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ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Methodology, Drugs and Bidirectional Chemotherapy

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Abstract Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) combined have been recognized as standard of care for treatment of a subset of patients with peritoneal carcinomatosis (PC). The aim of CRS is to eliminate all macroscopic disease through a series of visceral resections followed by targeting any residual microscopic disease with intraperitoneal chemotherapy, exposing the peritoneal surfaces to a high concentration of chemotherapy with a lower systemic toxicity. Different regimes of intraperitoneal chemotherapy include HIPEC, early postoperative intraperitoneal chemotherapy (EPIC) and bidirectional chemotherapy. The efficacy and modality of treatment with intraperitoneal chemotherapy is dependent on multiple factors including the chosen cytotoxic agent and its pharmacokinetics and pharmacodynamics. There is no standardized methodology for intraperitoneal chemotherapy administration. This review will discuss the pharmacological principles of the various intraperitoneal chemotherapy techniques.

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Introduction

The finding of a peritoneal malignancy raises major therapeutic concerns and is associated with a poor prognosis. Systemic chemotherapy regimens in the past functioned as a palliative approach and palliative surgery was offered only with the aim of reducing the symptoms. In the early 1990's, research began into the development of a therapeutic approach for the treatment of peritoneal surface malignancy. Since this time, cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) combined have been recognised as standard of care for treatment of a subset of patients with peritoneal carcinomatosis (PC) from pseudomyxoma peritonei, appendix adenocarcinoma, colorectal cancer and mesothelioma and has also showed promising results in selected patients with ovarian and gastric cancer. Long-term survival has been achieved in patients who have been treated with CRS followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Elias et al. [1] analysed the results of combined CRS and perioperative chemotherapy in 1290 patients with a variety of peritoneal malignancies reporting an overall 5-year survival of 37 %. CRS/HIPEC is a complex therapeutic modality. The aim of CRS is to eliminate all macroscopic disease through a series of visceral resections and standardized peritonectomy procedures [2] followed by targeting any residual microscopic disease with IPC, providing a high intraperitoneal concentration and with a lower systemic toxicity. Perioperative IPC includes HIPEC, which is delivered after the surgical procedure in the operating room and/or early post-operative intraperitoneal chemotherapy (EPIC), given via a port in the post-surgical

setting on days 1 to 5. More recently, bidirectional chemotherapy combining synchronous intraoperative intraperitoneal oxaliplatin and systemic chemotherapy with 5-fluorouracil has been introduced, targeting both the peritoneal cavity and subperitoneal blood vessels, and has shown long-term survival in patients with colorectal cancer and appendix adenocarcinoma. Oncologists acknowledge that disease control may be significantly improved when chemotherapy is administered through the intraperitoneal route [3]. This is supported by extensive clinical and pharmacological research studies and unprecedented therapeutic results have been reported [4–6]. The efficacy and modality of treatment with IPC is dependent on multiple factors including the chosen cytotoxic agent, pharmacokinetics and pharmacodynamics. Kusamura reported that there are eight parameters which impact on pharmacokinetics and the efficacy of HIPEC, which can be modified during HIPEC. These are: the type of drugs, concentration of the drugs, the combination of them, carrier solution, volume of the perfusate, temperature, duration, and the technique of either open or closed abdominal cavity [7]. There is no standardised method for the delivery of IPC, which varies according to the surgeon and/or unit's preference. Most peritoneal surface malignancy treatment centres use HIPEC exclusively, some use EPIC only, and others use both sequentially. In this review, the methodology, pharmacokinetics and pharmacodynamics of IPC, and the benefits and risks associated with each technique are discussed.

Background

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

CRS is the complete surgical removal of all macroscopic peritoneal disease. CRS is composed of five visceral or parietal peritonectomy procedures. The techniques of CRS have previously been described by Sugarbaker [8]. Clinical data strongly support in univariate and multivariate analyses that complete cytoreduction of nodules <2.5 mm is the single most important prognostic factor. Systemic chemotherapy is minimally effective even when combined with CRS [9] as peritoneal metastases are largely resistant to low intraperitoneal concentrations and adequate concentrations cannot be achieved safely using this method.

HIPEC is the most widely explored modality of treatment post-CRS that has a consistent, clinically improved outcome. It is a locoregional chemotherapy treatment, which is heated to increase the penetration and cytotoxicity of the chemotherapy on the tumour cells. HIPEC is most commonly delivered once CRS has been completed and before any digestive reconstruction or diversion is made, to expose bowel resection lines to the chemotherapy in an effort to minimize the chance of anastomotic recurrence. The rationale of HIPEC is to eliminate the peritoneal surface of any residual microscopic disease. Moderate hyperthermia above 41 °C has a direct anti-tumour effect by augmenting the cytotoxicity of some chemotherapeutic agents and increasing the penetration depth of the chemotherapy into tumour nodules. Constant hyperthermia is obtained during HIPEC by providing a continuous circuit with a pump and heat exchanger, and temperature monitoring. During the procedure, temperature probes are placed at different sites of the circuit and intraperitoneal cavity; the heat generator, inflow and outflow drains, bladder, liver and mesentery [10].

For various reasons, CRS and HIPEC must be performed at the same time. Surgery without HIPEC can lead to fibrin entrapment of microscopic intraabdominal residual disease causing the peritoneal malignancy to recur rapidly and even progress. If patients undergo HIPEC post surgical recovery, adhesions create barriers with a non-uniform drug distribution that may lead to treatment failure.

Hyperthermic Intraperitoneal Chemotherapy Drugs

Most centres have used mitomycin C as the HIPEC drug of choice in patients with PC of colorectal and appendiceal origin, and in a subset of patients with mesothelioma. The most widely applied doses range from 12.5 mg/m^2 to 35 mg/m^2 over 90 min [11]. The AUC ratio of mitomycin C is 23.5. Van der Speeten et al. [12] found that after 90 min, 71 % of the drug had left the peritoneal space, which indicates that 29 % was discarded with the removal of the peritoneal fluid. Patients that present with pseudomyxoma peritonei and a large volume of mucinous ascites will have an expanded peritoneal diffusion surface. A more rapid clearance of mitomycin C from the peritoneal space and higher plasma AUC is expected, with an increase in the incidence of bone marrow toxicity. Oxaliplatin and irinotecan have more recently been explored as HIPEC in PC from colorectal and appendix adenocarcinoma. Oxaliplatin is a third generation platinum complex with AUC ratio between 16 and 25 [13]. As oxaliplatin can only be administered in a 5 % dextrose solution, hyperglycaemia and hyponatremia should be expected during the perfusion [14]. Irinotecan is a camptothecin analogue that interacts with topoisomerase I-DNA complex and prevents resealing of single strand DNA breaks [11]. Pharmacokinetics suggest a beneficial pharmacologic profile at 42.5 to 43 °C during 30 min of HIPEC. The standard doses for oxaliplatin and irinotecan are reported to vary between 360 to 460 mg/m2 and 360 to 400 mg/m2 respectively [15]. Cisplatin HIPEC has been used in mesothelioma, ovarian and gastric cancer with an AUC ration of 7.8 [16]. Cisplatin is a platinum salt, which has shown improved survival when combined with CRS, however is associated with increased toxicity and complications [17], which has resulted in slow acceptance of this treatment modality within the scientific community. Cisplatin HIPEC is associated with an increased incidence of nephrotoxicity,

which is found in 5–15 % of patients [18]. Saline diuresis and a urine output of greater than 1 mL/kg/hr are necessary to reduce the risk of nephrotoxicity. Many questions remain unanswered in the treatment of gastric and ovarian cancer, including the timing of drug delivery, hyperthermia and the optimal choice of chemotherapeutic agent. As a result, the regimens of IPC administration vary amongst institutions for both gastric and ovarian cancers.

There is no standardised HIPEC dosimetry for the treatment of patients with PC.

Early Postoperative Intraperitoneal Chemotherapy

Early postoperative intraperitoneal chemotherapy is delivered via a catheter or subcutaneous port placed through the abdominal wall upon completion of CRS in the area at greatest risk of recurrence. An outflow drain is inserted. EPIC is given in patients with pseudomyxoma peritonei and in some units, patients with colorectal cancer, and can be applied with or without HIPEC. It is administered on postoperative days 1 to 5 prior to wound healing, but can be initiated immediately postoperatively or delayed, due to surgical complication or patient condition. EPIC does not involve hyperthermia. EPIC has the advantage of administering multiple cycles of chemotherapy over a 24-h period, with a 23-h dwell time. However, as the chemotherapeutic agents persist in the peritoneal cavity, there is a greater risk of systemic absorption and adverse effects [19]. The peritoneal surface tissues are repeatedly exposed to the cytotoxic drug, which increases the benefit of its cell cycle-specific activity [11]. The most common drug used in this technique is 5-fluorouracil (5FU), which has a high first-pass effect after portal absorption [20]. Jacquet et al. [20] reported an AUC ratio of >400 when studying the pharmacokinetics of intraperitoneal 5FU. It is a small molecule that moves rapidly out of the peritoneal fluid into the plasma. Regardless of the rapid metabolism of the drug in the liver and at other sites in the body compartment, a large AUC ratio of peritoneal fluid to plasma was maintained. An increased risk of infection has been reported in patients who have received EPIC [19]. In a large multi-institutional retrospective study, EPIC was found to significantly increase the rate of postoperative complications in 504 patients with colorectal PC treated with CRS/IPC [21]. Elias et al. compared two groups of patients with colorectal carcinomatosis where one was treated with EPIC using 5FU and mitomycin C and the other with HIPEC using oxaliplatin 43 °C. Morbidity, mortality, recurrence rate and overall survival favoured the HIPEC group [19, 22].

Bidirectional Chemotherapy

Many current centre protocols advocate bidirectional chemotherapy. It is a two compartmental approach to the treatment of PC that requires a simultaneous intraoperative intravenous plus intraperitoneal chemotherapy infusion to obtain a bidirectional fluid gradient in peritoneal tumour cells [11]. Timing is critical to the success of the chemotherapy in relation to the surgical procedure. Elias first reported this therapy and suggested perioperative intravenous 5FU and leucovorin in conjunction with oxaliplatin based HIPEC for colorectal cancer [23]. Earlier in-vivo and in-vitro studies suggested that these two drugs induced a synergic effect [24, 25]. The AUC ratio of peritoneal fluid to plasma was found to be 2.3 [23].

Van der Speeten [26] reported on the pharmacology of 5FU 400 mg/m^2, as a bidirectional protocol, administered by a drip intravenous infusion in 250 mL 5 % dextrose and water, over 7.5 min. Leucovorin 20 mg/m^2 was simultaneously administered through a separate line. Combined doxorubicin 15 mg/m^2 and mitomycin C 15 mg/m^2 HIPEC was also infused simultaneously in 1.5 L/m^2 of 1.5 % dextrose at 41.5 °C. 5FU levels were obtained from blood and peritoneal fluid at 15 min intervals for 90 min. It rapidly circulated within the plasma through both the arterial and venous systems to equilibrate within the body tissue, including the large peritoneal and subperitoneal surfaces of both the abdomen and pelvis. The large volume of peritoneal fluid became saturated by 5FU within approximately 20 min. High levels of 5FU persist in the peritoneal fluid as the drug leaves the peritoneal space by back diffusion through the peritoneal and subperitoneal tissues [11]. 5FU penetrated into the heated tumour nodules even though it was administered as a normothermic intravenous solution. Heat targeting is achieved by modulating the timing of intravenous chemotherapy [27]. The amount of 5FU present in the tumour nodule is governed by both pharmacokinetic (dose, duration, route of administration, volume, carrier solution and pressure) and non-pharmacokinetic (tumour size, density, vascularity, interstitial fluid pressure, binding) variables [26]. By acting synergistically, this study showed that bidirectional chemotherapy is pharmacokinetically beneficial and yields a high tumour drug concentration and that intravenous drugs can be targeted to the peritoneal surface if administered simultaneously with a large volume of intraperitoneal chemotherapy solution.

Our unit follows the French bidirectional protocol in colorectal and appendix cancers and it is widely used in both French and German centres [23]. The innovation of a simultaneous treatment of CRS plus perioperative intraperitoneal chemotherapy may be responsible for the current successes in treating some PC patients, considering previous failures [11].

Intravenous ifosfamide has also been given for ovarian and gastric cancers. It shows true heat synergy, with 5- to 10-times the duration of tumour control with 41.5 °C heat compared to normal temperatures [28]. Its anti-cancer effects only occur after it is metabolised in the liver and red blood cells to form 4-hydroxyifosfamide [26]. It is an unstable metabolite and only exists for few minutes within the plasma or red blood cell but has demonstrated excellent results when combined

with intraperitoneal cisplatin. It can be concluded that the cytotoxic effects of normothermic ifosfamide are maximised on heated peritoneal surfaces while the adverse effects of this agent would not occur at other sites within the body [11].

Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

NIPS is an intravenous and intraperitoneal chemotherapy regimen given as an option for reducing the tumour load prior to CRS and therefore may even facilitate definitive CRS [28]. Radiological and clinical responses with NIPS have been reported by several groups [28–30]. However, disadvantages include non-uniform intraperitoneal drug distribution due to adhesions and it is also associated with an increased morbidity and mortality on further surgical intervention as extensive fibrosis can also occur, which can interfere with surgical judgement [31]. NIPS is a promising approach that may be of benefit in the management of peritoneal metastases from gastric cancer [28].

Pharmacokinetics

Drug diffusion into tissue depends on tissue structure and drug properties [23]. The pharmacologic rationale behind IPC consists of dose intensification determined by the peritoneal plasma barrier. The peritoneum is a three dimensional organ covering the abdominopelvic organs and the abdominal wall. The peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and five layers of connective tissue, which together accounts for a total thickness of 90um. The accepted function of the peritoneum is to reduce friction between intraabdominal organs and the abdominal wall by producing a solution of glycosaminoglycan's and phospholipids [11]. It is of major importance in the host defence against intraabdominal infections. The plasma-peritoneal barrier inhibits attainment of effective intraperitoneal concentrations with systemic chemotherapy administration, however HIPEC uses this barrier in favour of the ability to maintain localised therapeutic drug concentration levels [32].

Dedrick studied the pharmacokinetics of IPC and found that hydrophilic cytotoxic drugs can maintain a significant concentration gradient along the peritoneal plasma barrier; with high intraperitoneal concentrations when added in the abdominal cavity in large volumes [33], however is limited by the restrictive penetration depth in tumour tissue of approximately 1-3 mm. He stated that the peritoneal clearance of the drug is inversely proportional to the square root of its molecular weight [34] and stated the peritoneal permeability to a certain drug is lower than the same drug's plasma clearance [35]. The two compartments, peritoneum and blood, are separated by a semipermeable membrane that allows a high peritoneal drug concentration, optimising its effect on the intraperitoneal target and at the same time limiting drug passage into the plasma stream, which causes treatment toxicity [23]. Following intraperitoneal delivery of the cytotoxic drug, high regional concentrations can be achieved even whilst keeping systemic concentrations low. The concentration differential is in part due to the slow movement of the drug from the peritoneal cavity into the plasma [36]. The peritoneal plasma barrier maintains continuous high concentration gradient of chemotherapeutic drug between the peritoneal cavity and the plasma compartment [32]. Extensive removal of the peritoneum during CRS does not seem to affect the pharmacokinetics of intraperitoneal chemotherapy [37] in the transport of chemotherapeutic agents from the peritoneal cavity to the plasma compartment. Additionally, the blood drainage of the peritoneal surface is by the portal vein. This, in theory, provides a first-pass effect exposing hepatic micrometastases to cytotoxic drugs, presenting additional means of therapy [38].

After intraperitoneal administration, dose intensification results in a higher concentration of chemotherapy in the peritoneal cavity than in the plasma. After cytoreduction, this concentration difference increases the possibility of exposing residual tumour cells to high doses of chemotherapeutic agents with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the area under the curve (AUC) ratios of intraperitoneal versus plasma exposure (Table 1). High intraperitoneal concentration does not automatically confer greater efficacy and penetration of the drug [11].

Different drug regimens have been used over the years for HIPEC. The choice primarily depends on suitability for administration with hyperthermia and its known activity against the disease being treated. Multiple single drug and drug

Table 1 Molecular weight and AUC ratios of intraperitoneal to systemic exposure of chemotherapeutic agents used to treat peritoneal metastases [11]

Drug	Molecular Weight	AUC Ratio
5-Fluououracil	130.08	250
Carboplatin	371.25	10
Cisplatin	300.10	7.8
Docetaxel	861.90	552
Doxorubicin	579.99	230
Etoposide	588.58	65
Floxuridine	246.20	75
Gemcitabine	299.50	500
Irinotecan	677.19	N/A
Melphalan	305.20	93
Mitomycin C	334.30	23.5
Mitoxantrone	517.41	115–255
Oxaliplatin	397.30	16
Paclitaxel	853.90	1000
Pemetrexed	597.49	40.8

combinations are currently in use. The carrier solution also plays an important role in the clearance of the drug from the peritoneal cavity to plasma. The chemical aspect of the carrier however is not the sole factor that impacts on pharmacokinetics and penetration ability. Factors such as concentration and volume should be taken into consideration [7].

The ideal carrier solution should provide enhanced exposure of the peritoneal surface, prolonged high intraperitoneal volume, slow clearance from the peritoneal cavity and absence of adverse effects to peritoneal membranes [11]. This improves both the distribution of the drug and efficacy of the treatment. The carrier solution of 1.5 % dextrose isotonic peritoneal dialysis solution is the most widely used, however some groups use normal saline or 5 % dextrose in water [34], dependent on the type of chemotherapy agent. Body surface area is an accurate predictor of drug metabolism and is useful to estimate systemic drug toxicity. The accuracy increases if the volume of the chemotherapy solution is determined by the body surface area [11]. Most researchers calculate both drug dose and carrier solution volume based on body surface area (mg/m^2). Common perfusate volumes are 1.5 L/m^2 or 2 L/m^2 [39, 40]. The total volume of intraperitoneal chemotherapy can vary widely between individuals and gender difference in peritoneal surface area can affect absorption characteristics. Females have a 10 % larger peritoneal surface in proportion to body size than males [11]. The entire surface of the abdominopelvic cavity should be targeted; therefore different HIPEC techniques result in a wide variety of perfusate volumes. Regulation of both the drug dose and carrier solution volume based on the patient's body surface area and HIPEC delivery technique (open or closed) is necessary [41].

The cytotoxic effect is also relative to the duration of exposure. In most reported studies, intraperitoneal drug half-life is 90 min or less. Gardner modelled the dose-response curves and their dependency on exposure time, and according to this model a plateau in tumour cell kill will be reached, after which prolonged exposure time offers no further cytotoxic advantage [11]. Intraperitoneal treatment length should be dependent on systemic exposure and bone marrow toxicity. There is clinical data demonstrating safety with different schemes established on an empirical basis which includes a temperature of 41 °C during 90 min and 43 °C for 30 to 40 min [15].

Pharmacodynamics

The basis for the use of hyperthermia in the treatment of peritoneal malignancy is multifactorial. An abundance of evidence exists to support that hyperthermia has a direct anti-tumour effect by enhancing the cellular uptake of cytotoxic drugs, increasing membrane permeability and membrane transport [42]. Synergism between various cytotoxic drugs and hyperthermia starts at a temperature of 39 °C, but is stronger at higher temperatures and as reported on in-vivo studies on culture cells at temperatures of 45 °C, limited by clinical tolerance [7]. Therefore, it is accepted that the moderate hyperthermia level of 41 to 43 °C is optimal and selectively induces cytotoxicity of malignant cells due to impaired DNA repair, protein denaturation, and inhibition of oxidative metabolism in the microenvironment of malignant cells, which leads to increased acidity, lysosomal activation, and increased apoptotic cell death [11] and inhibition of angiogenesis.

Applying hyperthermia augments the specificity of a subset of chemotherapeutic agents. Hyperthermia may also increase the penetration of the chemotherapeutic agent into the tissue and tumour nodules. Jacquet reported that tissue penetration of doxorubicin is enhanced when a chemotherapy solution is administered intraperitoneally at 43 °C [4] as well as temperature dependent increases in drug action inhibition of repair mechanisms [34]. Piche et al. showed that increasing the temperature of oxaliplatin HIPEC even reduces systemic toxicity [43]. The only study addressing thermo-tolerance was performed in an animal (murine) model. It was concluded that 44 °C during 30 min was the maximum well-tolerated temperature [7]. Based on Elias' experience, to obtain a minimum of 42 °C in the out-drains, it is necessary to have between 44 and 45 °C in the in-drains [39]. Uncontrolled hyperthermia can result in acute and late systemic side effects. During HIPEC, heat is applied locoregionally and the body's core temperature is controlled by an anaesthetics team by applying ice packs in the neck and groin regions.

In locoregional therapy, the drug passes from the periphery to reach the tumour centre and so a major influential factor is the interstitium and interstitial fluid pressure. Interstitial pressure in tumours is usually increased [23]. Leunig et al. reported that heat induced a dose-dependent reduction in the interstitial pressure, therefore increasing the ability of the drug to penetrate into the tissues [44]. Animal models show an increased accumulation and anti-tumour effect of intraperitoneal cisplatin, oxaliplatin and doxorubicin when abdominal pressure was increased. This is however limited by respiratory and haemodynamic tolerance [45].

Perfusion Techniques

There are various methods for intraperitoneal administration of HIPEC. There is no standardised methodology or consensus for a superior method as there are advantages and disadvantages to each.

In the closed abdomen technique, inflow and outflow lines are placed through separate incisions and afterwards, the abdominal wall is closed before the delivery of HIPEC. There has been no increased risk of anastomotic recurrence or gastrointestinal fistula reported by centres

that perform the closure prior to HIPEC [46]. The major advantage of the closed technique is the ability to rapidly achieve and maintain hyperthermia, as there is minimal heat loss from a closed abdomen. It has also been studied that the closed technique increases intraperitoneal pressure, which is reported to enhance the penetrative ability of the chemotherapy. However, deficiencies have been noted in the distribution of methylene blue dye with the closed technique, which may cause a higher frequency of complications and non-uniform treatment [19].

The non-uniform distribution of HIPEC in the closed technique prompted the development of the open method, which allows for the manual distribution of heat and the cytotoxic solution [8]. This method, or 'Coliseum technique', involves the skin edges of the abdominal incision being suspended from a Thompson or Bookwalter retractor by a running suture to create an open space in the abdominal cavity. A plastic sheet is incorporated into this suture with a small opening in the centre to allow for the surgeon's hand to access the abdomen and pelvis for manipulation during chemotherapy, usually with one inflow and two outflow catheters. Temperature probes are placed near the inflow catheters. Smoke evacuators are placed to guard against any potential cytotoxic aerosol contamination. Yonemura et al. introduced a 'peritoneal access device' to achieve optimal peritoneal expansion. According to this technique, larger volumes of perfusion fluid can be added allowing the small bowel to float in the cavity expander [47]. A major advantage of these open techniques is the creation of controlled distribution of heat and the cytotoxic drugs however, disadvantages are also heat loss and possible drug leakage, increasing potential exposure to theatre staff [48].

Halkia et al. found that there were no statistically significant differences observed in abdominal temperature, core temperature, central venous pressure, heart rate, systolic blood pressure and urinary output along with morbidity and mortality by adopting either open or closed technique [49]. A comparative study conducted on an animal model identified that good thermal homogeneity was reached with both techniques, however better chemotherapeutic absorption and tissue uptake were achieved with the open technique [50]. Elias et al. [10] performed a prospective phase II trial investigating seven techniques in 32 patients. They found that the closed technique restricted the volume of the perfusion, decreased spatial diffusion of the chemotherapy, and resulted in lack of thermal homogeneity. The peritoneal cavity expander allowed immediate thermal homogeneity but this technique isolated the abdominal wall from the chemotherapy. The coliseum method was identified as the best technique in terms of thermal homogeneity and spatial diffusion. Excessive heating of normal tissue that can exacerbate post-operative ileus and increase the incidence of post-operative perforation or gastrointestinal fistula formation may be avoided when using the open technique [51]. Stuart et al. evaluated the safety of operating theatre personnel during the open technique and reported that all assessments were found to be in compliance with established safety standards [52]. The consensus statement issued by the Peritoneal Surface Oncology Group International, after the meeting in Milan, 2006, reached the conclusion that the best technique for HIPEC delivery is via the open method [7].

Laparoscopic HIPEC has been successfully administered in palliating patients with malignant ascites from peritoneal metastases. It has shown to provide treatment benefits greater than conventional methods including diuretics, repeated paracentesis and systemic chemotherapy with a complete and definitive resolution of the ascites was observed in up to 94 % of patients [53, 54, 55]. Some centres have also performed curative intent laparoscopic CRS/HIPEC in selected patients with limited PC. Esquivel et al. concluded that the laparoscopic procedure was feasible and safe in patients with an appendiceal malignancy, a low tumour volume and no small bowel involvement [56]. A longer follow-up period would be beneficial to evaluate its long-term efficacy. Laparoscopic CRS/HIPEC is not yet accepted as a standard of care method as this procedure reduces the ability of assessing all abdominopelvic areas and any prior surgical procedure creates difficulty with adhesions, therefore tumour implants can be missed promoting early recurrence, however it has shown promising results in the palliative treatment of malignant ascites.

There are a variety of hyperthermic perfusion pumps available internationally and some units deliver HIPEC via a modified cardiac bypass/perfusion machine and disposable cardiac lines, which is operated by a cardiac perfusionist. Automated pumps, specifically designed for intraoperative chemotherapy, are now being used in many centres. These are portable, temperature regulated perfusion pumps that continually monitor the infusion process and all control systems. There has been no review to date on the comparison of each of the commercially available perfusion machines.

Conclusion

CRS and IPC combined are recognised as standard of care for treatment of a subset of patients with PC. There is no standardised method for the choice of drug or the delivery of IPC however a significant improvement in disease control is seen when chemotherapy is administered through the intraperitoneal route following CRS. The pharmacokinetic and pharmacodynamic data provides a strong pharmacologic rationale for using perioperative chemotherapy to treat patients with peritoneal surface malignancy.

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