Intraperitoneal Chemotherapy as First-Line Treatment in the Management of Epithelial Ovarian Cancer

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Abstract: Recent evidence has suggested improved outcomes following incorporation of intraperitoneal chemotherapy administration with intravenous systemic chemotherapy as first-line treatment of small volume residual epithelial ovarian cancer. This review focuses on the mechanism of actions of the chemotherapeutic drugs and reviews the possible reasons for the superior outcomes of intraperitoneal chemotherapy.

Key Words: Intraperitoneal chemotherapy, cisplatin, carboplatin, paclitaxel, ovarian cancer management.

INTRODUCTION

Ovarian cancer represents the fourth commonest cancer in women in the UK, and is the most common gynaecological cancer. Nearly 7000 women are diagnosed with this disease each year with over 4,600 deaths annually [1-4]. Whilst treatment for ovarian cancer has advanced over the last 20 years, long term survival rates have not changed much [5].

The most important determinant of survival is the stage of disease at diagnosis. The 5-year survival rate may be as high as 90% if the cancer is confined within one or both ovaries (stage Ia/Ib disease); 60-80% if the cancer has spread into the pelvis (stage II); 30-50% for stage III abdominal spread, and less than 15% in stage IV disease [6] (Table **1**). The majority of women (> 70%) are diagnosed with advanced disease where the pelvic and abdominal peritoneal surface is involved [6]. Main reasons for late presentation are the absence of symptoms in early-stages of disease, lack of readily recognizable and detectable precursor lesions, and the absence of specific and sensitive screening tests.

The standard initial management for advanced ovarian cancer remains surgical excision of all resectable disease, followed by adjuvant chemotherapy. The goals of treatment are to increase survival and disease-free interval, and to improve quality of life. Surgery is performed initially for accurate staging of disease (staging laparotomy) and for primary resection or debulking of tumour (cytoreductive surgery). It is often also required for reassessment immediately following chemotherapy (second-look surgery), often with secondary cytoreductive surgery performed for progressive disease; and is sometimes used for palliation [7]. Optimal cytoreduction at initial surgery has been proven to provide maximal survival benefit [8-11] and improvement in symptoms and quality of life [12]. Optimal cytoreduction often requires removal of the uterus and both ovaries and resection of as much metastatic disease as possible. It is defined as either the absence of visible residual disease or the presence of residual disease of less than 1 cm in diameter at each site. If optimal cytoreduction is not possible during the initial operation, interval debulking surgery after a few courses of chemotherapy is sometimes considered [7, 13, 14].

Following optimal cytoreductive surgery, patients at high risk of recurrence, in whom the cancer has breached the ovarian capsule surface (Stage Ic or above) are usually followed up with combination systemic chemotherapy. First-line chemotherapy for ovarian cancer has generally remained unchanged following the Gynaecology Oncology Group (GOG) publications by McGuire *et al.* (GOG-111) and Ozols *et al.* (GOG-158), which respectively showed the superiority of a taxane-platinum combination over a cyclophosphamide-platinum combination for intravenous therapy [15]; and of a carboplatin-paclitaxel combination compared to a cisplatin-paclitaxel combination [16] in patients with optimally-resected advanced ovarian cancer. These findings were confirmed by subsequent studies [17, 18]. In the UK, the National Institute of Clinical Excellence (NICE) guidelines recommend using a platinum-based treatment (cisplatin or carboplatin), either alone or in combination with paclitaxel for first-line chemotherapy following surgery [19].

CHEMOTHERAPY AGENTS USED IN EPITHELIAL OVARIAN CANCER AND THEIR MECHANISMS OF ACTION

The standard chemotherapy regimen most commonly used for initial chemotherapy for ovarian cancer is a platinum and paclitaxel combination, administered intravenously every 3 weeks and repeated for 6 cycles, for all patients with optimally or sub-optimally resected advanced disease.

THE PLATINUM COMPOUNDS – CISPLATIN AND CARBOPLATIN

Cisplatin or *cis*-diamminedichloroplatinum(II) (CDDP) is an inorganic chemical compound (molecular formula $Cl_2H_6N_2Pt$; a molecular weight of 300.1 g/mol) widely used in the treatment of several cancers. Fig. (**1a**) illustrates the chemical structure of cisplatin. It was first described in 1845, known then as 'Peyrone's chloride', but its structure was not elucidated until 1893. It was relative obscure until the 1960s when an experiment designed to measure the effect of electrical currents on cell growth was found to yield bacteria that grew to 300 times their normal length [20]. The reaction between the platinum electrodes and solution had led to a chemical compound being formed, which had prevented cell division but not other growth processes in *Escherichia coli* bacteria, leading to cellular elongation. This compound was found to be cisplatin. It was subsequently found to be effective in eliminating tumours in mice [21], and human trials that followed produced promising results, leading to its approval for use by the US Food and Drug Administration (FDA) in 1978, when it revolutionised the treatment of several cancers. Cisplatin is the first member of the platinum-based class of drugs known as alkylating agents, which now also includes carboplatin and oxaliplatin.

Cisplatin is believed to exert its cytotoxic activity by binding to DNA and interfering with its repair mechanism, eventually leading to cell death [22]. It forms irreversible cross-links with DNA in several different ways, making it impossible for rapidly dividing cells to duplicate their DNA for mitosis. The damaged DNA sets off DNA repair mechanisms, which go on to activate apoptosis when repair proves impossible.

Following entry into the cell, one of the chloride ions on the cisplatin molecule is replaced by a molecule of water, and the resulting structure can bind to a single nitrogen on a DNA nucleotide. The second chloride is then replaced by another H_2O molecule and the platinum can then bind to a second nucleotide - Fig. (**2**). Bind-

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Table 1. Surgical Staging of ovarian cancer (FIGO / AJCC Staging System)

Stage I: Disease limited to one or both ovaries

Ia	One Ovary only: Capsule intact, no tumour on ovarian surface. No malignant cells in ascites or peritoneal washings
Ib	Both Ovaries: Capsule intact, no tumour on ovarian surface. No malignant cells in ascites or peritoneal washings
Ic	Ia / Ib with any of the following: Ruptured capsule, tumour on ovarian surface, malignant cells in ascites or peritoneal washings

Stage II: Disease involving one or both ovaries with pelvic extension

IIa	Extension onto uterus +/- fallopian tube : No malignant cells in peritoneal washings
IIb	Extension onto other pelvic structures: No malignant cells in peritoneal washings
IIc	IIa / IIb with tumour on the surface of one or both ovaries, or with capsule(s) ruptured, or with ascites or +ve peritoneal washings containing malignant cells

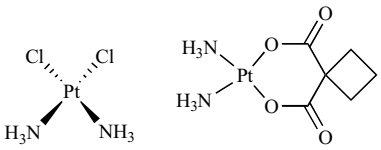
Stage III: Microscopic peritoneal implants outside the pelvis; or limited to the pelvis with disease extension to the small bowel or omentum or superficial surface of the liver; +/- involvement of retroperitoneal or inguinal lymph nodes

IIIa	Microscopic peritoneal metastases beond the pelvis
IIIb	Macroscopic peritoneal metastases beyond the pelvis < 2cm's in size
IIIc	Peritoneal metastases beyond pelvis >2cm's +/- retroperitoneal / inguinal lymph node metastases

Stage IV: Presence of parynchemal liver metastases or distant metastases

IV	Presence of parenchymal liver metastases or distant metastases

ing studies of cisplatin with DNA have indicated a preference for nitrogen 7 on two adjacent guanine bases on the same strand. Other adducts include binding to adenine, and formation of inter-strand cross-links [23-27]. Fig. (**3**) illustrates the various binding sites of cisplatin on DNA – the most abundant adduct is that with the drug bound to 2 adjacent guanine bases on the one strand – intra-strand GpG adduct. X-ray crystallography show that the DNA duplex bends and unwinds at the site of cisplatin attachment, and the resulting distortion to the shape of the DNA prevents effective repair. The structural damage at the cisplatin-DNA complex site attracts the attention of high mobility group (HMG)-1 and other DNA repair proteins which become irreversibly bound. The HMG-domain proteins may then mediate the cytotoxic properties of cisplatin by preventing cancer cell replication, arresting the cell cycle at the G2 phase [28-32]. There is however emerging evidence of alternative cytotoxic pathways utilised by cisplatin [33], which include induction of apoptosis in cancer cells *via* pro-apoptotic proteins [34-37]. Cisplatin was considered in the 1980s to be the single most important drug in the management of ovarian cancer.



(a) cisplatin (b) carboplatin

Fig. (1). Structures of cisplatin and carboplatin.

Carboplatin (molecular formula $C_6H_{12}N_2O_4Pt_2$; molecular weight of 371.249 g/mol) was introduced in the late 1980s and has since gained popularity in clinical treatment due to its vastly reduced side-effects compared to cisplatin. It differs from cisplatin in that it has a closed cyclobutane dicarboxylate moiety on its leaving arm in contrast to the readily leaving chloro groups - Fig. (**1b**). This results in different DNA binding kinetics, though it forms the same reaction products *in vitro* at equivalent doses with cisplatin [38, 39]. The potency of carboplatin is lower compared to cisplatin. Depending on the type of cancer, carboplatin can be over 8 to 45 times less effective compared to cisplatin. The clinical standard of dosage of carboplatin is usually a 4:1 ratio compared to cisplatin [40]. Following uptake, its retention half-life is considerably longer than cisplatin, and this stability is also responsible for up to 70% of administered carboplatin to 'pass' right through the body and excreted in urine [41-43].

PACLITAXEL

Paclitaxel (Taxol®) (molecular formula $C_{47}H_{51}O_{14}$; molecular weight of 853.906 g/mol), Fig. (**4**), is a complex poly-oxygenated diterpene compound, found to have good anti-cancer properties against various cancers. It was discovered in the 1960s following a programme of biological screening of extracts taken from a wide variety of natural sources initiated by the National Cancer Institute (NCI) in the United States. Botanists collected samples from over 30,000 plants to test for anti-cancer properties, from which one of these extracts was found to exhibit marked anti-tumour activity against a broad range of rodent tumours [44]. It is metabolised by the liver (CYP2C8 and CYP3A4), has a half-life of 5.8 hours, and is excreted in urine and faeces. Together with docetaxel, it falls into the category of drugs known as 'taxanes', named after plants of the genus *Taxus* (Yews) - small coniferous trees or shrubs in the yew family *Taxaceae*, from where they were first derived. All species of yew contain the highly poisonous alkaloids known as taxanes, with

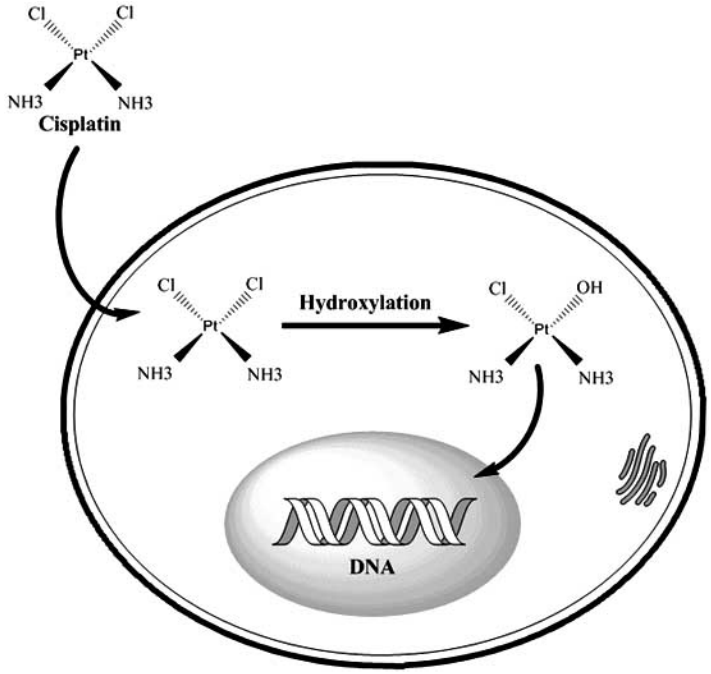


Fig. (2). Diagrammatic representation of cisplatin hydroxylation to facilitate DNA binding.

small variations in the exact formula of the alkaloid between the different species. The Pacific Yew *Taxus brevifolia*, native to the Pacific Northwest of North America, and the Canada Yew *Taxus canadensis* are the main sources of paclitaxel. Docetaxel, an analogue of paclitaxel commonly used in breast and prostate cancer, is derived from the *Taxus baccata*.

Despite its well documented biological activity, very little interest was shown in taxanes until scientists at the Albert Einstein Medical College reported on its unique mode of action [45]. The principal mechanism of taxanes is inhibition of microtubule function. Microtubules are essential to cell division, and taxanes therefore stop cells from properly dividing. Until 1980, it was generally believed that the cytotoxic properties of taxanes were due to its ability to de-stabilize microtubules. Taxanes were however found to arrest their function by having the opposite effect – by hyper-stabilizing its structure to the extent that the cell is unable to use its cytoskeleton in a flexible manner and mitosis is disrupted. Paclitaxel binds to the β subunit of tubulin and induces the assembly of tubulin into microtubules. The resulting microtubule-paclitaxel complex does not have the ability to disassemble, and this adversely affects cell function [45-54]. A common characteristic of most cancer cells is their rapid rate of cell division. In order to accommodate this, the cytoskeleton of a cell undergoes extensive restructuring. Shortening and lengthening of microtubules is necessary for transport of cellular components. Paclitaxel is thus an effective treatment

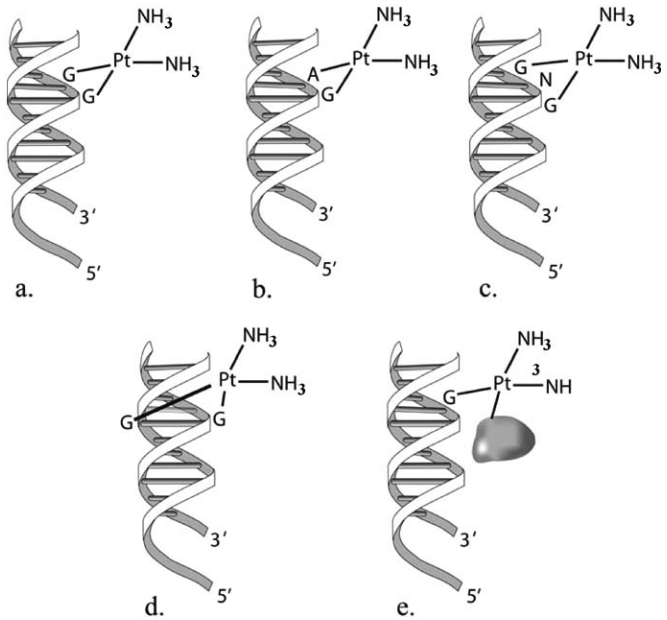


Fig. (3). Various types of cisplatin-DNA adducts formed; fig (e) demonstrates cisplatin binding to DNA strand and protein.

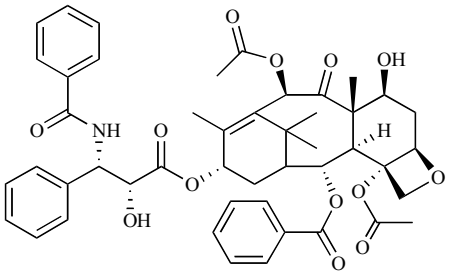


Fig. (4). Structure of paclitaxel.

for aggressive cancers because it adversely affects the process of cell division by preventing this restructuring. Other cells are also affected, but since cancer cells divide much faster than non-cancerous cells, they are far more susceptible to paclitaxel treatment. Further research has indicated that paclitaxel additionally induces apoptosis in cancer cells by binding to the anti-apoptotic protein Bcl-2 (B-cell leukemia 2) thus arresting its function. These modes of action are novel and taxanes represented a prototype for a new class of anticancer drugs.

Results published in 1989 showed paclitaxel to exhibit promising activity against advanced ovarian cancer [55], and in 1992 the US Food and Drug Administration (FDA) approved paclitaxel for the treatment of this condition [56].

THE INTRAPERITONEAL ROUTE FOR ADMINISTRATION OF CHEMOTHERAPY DRUGS

Ovarian cancer characteristically spreads by local extension through the peritoneal cavity and tends to confine itself to the peritoneal surface for much of its natural history. More than 70% of patients with epithelial carcinoma of the ovary have peritoneal or intra-abdominal spread present at time of diagnosis. Death commonly involves intra-abdominal complications arising from this spread. Even though bulky tumour masses can be surgically removed, remaining residual tumour often enlarges despite further therapy, resulting in poor prognosis. For these reasons and because these tumours generally tend to be chemo-sensitive, the administration of chemotherapeutic drugs directly into the intraperitoneal cavity has long been suggested as an ideal consolidation strategy.

RATIONALE AND BENEFITS OF ADMINISTRATION OF CHEMOTHERAPY *VIA* THE INTRAPERITONEAL ROUTE

The use of the intraperitoneal route for chemotherapy administration is not new and has been described over half a century ago [57]; it has been utilised in ovarian cancer since the 1960s [58]. The safety of drug administration *via* this technique has been demonstrated in several phase I and phase II trials, which have also suggested better outcomes with incorporating intraperitoneal chemotherapy for small-volume residual ovarian cancer [59-62]. The use of the intraperitoneal route for drug delivery in treatment of malignant disease involving the peritoneal cavity is based on the potential for increased exposure of tumour to anti-neoplastic agents, leading to improved cytotoxicity.

Besides delivery of cytotoxic drugs directly to the site of disease, regional peritoneal chemotherapy also provides a pharmacokinetic advantage based on the chemical properties of the drugs used and the specialised nature of the peritoneal membrane. The peritoneal membrane is a continuous serous membranous sac that lines the entirety of the peritoneal cavity, interrupted only by the small openings in the free ends of the fallopian tubes in the female. The base of the peritoneum is richly supplied with blood vessels, allowing for drug administered locally into this site to be absorbed into the systemic circulation. Passage of drugs across the peritoneal membrane can occur *via* intercellular pores or trans-cellularly [63]. Absorption is determined by molecular size, lipid solubility and extent of ionization of the drug at physiologic pH [64]. Permeability of drugs through the inter-cellular pores is determined by molecular size, whereas transcellular diffusion of drugs is dependent primarily on lipid solubility. Increasing molecular size and reducing lipid-solubility of a drug results in decreased trans-peritoneal absorption ("peritoneal clearance") [64, 65]. Once a drug is absorbed from the peritoneum, it is eliminated from the body by systemic metabolism and excretory routes (e.g. renal excretion, hepatic metabolism, biliary excretion etc), often termed the "total body clearance of drug". The ideal drug for intraperitoneal use should have slow trans-peritoneal drug absorption but rapid elimination from plasma by excretion or through metabolic degradation once absorbed, thus providing a high drug concentrations in the peritoneal cavity while minimizing systemic (extra-peritoneal) toxicity.

The peritoneal permeability of many hydrophilic anti-cancer drugs is considerably less than their plasma clearance. Pharmacokinetic calculations indicate that because of their slow exit from the peritoneal cavity, these drugs maintain a significantly greater concentration in the peritoneal cavity than in plasma when administered intraperitoneally [66-76]. This results in much higher intraperitoneal concentrations of these drugs (10-20 fold exposure for cisplatin [67, 68], and about 1000 times higher for paclitaxel [71]) compared to intravenous administration. This concentration difference offers a biochemical advantage in the treatment of patients with microscopic residual ovarian cancer confined to the peritoneal cavity allowing increased and effective exposure of cancer cells within the peritoneal cavity to high concentrations of the drug [77] which is not possible to achieve safely with intravenous drug administration. Even higher doses of intraperitoneal cisplatin can be used when it is combined with simultaneous infusion of intravenous sodium thiosulfate, without resulting increase in systemic toxicity [78, 79].

The unique properties of these drugs and the selective nature of the peritoneal membrane also allow a controlled-absorption of intra-peritoneal administered drug into the systemic circulation, thus resulting in a prolonged and stable distribution of the drug into the systemic circulation following IP administration. Pharmacokinetic studies of intraperitoneally administered drugs have revealed that the drug concentration in the peritoneal fluid equilibrated slowly with plasma, resulting in sustained slow 'release' of the drug into the systemic circulation over a prolonged period [69, 71, 72, 76, 80]. This allows both the prolonged and continuous exposure of the peritoneal cavity to high concentrations of the drug, as well as a systemically non-toxic dose of the drug to be released into the systemic circulation over a prolonged period (in some cases more than a week following administration) [72, 74], suggesting that intraperitoneal chemotherapy infusion is beneficial not only as an intraperitoneal regional therapy but also as a reasonable route for systemic chemotherapy [76]. Because some of the intraperitoneally administered drug is absorbed into the systemic circulation, regional chemotherapy delivery allows a 'dual mechanism of action' on peritoneal deposits – firstly *via* a local effect by direct penetration of cytotoxic agents into residual peritoneal disease, and secondly by re-delivery of the drug to peritoneal tumour by capillary flow following systemic absorption, thereby reinforcing its cytotoxic activity on peritoneal deposits not penetrated by local penetration of the drug. The systemically absorbed drug may also target distant disease *via* systemic circulation. This may be especially important in gastrointestinal cancers where metastatic deposits in the liver arise from and receive a portion of their blood supply *via* the portal vein [81]; since drug absorbed from the peritoneal cavity largely enters the portal circulation.

TECHNIQUE FOR ADMINISTRATION OF INTRAPERITONEAL CHEMOTHERAPY

Unlike conventional systemic intravenous chemotherapy where the drugs are administered *via* a needle into a vein, intraperitoneal

chemotherapy involves the administration of chemotherapeutic agents directly into the abdominopelvic cavity; usually *via* a surgically-implanted catheter which is often placed during or soon after initial surgery. Successful intraperitoneal chemotherapy requires accessibility of drug to all tumour-bearing areas. To achieve wide distribution, the drug is administered in a large volume of fluid so that all surfaces might be adequately exposed [82]. The drugs are dissolved in saline warmed to body temperature, and then infused into the peritoneal cavity *via* the catheter, which communicates directly from a port-site buried under the skin into the peritoneal space - Fig. (**5**). An additional litre of warmed saline is usually infused following drug administration to encourage distribution of the drug within the abdominal cavity. This may not be completely infused if the patient develops abdominal or respiratory discomfort. The infused fluid is left within the peritoneal cavity and the patient is encouraged to move into various positions at 15 minute intervals for about two hours following administration to facilitate adequate drug distribution. This procedure is usually commenced between 4 to 6 weeks following initial laparotomy and cytoreductive surgery, and is repeated for up to 6 cycles (if tolerated) at three to four-weekly intervals, often administered in parallel with an intravenous systemic chemotherapy.

EVIDENCE SUPPORTING INTRAPERITONEAL CHEMOTHERAPY FOR INITIAL MANAGEMENT OF EPITHELIAL OVARIAN CANCER

8 prospective randomised trials published spanning the last 2 decades comparing standard intravenous chemotherapy to intraperitoneal chemotherapy have demonstrated equivalent or better outcomes with incorporation of intraperitoneal administration of chemotherapy for first-line treatment of patients with small-volume residual ovarian cancer following cytoreductive surgery [83-90] (Table **2**).

The first good evidence of a survival benefit from intraperitoneal chemotherapy in advanced ovarian cancer was provided by the Southwest Oncology Group (SWOG) and Gynecologic Oncology Group (GOG) led Phase III trial published in 1996 by Alberts *et al.* (GOG-104 / SWOG-8501). This large trial directly compared intraperitoneal cisplatin against intravenous cisplatin over a 6 year period in 654 women with previously untreated Stage III epithelial ovarian cancer, with residual disease no greater than 2 cm post cytoreductive surgery. All patients also received intravenous cyclophosphamide. Patients were randomised to receive intravenous cisplatin 100mg/m^2 plus IV cyclophosphamide 600mg/m^2 *or* intraperitoneal cisplatin 100mg/m^2 plus IV cyclophosphamide 600mg/m^2; every 3 weeks for 6 cycles. The trial was extended a further year to include sub-group analysis for patients with tumour size less than 0.5cm. It demonstrated an 8-month improvement in overall survival (49 *vs* 41 months; p=0.02) and a 24% reduction in the risk of death (p=0.02) with intraperitoneal cisplatin [85]. Patients treated by the intraperitoneal route also experienced less toxic effects. However, despite the clear benefit of intraperitoneal chemotherapy, it was not adopted as standard management for advanced ovarian cancer because overall survival was not greater than that observed with combination intravenous chemotherapy using the then newly discovered agent paclitaxel [15, 17].

A subsequent prospective multi-centre trial (GOG-114 / SWOG-9227), published in 2000 by Markman *et al.*, took this into account when it compared intravenous cisplatin and intravenous paclitaxel against intraperitoneal cisplatin and intravenous paclitaxel in women with Stage III ovarian cancer following optimal cytoreductive surgery (< 1 cm residual tumour nodules). This study randomised 532 women to receive either 6 courses of IV paclitaxel 135 mg/m^2 + IV cisplatin 75 mg/m^2 *or* 2 doses of IV carboplatin (AUC 9) (designed to chemically debulk any residual tumour before the delivery of intraperitoneal cisplatin), followed by 6 courses of IV paclitaxel 135 mg/m^2 + IP cisplatin 100 mg/m^2; and demonstrated significant improvement of progression-free survival (28 *vs* 22 months; p=0.01), and 11-month improvement in overall survival (63 *vs* 52 months; p=0.05) in patients assigned to receive intraperitoneal cisplatin [89]. However, as there was significantly greater toxicity associated with the IP regimen, a significant proportion

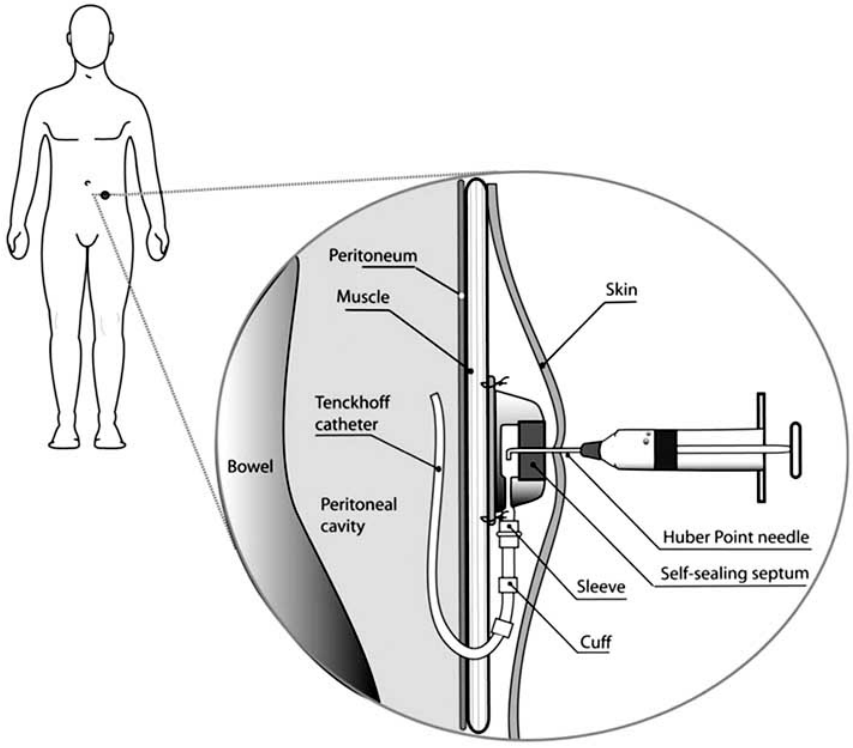


Fig. (5). Diagram illustrating technique for administration of intraperitoneal chemotherapy.

Table 2. Series of Phase III Trials Comparing Standard IV Chemotherapy with Regimen Containing IP Chemotherapy [83-90]

Lead Author (Year) [Accrual dates]	No. patients evaluated	Eligible patients	Control Regimen	Experimental Regimen	Median PFS (mths) Cont *vs* Exp	Median OS (mths) Cont *vs* Exp
Zylberberg *et al.* (1986) [Jan 1980 – March 1984]	20	FIGO Stage III	IV Adr + IV FU + IV Bleo + IV Cp +IV Vin + IV Ifos	IV Adr + IV FU + IV Cp + IV Vin + IV Ifos + IP Bleo +IP Cp + IP FU + IP Adr	NA	NA
Kirmani *et al.* (1994) [Jan 1988 – Feb 1992]	62	FIGO Stage IIc – IV "minimal residual"	IV Cisplatin 100mg/m^2 IV Cyclophos 600mg/m^2 Q 3 weeks x 6	IP Cisplatin 200mg/m^2 IP Etoposide 350mg/m^2 Q 4 weeks x 6	14 *vs* 12 (Not significant)	NA (p = 0.45)
Alberts *et al.* (1996) [June 1986 – July 1992]	546	FIGO Stage III <2cm residual	IV Cisplatin 100mg/m^2 IV Cyclophos 600mg/m^2 Q 3 weeks x 6	IP Cisplatin 100mg/m^2 IV Cyclophos 600mg/m^2 Q 3 weeks x 6	NA	41 *vs* 49 (p = 0.02)*
Polyzos *et al.* (1999) [1990 -1996]	90	FIGO Stage III No upper limit of tumour size	IV Carboplatin 350mg/m^2 IV Cyclophos 600mg/m^2 Q 3 weeks x 6	IP Carboplatin 350mg/m^2 IV Cyclophos 600mg/m^2 Q 3 weeks x 6	19 *vs* 18 (Not significant)	25 *vs* 26 (Not significant)
Gadducci *et al.* (2000) [April 1989 – Dec 1996]	113	FIGO Stage II – IV <2cm residual	IV Cisplatin 50mg/m^2 IV Cyclophos 600mg/m^2 IV Epidox 60mg/m^2 Q 4 weeks x 6	IP Cisplatin 50mg/m^2 IV Cyclophos 600mg/m^2 IV Epidox 60mg/m^2 Q 4 weeks x 6	25 *vs* 42 (p = 0.13)	51 *vs* 67 (p =0.14)
Yen *et al.* (2001) [April 1990 – March 1995]	118	FIGO Stage III <1cm residual	IV Cisplatin 50mg/m^2 IV Cyclophos 500mg/m^2 IV Epidox/Dox 50mg/m^2 Q 3 weeks x 6	IP Cisplatin 100mg/m^2 IV Cyclophos 500mg/m^2 IV Epidox/Dox 50mg/m^2 Q 3 weeks x 6	NA	48 *vs* 43 (p = 0.47)
Markman *et al.* (2001) [Aug 1992 – April 1995]	462	FIGO Stage III <1cm residual	IV Cisplatin 75mg/m^2 IV Pacl 135mg/m^2 (24hr) Q 3 weeks x 6	IV Carboplatin Q 28d x 2 IP Cisplatin 100mg/m^2 IV Pacl 135mg/m^2 (24hr) Q 3 weeks x 6	22 *vs* 28 (p = 0.01)*	52 *vs* 63 (p = 0.05)*
Armstrong *et al.* (2006) [March 1998 – Jan 2001]	415	FIGO Stage III <1cm residual;	IV Cisplatin 75mg/m^2 IV Pacl 135mg/m^2 (24hr) Q 3 weeks x 6	IV Pacl 135mg/m^2 (24hr) IP Cisplatin 100mg/m^2 IP Pacl 60mg/m^2 (d8) Q 3 weeks x 6	18 *vs* 24 (p = 0.05)*	50 *vs* 66 (p = 0.03)*

Abbreviations: Cp = Cisplatin; Cyclophos = Cyclophosphamide; Pacl = Paclitaxel; Epidox = Epidoxorubicin; Dox = Doxorubicin; Adr = Adriamycin; FU = Fluorouracil; Bleo = Bleomycin; Vin = Vinblastine; Ifos = Ifosfamide; PFS = Progression Free Survival; OS = Overall Survival; Cont = Control arm; Exp = Experimental arm; *vs* = versus.

(18%) of patients in the experimental group were unable to complete their assigned treatment, and because the improvement in overall survival was only of borderline statistical significance (p=0.05), this experimental regimen again could not be accepted as standard treatment.

The latest trial (GOG-172) published this year by Armstrong *et al.* has however convincingly demonstrated the benefit of intraperitoneal chemotherapy. This study randomised 429 patients with optimally debulked stage III epithelial ovarian cancer, including some with primary peritoneal cancer, to receive either a standard intravenous chemotherapy regimen of cisplatin and paclitaxel *or* an experimental combination of intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel, with a median follow up of 50 months. It demonstrated significant improvement in progression-free survival and overall survival in the intraperitoneal group – (18.3 *vs* 23.8 months, a *benefit* of 5.5 months, p=0.05) and (49.7 *vs* 65.6 months, an improvement of 15.9 months, p=0.03) respectively, with a 28% reduction in recurrence risk in the IP group [90] (Table **2**). This was despite less than half (42%) of the patients in the IP arm completing their assigned therapy. A 15.9 month improvement in median overall survival is one of the largest benefits ever observed for a new therapy in gynaecology oncology [91].

These trials together have demonstrated superior overall and progression-free survival associated with incorporation of intraperitoneal chemotherapy in patients with optimally resected stage III ovarian cancer. Meta-analysis of the outcomes from this series of prospective randomised trials has confirmed significant differences in time to recurrence (HR=0.79) and risk of death (again HR=0.79), reinforcing support for intraperitoneal chemotherapy [92].

The recent GOG-172 study alone provided enough compelling evidence in support of intraperitoneal chemotherapy that it generated calls for intraperitoneal chemotherapy to be included as first-line treatment in management of epithelial ovarian cancer. The National Cancer Institute (NCI) issued an announcement on its website on the day of publication of this study, recommending for a combination of intravenous and intraperitoneal chemotherapy to be set as standard for treatment of women with advanced ovarian cancer following surgery [93]. The US Society of Gynecologic Oncologists (SGO) and the Society of Gynecologic Oncologists of Canada similarly issued public statements on their websites in support of inclusion of intraperitoneal modality in administration of systemic chemotherapy [94, 95]. The findings of this trial will result in a significant change in the management of ovarian cancer.

CONCERNS AND LIMITATIONS OF INTRAPERITONEAL CHEMOTHERAPY

Despite the positive effects of intraperitoneal chemotherapy demonstrated on progression-free and overall survival, there is some reticence regarding widespread adoption of this technique for cancer treatment. Firstly, although there is good evidence for regional peritoneal chemotherapy for first-line therapy of small-volume residual advanced ovarian cancer following primary surgical cytoreduction, equally good evidence of similar benefit for second-line treatment and in salvage therapy is still lacking.

There is also uncertainty regarding the adequacy of drug distribution throughout the entire peritoneal cavity when administered intraperitoneally. Diluting the drug in a large volume of fluid will aid in a wider surface distribution of the drug [82], but this cannot overcome the difficulty arising from pockets of peritoneal surface

'sealed off' by fibrosis and scar tissue formation sometimes present following surgery, resulting in areas inaccessible to the administered peritoneal fluid.

A further concern is the limited direct penetration of cytotoxic drugs into tumour tissue by free-surface diffusion following regional delivery. Because data available suggest that penetration depth is limited, and may be up to only 1-2 mm of tumour [96-101], it has been accepted that intraperitoneal chemotherapy is best administered in patients following initial debulking surgery (optimal cytoreduction) whose residual tumour masses are less than 0.5 cm in diameter (minimal residual disease), thereby increasing the probability of adequate penetration of the tumour by the drug [102-105]. There is however a belief that repeated cycles of intraperitoneal chemotherapy can lead to 'stripping away' of cancer cells 'layer by layer' ("onion-skin effect") thereby sequentially getting rid of more of the tumour with each cycle [106].

A lot of these limitations above can be overcome when peritoneal chemotherapy is included as a component of a multi-modality therapy which includes intravenous chemotherapy, thus reaping the benefits of the combined modalities of drug delivery [85-90].

The local delivery of chemotherapy is associated with morbidity unique to intraperitoneal drug administration. These include catheter-associated complications like catheter obstruction, bowel perforation and infection (peritonitis); abdominal pain, treatment-associated respiratory complications, administration of chemotherapy into the wrong compartment (abdominal wall, into bowel) and sometimes death [83-90, 107, 108]. The additional time, effort, 'inconvenience', costs, and trained personnel required for this mechanism of drug delivery (both for catheter placement and drug administration) also add to the difficulty in providing this service. There is a learning-curve associated with placement of indwelling intraperitoneal catheters and the management of associated complications. A lot of these issues will however become less significant following widespread use of this technique.

FUTURE OF IP CHEMOTHERAPY FOR OVARIAN CANCER

At present, there is insufficient evidence for the benefit of intraperitoneal chemotherapy outside first-line treatment of newly diagnosed epithelial ovarian cancer following optimal cytoreductive surgery. There is a shortage of Phase III trials examining its role in cancer recurrence or as second-line treatment. However, intraperitoneal chemotherapy has demonstrated benefit in these situations [109, 110], suggesting future wider application for its use in ovarian cancer. Intraperitoneal chemotherapy administration may however help in the palliative setting by reducing accumulation of ascites within the cavity, thus providing symptomatic relief [111, 112]. It is unclear however if the reduction in ascites is due to a direct cytotoxic effect or a result of an indirect sclerosing effect of the drug on the cells lining the peritoneal cavity. Furthermore, since intraperitoneal drainage occurs through the portal system, intraperitoneal drug administration may also prove especially useful in intraperitoneal cancers that are associated with a high risk of dissemination to the liver.

The future of intraperitoneal chemotherapy will probably see refinement of the administration techniques to improve efficacy with fewer complications. Possible developments include improvement in types of catheters used and ports with easier access for drug administration. There is bound to be improvements in the timing of drug administration, with administration of first-dose chemotherapy likely being administered perioperatively at time of initial debulking surgery [113]. Other possible changes in mode of delivery include investigation of the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer [114-116].

There will also be modifications in the types of drugs used, with the discovery of newer cytotoxic agents that may function better when administered intraperitoneally, or of newer combinations of drugs that give better outcome with less toxicity. Changes to the doses of drugs used intraperitoneally may provide benefit by reducing some of the side effects observed without compromising much on outcome. The incorporation of 'molecular targeted therapy' using newer biological or immunological agents ('immunomodulators') administered using this approach may also provide better outcomes in the future. Intraperitoneal delivery has the potential to activate local immunoregulatory mechanisms directly at the site of administration leading to activity against cancer cells. Several biological agents explored in this setting include interferons α and γ, interleukin 2 and tumour necrosis factor, which have shown mixed results [117-121]. Other potential biological agents that may be useful when administered intraperitoneally include monoclonal antibodies targeting proteins or receptors selectively expressed on cancer cells inducing antibody-dependent cellular cytotoxicity (e.g. radio-labelled monoclonal antibodies), agents designed to target drug resistance mechanisms or angiogenesis [122-124]. The rapid advances in the fields of immunoregulation and tumour biology should permit an accelerated introduction of intraperitoneally-administered biological agents for the treatment of ovarian cancer.

CONCLUSION

Intraperitoneal chemotherapy represents an important advance in the treatment of ovarian cancer. The natural history of ovarian cancer together with the pharmacokinetics of the drugs and the unique properties of the peritoneal membrane offer intraperitoneal chemotherapy a unique ability to deliver superior results. There is still room for improvement using this technique with the development of newer drugs and use of biological agents for targeted molecular therapy.

ABBREVIATIONS:

AJCC	=	American Joint Committee on Cancer
Bcl-2	=	B-cell leukemia 2
CDDP	=	*cis*-diamminedichloroplatinum
DNA	=	Deoxyribonucleic acid
FDA	=	Food and Drug Administration
FIGO	=	International Federation of Gynecology and Obstetrics
GOG	=	Gynaecology Oncology Group
HIPEC	=	Hyperthermic intraperitoneal chemotherapy
HMG	=	High mobility group
IP	=	Intraperitoneal
IV	=	Intravenous
NCI	=	National Cancer Institute
NICE	=	National Institute of Clinical Excellence
SWOG	=	Southwest Oncology Group

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