose-finding studies.^{63–65}

Both the threshold and peak doses are determined by a third (and probably most important) variable, namely, the duration of exposure. In the high-dose oxaliplatin regimen, the high dose of the drug was used to account for the short perfusion time. In an experimental study (unpublished

TABLE 2 Peak and threshold doses of common drugs used in hyperthermic intraperitoneal chemotherapy (HIPEC) and their mode of calculation

Drug	Threshold dose (mg/m ²)	Mode of calculation	Peak dose (mg/m ²)	Mode of determination
Cisplatin ^{62,63}	50	Multiples/fraction of IV dose	100	Phase 1 studies
Mitomycin C ⁵⁶	10	Dose required for minimum cell kill in the experimental setting	35	Phase 1 studies
Oxaliplatin ^{60,61}	120	Multiples /fraction of IV dose	460	Phase 1 studies
Doxorubicin ⁵¹	—	—	15	Phase 1 studies
Gemcitabine ^{66–68}	500	Multiples/fraction of IV dose	1500	Clinical study ^a
Melphalan ^{64,65}	50	Multiples/fraction of IV dose	70	Clinical study ^a
Irinotecan ^{55,59}	50	Dose required for minimum cell kill in the experimental setting	360	Phase 1 study
Paclitaxel ^{69–71}	75	Multiples/fraction of IV dose	175	Clinical study ^a
Carboplatin ⁷²	800	Multiples /fraction of IV dose	1200	Phase 1 study
Docetaxel ^{69,73}	45	Multiples/fraction of IV dose	75	Clinical study ^a

IV, intravenous

^aClinical study that does not have the phase 1 design

data), 30 min of oxaliplatin HIPEC did not induce any significant apoptosis in tumor nodules in a rat model, but 200 mg/m² at 90 and 120 min induced significant apoptosis.

For some drugs, such as mitomycin C, doxorubicin, and cisplatin, the lower doses are used when a combination of drugs is used to perform HIPEC. When a single agent is used, the peak dose usually is preferred.

Concentration-based or body surface area-based dosing. Conventionally, the drug dose is calculated using the body surface area (BSA) (mg/m²),^{74,75} This calculation is based on the Dedrick formula, which shows a correlation between the BSA and the surface area of the peritoneum. However, a discrepancy exists in the BSA and the calculated peritoneal surface area, with variations observed according to the sex of the patients as well.^{74,75} Van der Speeten et al.⁷⁶ hypothesized that using a concentration-based dose with a fixed volume of perfusate would be more efficacious than using a BSA-based dose in which the volume of perfusate remains variable. The COBOX trial showed an increased tumor uptake of oxaliplatin with a concentration-based regimen compared with the BSA-based regimen at 30 min, with similar morbidity in the two groups.

Stat versus split dosing. Several studies have demonstrated that the peritoneal fluid drug concentration declines during the course of HIPEC. Therefore, instead of adding the entire dose at the beginning of the procedure, some surgeons add it in two or three installments to maintain a relatively constant peritoneal fluid concentration of the drug.^{56,77} The uptake of the drug by the tumor nodules is

dependent on the peritoneal fluid concentration of the drug and the time of exposure. Although it is not possible to demonstrate the clinical benefit of split dosing over stat dosing, the former seems to be the more reasonable approach.

Perfusion Time The drug should remain in the peritoneal cavity for a sufficient time to obtain the maximum cell kill. This time is not set arbitrarily but according to the peritoneal half-life of the drug (Table 3).⁷⁸ Prolonged exposure carries the risk of systemic toxicity, providing little benefit as the dose response curve plateaus. Application times for different drugs and regimens range from 30 to 120 min, with 30 min currently considered “too short” by most surgeons.⁷⁹ With the 30-min high-dose oxaliplatin regimen, it was assumed that the high dosing with a strictly maintained temperature of 42–44 °C would lead to a fast absorption of the drug into the tumor nodules and rapid systemic clearance, thus making up for the short perfusion time.⁸⁰ This regimen, after the negative results of three randomized trials, has been discarded by most surgeons and centers, although the regimen itself may not be the only cause of the negative results.^{1,81,82} This regimen still is one of the two regimens used in the CAIRO-6 trial.⁸³ A longer perfusion time is necessary for the benefit of hyperthermia to be obtained, and the peritoneal half-life of most drugs is more than 30 min (40 min for oxaliplatin; 30–70 min for cisplatin).⁸⁴

Carrier Solution The carrier solution used has an impact on the efficacy of IPC. An ideal carrier solution

TABLE 3 GRADE of clinical evidence for various components of hyperthermic intraperitoneal chemotherapy (HIPEC) regimens

Drug	Thermal enhancement	Clinical benefit of hyperthermia ^a	Perfusion times (min)	Comparison between different perfusion times ^a	Comparison between stat and split dosing ^a	Concentration-based vs BSA-based dosing ^a
Cisplatin	Constant	Very low	60; 90	Very low	Very low	Very low
Mitomycin C	Moderate	Very low	90	Very low	Very low	Very low
Oxaliplatin	Moderate	Very low	30; 120	Very low	Very low	Moderate
Doxorubicin	Moderate	Very low	90; 120	Very low	Very low	Very low
Gemcitabine	Moderate	Very low	90	Very low	Very low	Very low
Melphalan	Constant	Very low	60; 90	Very low	Very low	Very low
Irinotecan	Moderate	Very low	30	Very low	Very low	Very low
Paclitaxel	Mild/none	Very low	90	Very low	Very low	Very low
Carboplatin	At high temperature	Very low	90	Very low	Very low	Very low
Docetaxel	Mild/none	Very low	90	Very low	Very low	Very low

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; BSA, body surface area

^aGrade of evidence could be high, moderate, low, or very low as elaborated in Table 5.

should lead to increased exposure of the peritoneal surface to the drug, should maintain a high intraperitoneal volume for a prolonged period, should be cleared slowly, and should not have a detrimental effect on the peritoneum itself.⁸⁵ The solution used can be hypotonic, isotonic, or hypertonic.⁸⁶ Different carrier solutions have been used to deliver both low- and high-molecular-weight drugs. For example, both hypotonic and isotonic solutions have been used as carriers for oxaliplatin. Problems with each solution have been reported (with hypotonic solutions resulting in hyperglycemia and unexplained hemorrhage, and hypertonic solutions leading to chelation of the drug), and surgeons exercise their own preference for the carrier that is used.^{87–89}

Volume of the Perfusate A volume of 1.5–2.5 l/m² is required to perfuse all the peritoneal surfaces adequately.⁹⁰ A higher perfusate volume limits the systemic absorption of the drug, whereas a lower volume hastens it.⁹⁰ The dose and the volume of the perfusate are linked. Two options are possible:

1. The dose and volume of the perfusate are both BSA-based, resulting in a fixed drug concentration and thus a concentration-based IPC.
2. The dose is BSA-based, and the volume is determined by the volume of the abdominal cavity, resulting in a BSA-based IPC but with variable drug concentration.

Pressure In preclinical studies, it has been hypothesized and demonstrated that an increase in the intraabdominal pressure (IAP) during HIPEC can increase

the intra-tumoral concentration and cytotoxicity of drugs such as cisplatin, oxaliplatin, and doxorubicin.^{91–94} No clinical study has shown the benefit of increasing the IAP. With an increase in the IAP beyond a point, respiratory and hemodynamic functions are compromised. With the closed method, the IAP is higher and can be increased using the flow rate and perfusate volume.

In a recently concluded phase 2 randomized study evaluating the impact of a raised IAP during HIPEC, Kusamura et al.⁹⁵ showed an increased concentration of cisplatin in the mesenteric peritoneum in the study arm with a raised IAP, but a similar concentration in residual tumor nodules and the subperitoneal tissue in the two arms of the trial. The pharmacokinetic advantage and morbidity were similar in the two arms of the study. The oncologic advantage of such an approach remains to be demonstrated.

Temperature Numerous theoretical benefits are achieved by combining IPC and hyperthermia. Exposure to hyperthermia itself is cytotoxic to tumor cells by causing impairment of DNA repair, increased protein denaturation, lysosomal activation, and thus, apoptotic cell death.⁵¹

The drugs used for HIPEC undergo various degrees of thermal enhancement. Cisplatin, melphalan, and ifosfamide undergo constant thermal enhancement with increases in the temperature and are considered ideal drugs to combine with hyperthermia or “super drugs” for hyperthermia.⁵² Oxaliplatin and gemcitabine undergo thermal enhancement up to 41 °C, which is moderate enhancement.⁹⁶ For mitomycin C and doxorubicin, a threshold temperature of 41.5 °C is required for thermal enhancement. Others such as paclitaxel and docetaxel undergo very little or no thermal

enhancement. Hyperthermia reduces the interstitial fluid pressure and increases the depth of drug penetration in tumor nodules.^{97,98} Hyperthermia with cisplatin can overcome platinum resistance, as shown by experimental data.^{99–101}

Combining Chemotherapeutic Agents The combination of chemotherapeutic agents is based on even more limited preclinical and clinical data.^{102,103} The benefit of combining multiple agents has been demonstrated by the success of SC across tumor types, and the same rationale has been applied by surgeons to HIPEC. Some of the most common drug combinations used for HIPEC are cisplatin and doxorubicin, mitomycin C and doxorubicin, cisplatin and mitomycin C, oxaliplatin and irinotecan, and cisplatin and paclitaxel. One retrospective study has shown the benefit of using the combination of two drugs versus using one drug alone for peritoneal mesothelioma.¹⁰⁴ Another bi-institutional study showed no benefit of combining oxaliplatin and irinotecan versus using oxaliplatin alone.¹⁰⁴

The recent propensity score-matched analysis of patients undergoing CRS±HIPEC for pseudomyxoma peritonei showed a survival benefit using the combination of cisplatin and mitomycin C.²⁷ This combination is supported by experimental data showing that mitomycin enhances the intracellular accumulation of cisplatin and the production of platin DNA adducts.^{106–107} For the other combinations, no evidence or rationale exists for combining the two drugs. Often, these drugs have different thermal enhancement properties. For example, cisplatin is a super drug for hyperthermia compared with mitomycin and doxorubicin, which undergo moderate thermal enhancement.

Bidirectional Intraoperative Chemotherapy Frequently, HIPEC is combined with intravenous chemotherapy, which is administered just before the commencement of HIPEC or throughout its course. Intravenous chemotherapy reaches the tumor nodules through the systemic circulation and potentiates the effect of HIPEC.⁸⁹ When IPC is performed under hyperthermic conditions, an intravenously delivered drug may profit from the local synergistic effect of hyperthermia. Many recent treatment protocols involve bidirectional intraoperative chemotherapy.^{108–110}

Nonpharmacologic Factors

Extent of Peritoneal Resection In CRS, varying amounts of the parietal and visceral peritoneum are resected with or without resection of the adjacent or underlying viscera. It was assumed that once the peritoneal barrier (i.e., the peritoneal layer itself) has been removed,

the diffusion of the drug into the systemic circulation should be greater.¹¹¹

Subsequently, it has been shown that it is not the mesothelial layer itself but the sub-mesothelial tissue that constitutes the peritoneal barrier. Clinical studies have shown conflicting results. One study showed no impact of the extent of peritoneal resection, whereas others showed increased drug absorption when the extent of surgical resection was greater.^{111–114} Although, the absorption rates may vary, it is unlikely that adjustment of the drug dose is required after more extensive procedures because the difference in drug clearance is likely to be small.

Open Versus Closed Method Both open and closed methods of performing HIPEC have their advantages and disadvantages, and superiority of the one method over the other has not been proven.^{115,116} The studies have not accounted for the impact the method of performing HIPEC would have on the efficacy of HIPEC. After CRS, minimum/microscopic residual disease is targeted by HIPEC. The second role of HIPEC is to destroy the free intraperitoneal cancer cells shed during surgery and to prevent their implantation at the surgical sites. Experimental and clinical studies cannot demonstrate the impact of either technique on these cells. The choice of open versus closed method is dictated by the surgeon's preference, the availability of equipment, and the local governing regulations.¹¹⁷

Chemosensitivity Perhaps one of the most important factors is the sensitivity of the cancer cells to the chemotherapeutic drugs. Clinical and experimental data can determine only the drug concentration in tumor nodules. Drug concentration in tumor nodules cannot be assumed to be a measure of the regimen's efficacy (cell kill). This is one of the main problems with HIPEC because the drug or the regimen with the most suitable pharmacokinetic profile for HIPEC may not be the most effective in killing the cancer cells.

Initially, the drug concentration in peritoneal fluid was considered to be a measure of efficacy. Subsequently, it was the concentration in the tumor nodules, and some investigators currently are evaluating the utility of intratumoral apoptosis as a measure of efficacy. As mentioned earlier, the impact of HIPEC on the residual tumor nodules can be studied, but there is no way of studying its impact on free intraperitoneal cancer cells shed during CRS.

Cancer cell lines and xenograft models are far from accurate in predicting the effectiveness of a drug/HIPEC regimen. Recently, patient-derived tumor organoids have been used to study the efficacy of one HIPEC regimen compared with another.^{118,119} A biopsy sample from the patient's tumor is used to reconstruct not just the three-

dimensional structure of the tumor, but also the surrounding stroma and its immune microenvironment.¹²⁰ These organoids are then used to compare different regimens that may be used with or without hyperthermia, and thus to select the most effective regimen for the patient. A proof-of-principle study has shown the 2-h 200 mg/m² oxaliplatin regimen to be more effective on the organoid platform than the 30-min, 460 mg/m⁰ regimen.¹²⁰ This approach still needs clinical validation, which will be a challenging task.

Variations in HIPEC Regimens and Comparisons Between Different Regimens

A systematic review reported the use of 60 different regimens for colorectal PM in 135 different publications.¹²¹ When the PRODIGE 7 trial did not show a benefit of short-duration, high-dose oxaliplatin HIPEC, many surgeons opined that the outcome could have been different with longer-duration mitomycin C HIPEC.¹ A recent propensity score-matched analysis showed no benefit of mitomycin C HIPEC in colorectal PM.¹²² Another study showed the superiority of oxaliplatin HIPEC over mitomycin C HIPEC, whereas a third study showed a benefit of mitomycin C HIPEC for patients with a low Peritoneal Cancer Index (PCI).^{123,124}

Given the heterogeneity of patients with colorectal PM as a whole, it is unlikely that the HIPEC regimen was the only factor that made a difference. For peritoneal mesothelioma, HIPEC using a combination of two drugs resulted in a significantly longer survival than HIPEC with a single drug. The choice of regimen can be based on the toxicity profile of each regimen. A randomized trial comparing oxaliplatin and mitomycin C HIPEC for appendiceal malignancies showed a higher hematologic toxicity with mitomycin, and the authors recommended mitomycin C HIPEC for patients with thrombocytopenia and oxaliplatin HIPEC for those with leucopenia (Table 4).^{125–127} For pseudomyxoma peritonei, the recent multi-institutional propensity score-matched study showed a survival benefit of the 30-min, 460 mg/m² oxaliplatin regimen with bidirectional 5-fluorouracil and the combination of cisplatin and mitomycin C, but failed to show a benefit with lower doses of oxaliplatin and mitomycin C used as single agents.²⁷ Head-to-head comparisons between the regimens were not performed in the study and it should not be inferred because the distribution of clinicopathologic features of groups receiving different regimens might not be homogeneous.

DISCUSSION

From the preceding discussion, it is clear that a multitude of permutations and combinations is possible and therefore a plethora of regimens can be used. There were many regimens neither supported by preclinical rationale/data nor validated by a dose-escalating formal phase 1 trial.

The HIPEC procedure should be considered a surgical therapy performed to destroy microscopic residual disease after CRS. Experimental studies can mimic the conditions *in vivo* only to a certain extent, and it is difficult to prove the benefit of one regimen or protocol over another. When HIPEC is performed with methodologic precision using an “adequate dose,” maintenance of mild or moderate hyperthermia, and an adequate perfusion time, different regimens may produce the same or different results in different patients. This statement is borne out by the variability of the results obtained from the different clinical studies presented in Table 4.

Future Research

Comparison between the different HIPEC regimens will remain an area of future research, and such comparisons are best performed between specific subgroups of patients (e.g., patients with colorectal PM treated using HIPEC after neoadjuvant chemotherapy). The objective would be to find not only the best regimen but also the one that is best for each patient. In addition to randomized trials, which are challenging to conduct, more translational research and phases 1 and 2 studies are needed. The biologic mechanisms underlying the drug-heat interaction and chemotherapy cytotoxicity are areas that require further research. In contrast to the current mainstream “one-size-fits-all” policy, identification of factors predictive of treatment response and personalized medicine approaches like the use of organoids to determine the chemosensitivity of tumour cells to different HIPEC regimens could help in offering personalized treatment.

Comparison with Systemic Chemotherapy

Systemic chemotherapy involves administration of the drug in a closed compartment, with fewer pharmacokinetic and pharmacodynamic factors coming into play versus IPC. Despite this, the plasma levels, tumor concentrations, and half-lives vary significantly among patients.¹³⁵ Findings have shown that drug elimination can vary up to fourfold between patients.¹³⁶ Usually, BSA-based calculations are used for dosing, which are not very accurate and have the probability of under-dosing.^{137–139} Rounding of doses also is done, and it is unlikely that variations of

TABLE 4 Summary of studies comparing different hyperthermic intraperitoneal chemotherapy (HIPEC) drug regimens

Lead author [ref]	Year	n	Primary tumor site(s)	Regimens compared	Centers	End points and type of study	Results
Quénet et al ¹⁰⁵	2011	146	Colorectal	460 mg/m ² oxaliplatin and 360 mg/m ² irinotecan vs oxaliplatin alone	Bi-institutional; retrospective	Morbidity; OS	No difference
Hompes et al ¹²⁸	2014	95	Colorectal	460 mg/m ² oxaliplatin vs 35 mg/m ² mitomycin C	Bi-institutional; retrospective	Recurrence-free and OS	No difference
Votanopoulos et al ¹²⁹	2013	187	Colorectal and appendiceal	200 mg/m ² oxaliplatin vs mitomycin C (dose not specified)	Single institution; retrospective	Hematologic toxicity	In patients undergoing splenectomy, the platelet and neutrophil toxicity was higher in the oxaliplatin group
Glockzin ¹⁰⁸	2014	32	Colorectal	300 mg/m ² oxaliplatin vs 300 mg/m ² irinotecan	Single institution; retrospective	Morbidity; OS	Similar morbidity; trend in improved OS at 3 years with oxaliplatin
Prada-Villaverde et al ¹²⁴	2014	584	Colorectal	460 mg/m ² oxaliplatin vs 40 mg/m ² mitomycin C	Multi-institutional; retrospective	OS with stratification according to the PSDSS	For PSDSS 1/2 mitomycin C was better
Leung et al ¹²³	2017	201	Colorectal	350 mg/m ² oxaliplatin vs 12.5 mg/m ² mitomycin C	Single institution; retrospective	OS	Oxaliplatin was better
Van Eden et al ¹³⁰	2018	177	Colorectal	460 mg/m ² oxaliplatin vs 35 mg/m ² mitomycin C	Single Institution; retrospective	Major morbidity and short-term survival	No difference
Sipok et al ¹³¹	2018	48	Colorectal	40 mg/m ² mitomycin vs 60 mg/m ² melphalan	Single institution; retrospective	OS	Mitomycin was better
Bakkers et al ¹³²	2020	297	Synchronous colorectal	Mitomycin C vs oxaliplatin ^a	Multi-institutional; retrospective	OS	No difference
Bae et al ¹³³	2007	77	Recurrent ovarian	175 mg/m ² paclitaxel vs 350 mg/m ² carboplatin	Single institution; retrospective	Progression-free and OS	No difference
Cascales-Campos et al ¹³⁴	2016	111	Advanced ovarian	75 mg/m ² cisplatin and 60 mg/m ² paclitaxel	Single institution; retrospective	DFS	No difference
Malgras et al ¹⁰⁴	2018	249	Peritoneal mesothelioma	Single drug vs 2-drug HIPEC regimens	Multi-institutional; retrospective	OS	Two-drug regimens (platinum based) were better
Levine et al ¹²⁵	2018	121	Appendiceal	Mitomycin 40 mg/m ² vs oxaliplatin 200 mg/m ²	Single institution; randomized controlled trial	Toxicity profiles	Mitomycin HIPEC resulted in more hematologic toxicity and lower quality of life

OS, overall survival; PSDSS, peritoneal surface disease severity score; DFS, disease-free survival

^aMore than one regimen was used for each drug.

10–50 mg have a significant impact on the oncologic outcomes.¹⁴⁰

Some investigators have proposed that a range of fixed doses should be determined for use as a starting point.¹⁴⁰ For patients prone to the development of complications, especially neutropenia, or for those with comorbidities, clinicians often start off with a dose lower than the standard dose. Dose reductions of 20–50 % are not uncommon, but can result in lower efficacy.^{141,142} A dose reduction of less than 50% is not recommended.¹⁴⁰ Thus, although SC regimens for the adjuvant, neoadjuvant, and metastatic setting have been standardized, modifications and dose reductions are common and rampant.

Standardization of HIPEC Regimens: The Need for an Expert Consensus

Standardization of HIPEC regimens should result in the identification of only a few active regimens for each indication and should clearly define the methodology and all other parameters/variables of each regimen. The number of regimens can be reduced by eliminating regimens not supported by preclinical rationale/data and regimens not validated by a dose-escalating formal phase 1 trial.

With the multitude of factors having an impact on the efficacy of the procedure, it is difficult to have a few standardized regimens, as shown by the American Society of Peritoneal Surface Malignancies consensus for colorectal PM.⁷⁷ The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system for rating quality of evidence could be used to rate the evidence for such a consensus, especially because the evidence is limited (Table 5).^{143,144} There are benefits from having uniform regimens, which can be determined by a consensus among the teams most experienced in performing these procedures. These benefits include the following:

- Larger combined experience of the peritoneal oncologic community and the scope for minimizing the morbidity.
- Larger evidence pool favoring or disfavoring the use of a particular regimen. Large-scale datasets of homogeneously performed procedures can fill the gap until we have (more) randomized controlled trials (RCTs) according to the ‘Ideal Development, Exploration, Assessment, Long-term study (IDEAL)’ framework. This homogeneity also can help in designing better RCTs.
- Adoption of a limited number of regimens. This will lead to greater acceptance of the results of RCTs by the oncology community at large.

- Selection of the regimen based on the anticipated toxicity in each patient. Each regimen has its own toxicity profile.
- Merging or comparison of data, which requires homogeneous treatment standards.

Modifications in HIPEC regimens will remain inevitable as with SC, largely to control of the morbidity. Such modifications commonly comprise a reduction in the dose, a reduction maximum temperature, and a reduction in the duration of perfusion or a combination of one or more of these. The HIPEC procedure could be divided into the method of performing HIPEC and the HIPEC regimen itself. The former refers to the method (open or closed). For each method, the technical aspects such as properly placing the perfusion tubes, avoiding direct contact of the inflow channel with the bowel, ensuring proper perfusion of all areas, and maneuvering the bowel in the open method would constitute “methodologic accuracy” as previously described.^{145,146}

The HIPEC regimen includes the drug dose, the time or times of instillation, the choice of perfusate and its volume, the duration of perfusion, and the degree of hyperthermia. Three important components of HIPEC are hyperthermia, drug dose, and perfusion time, with adherence to a minimum standard for each component (Table 6).

Hyperthermia Mild or moderate hyperthermia should be used. Most regimens require the use of moderate hyperthermia (41–43 °C). Severe hyperthermia is not recommended. A temperature higher than 44 °C leads to cell death.¹⁴⁷ For the procedure to be called HIPEC, the intraabdominal temperature should be at least 40 °C.

Perfusion and Application Time All adhesions should be lysed to ensure that the maximum surface area of the peritoneum is exposed to the chemotherapy solution. During the open method, the small bowel loops are maneuvered to ensure uniform exposure to all peritoneal surfaces. As discussed earlier in this report, a perfusion time of 30 min currently is considered too short for the effect of heat to set in and for the perfusion of all peritoneal surfaces. The perfusion time of other regimens is also based on the peritoneal fluid half-life of the drug. The preferred perfusion times are 60 to 120 min. Perfusion longer than 120 min could have more side effects with little additional benefit.¹⁴⁸

Drug Dose The drug dose should be more than the threshold dose and less than the peak dose. Stat or split dosing can be used. The dose should be tailored to the volume of the perfusate to maintain an adequate concentration in the peritoneal fluid. The perfusion time

TABLE 5 The GRADE method of rating clinical evidence (from refs 143 and 144)

Assigned GRADE quality	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation

TABLE 6 Minimum standards for performing hyperthermic intraperitoneal chemotherapy (HIPEC)

Hyperthermia	Drug	Perfusion time
Mild to moderate hyperthermia	Threshold and peak doses Stat or split dose Concentration-based dosing Acceptable drug combinations	Minimum and maximum perfusion times

should be adequate as well. Other parameters such as type of perfusate, volume, and method of performing HIPEC should be selected as described earlier.

SUMMARY AND CONCLUSIONS

A certain degree of variability in HIPEC regimens and methodology may be inevitable but should be reduced. Randomized trials comparing different regimens are difficult to conduct, and it would be difficult to derive meaningful conclusions given the heterogeneity of the patient population itself. More preclinical and phases 1 and 2 studies are warranted. The biologic mechanisms underlying the drug-heat interaction and the cytotoxicity of chemotherapeutic agents need further study.

Until better evidence is available, the best way to minimize the heterogeneity in HIPEC protocols is by reaching an expert consensus that aims to identify and define a limited number of regimens for each indication and primary site. The GRADE method could be used to rate the evidence and consensus among the most experienced teams in the world based on the factors outlined in this report. Adoption of a limited number of regimens will increase the experience of the peritoneal oncology community as a whole, make comparison between studies more meaningful, and lead to greater acceptance of the results of

randomized trials. The choice of regimen then can be tailored to the patient profile and expected toxicity of the regimen, and the methodology can be tailored according regional preferences, availability of equipment, and local governing regulations. Surgeons should focus on methodologic accuracy and the three key elements, namely, adequate drug dosing, maintenance of hyperthermia, and adequate perfusion.

The HIPEC regimens in current use are based on pharmacokinetic data and do not account for chemosensitivity. Personalized medicine approaches such as patient tumor organoids could offer a solution to this problem in the future, although clinical validation is likely to be challenging.

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