Future trials should standardize 5-FU dose and schedule, and link these to some biological or biochemical end-point. The mechanism of action of levamisole needs investigation. Trials based on the results of the 5-FU/levamisole combination are hampered by the lack of data on the immunomodulatory effect, if any, or on the mechanism of action of the combination. This regimen is the standard with which new therapies should be compared. Other modulators of 5-FU, including leucovorin, interferon and PALA (N-(phosphonoacetyl)-L-aspartate), need study.

Adjuvant therapy is most conclusively established for patients with stage III disease. However, newer prognostic markers such as DNA content, proliferative activity, surface glycoprotein, gastrin receptor, oncogenes/tumour-suppressor genes and allelic deletions may allow the refinement of prognostic groups. Although local relapse is not common in colon cancer, there are certain groups (i.e., T_4, N_1/N_2) that have significant local failure rates and should be included in separate trials of radiotherapy combined with chemotherapy. Systemic adjuvant chemotherapy should be compared with direct portal infusion.

Since combined therapy can significantly reduce symptomatic local recurrence in rectal cancer, the next series of trials must define the proper dose, sequence and integration of these modalities. The impact on local recurrence and disease-free and overall survival must be measured against any increased toxicity inherent in the combined approach.

Quality of life and the cost-benefit ratio of adjuvant therapy should be investigated.

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Experimental and Clinical Status of Intraperitoneal Chemotherapy

Gerrit Los and J. Gordon McVie

INTRODUCTION

TRADITIONAL intravenous or oral therapy for cancers within the peritoneal cavity may soon give way to the anatomically more appropriate intraperitoneal route for adjuvant postsurgical or palliative treatment. The Second International Conference of Intracavitary Chemotherapy emphasized the important role of intraperitoneal chemotherapy in improving the complete remission rate of cancers restricted to the peritoneal cavity [1].

The peritoneal cavity is a common site of tumour recurrence after initial 'radical' surgical treatment of ovarian and various gastrointestinal malignancies. Dissemination in this cavity is often widespread. Because of the unusual natural course of ovarian cancer and low-grade gastrointestinal neoplasms, characterized by their tendency to be confined into the peritoneal cavity, control of metastatic disease in the peritoneal cavity is an important and challenging problem. During the past decade, a theoretical basis has been established from which the pharmacokinetics of drugs administered intraperitoneally can be predicted [2, 3]. Improved understanding of the principles of intraperitoneal chemotherapy has permitted the design of clinical trials which indicate that a large pharmacological advantage can be translated into improved survival. Further development of an effective therapeutic approach would have a major impact on survival of patients with ovarian cancer and might, to a lesser degree, improve survival in colorectal cancer. Our review describes the current knowledge of intraperitoneal chemotherapy and we point out the direction in which innovative treatments could be developed.

NATURAL HISTORY OF OVARIAN AND GASTROINTESTINAL MALIGNANCIES

Epithelial carcinomas account for 80–90% of ovarian malignancies. They appear to have a common origin, arising from the serosal mesothelial layer of the gonads. The most common mechanism of spread is by transperitoneal dissemination [4]. Table 1 shows the FIGO staging (the classification of the International Federation of Gynecology and Obstetrics) with 5 year survivals. Symptoms tend to appear late—only 25% of patients present in stage I or II [4].

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Table 1. FIGO staging for ovarian cancer and survival after surgery with or without irradiation and/or chemotherapy

	Stage	5-year survival (%)	Ref.
I	Growth limited to ovaries	75–80	5
II	Growth involving one or both ovaries with pelvic extension	50–75	6
III	Growth involving one or both ovaries with intraperitoneal metastases	17–33	7,8
IV	Growth involving one or both ovaries with distant metastases	6	7

*Table 2. Sites of recurrence of gastrointestinal cancer**

	Recurrence site†			
Cancers	Resection site (%)	Peritoneal site (%)	Liver metastases (%)	Distant disease (%)
Gastric	90	50	30	30
Colon	60	50	50	20
Rectal	50	20	50	20
Retroperitoneal sarcoma	90	60	10	20

*Modified from Sugarbaker *et al.* [10]
†Percent of all patients in whom disease recurred.

The amount of residual tumour remaining after initial surgery affects the final results of treatment [7]. Thus it is now commonly accepted that aggressive debulking of disease, which reduces residual tumour to nodules of less than 2 cm, may result in improved survival and quality of life. It is this small-volume residual disease in the peritoneum that is theoretically appropriate for intraperitoneal chemotherapy [3,9].

Gastrointestinal cancer encompasses a wide variety of lesions, from gastric cancer to gall bladder and biliary tract cancer [10]. The anatomic sites of recurrence for gastric, colon and rectal cancer after primary surgery have been defined [10,11]: the resection site and adjacent lymph nodes, the liver, and the peritoneal surfaces (Table 2). At resection, tumour cells are frequently present at or near margins of resection and may implant into connecting surfaces. The local resection site may therefore be a major target for adjuvant therapies in an attempt to improve survival in patients undergoing potentially curative surgery.

Thus after initial therapy for intra-abdominal tumours, such as ovarian carcinomas and to a lesser extent gastrointestinal malignancies, microscopic tumours will remain in the peritoneal cavity. Since cytotoxic agents do not penetrate into the peritoneal cavity at concentrations high enough to eliminate residual disease effectively, it would seem reasonable to explore intraperitoneal administration.

THEORETICAL BACKGROUND

Pharmacokinetic principles

The major attraction of intraperitoneal therapy is that the peritoneal cavity is exposed to higher drug concentrations than the rest of the body, with the hope of an improved therapeutic index. The concentration differential arises because the rate of drug movement from the peritoneal cavity into the plasma (peritoneal clearance) is generally slow compared with total body drug clearance. Dedrick [2] has described the theoretical aspects of intraperitoneal administration in two mathematical models: 'lumped' and 'distributed'. The first considers the concentrations in the peritoneal fluid and plasma, whereas the second involves the penetration of drugs into the tissues adjacent to the peritoneal cavity.

The initial model is a two-compartment analysis of the kinetics of drug exchange between the peritoneal fluid and plasma (Fig. 1). The body is represented by a single volume (V_D) and a single concentration (C_P), the total body clearance by k and the intercompartmental transport between the peritoneum and the body by PA, whereas the volume and concentration of the peritoneal cavity are represented by V and C, respectively. This simple model underestimates the pharmacokinetic advantage of intraperitoneal adminstration. When k greatly exceeds PA, the concentration at steady-state in the peritoneal cavity substantially exceeds the body concentration. When mannitol, for example, is administered to rats intraperitoneally, the drug concentration in the peritoneal cavity falls log-linearly over time while the plasma concentration increases transiently, reaches a peak, and then begins to fall more or less in parallel with the peritoneal concentration but at about a ten-fold lower value [2]. This pattern may be expected with any hydrophilic agent administered intraperitoneally to mammals, even though the ratios and the time scales may differ. Lumped models can successfully predict the concentration of drugs in the peritoneal cavity, but this concentration is relevant only for serosal surfaces and free-floating cells.

Dedrick *et al.* [2,12,13] therefore developed a spatially distributed model of solute transport between the peritoneal cavity and the plasma to predict drug penetration into tissues adjacent to the peritoneal space. Drug penetration into tumour, defined by the concentration gradient from the peritoneum into tissue, is predicted by this theory. The actual tissue drug concentration gradient is a function of the rates of diffusion and convection through the tissue and the rates of removal by chemical reaction and uptake into capillaries or lymphatics. Capillary permeability falls approximately inversely with the 0.6 power of molecular weight, whereas the diffusibility in water of these small molecules falls a little less rapidly than the square root of molecular weight [14]. If the diffusibility in tissue is proportional to the diffusion in water, then perhaps, contrary to intuition, larger molecules will penetrate further. Studies in the rat showed a

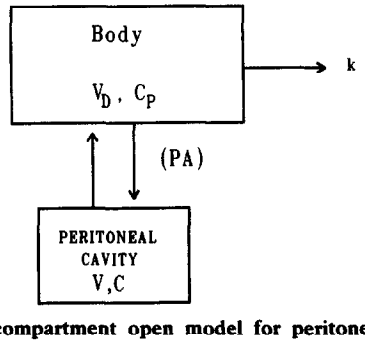

Fig. 1. Two compartment open model for peritoneal pharmacokinetics. See text for explanation.

steep concentration gradient of small marker molecules (EDTA) in a variety of normal tissues. The concentration in the stomach and small intestines decreased to 10% of the value at the serosal surface within about 0.5 mm or less [2]. Findings for larger molecules such as human serum albumin were different: over the visceral tissues concentration decreased with distance, though more slowly than EDTA while over the parietal tissue the concentration was both high and constant [13].

Thus although there are guidelines, especially for normal tissues, the actual penetration distances in pathologic tissues such as tumour nodules and in smaller, avascular or partially vascular tumours is a largely unexplored area. The models predict that optimal results of chemotherapy, including intraperitoneal administration, will be obtained if: (1) the drug possesses a low peritoneal permeability (*PA*), (2) the drug is rapidly cleared from the plasma and (3) the tumour has a minimal volume (thickness).

The peritoneal cavity

In the peritoneal cavity, which can be thought of as viscera (intestines, omentum, mesentery), the peritoneal membrane plays an important role in the pharmacokinetics of intraperitoneally administered cytostatic drugs. The peritoneal surface of this semipermeable membrane allows for the passive diffusion of water and solutes between the peritoneal cavity and the subperitoneal vascular (blood and lymphatics) channels. The total area of the peritoneum is about the same as that of the skin [15], but may be better correlated with body weight. The functional area of the peritoneum that participates in dialysis is estimated to be 0.5% of the total area, representing a total exchange surface area of approximately 90 cm^2 in adult man [16]. The interstitium of the peritoneal membrane consists of loose tissue made up of bundles of collagenous fibrils separated by areas free of visible structure. It has been suggested that the structureless areas form channels for fluid and solute movements [17]. These channels would consist of 'small pores' of radius 4.5–6.0 nm ($4–7 \times 10^9/cm^2$), the main diffusion pathway for small water-soluble substances and water across the peritoneal membrane [17,18]. In addition a few functional 'large pores', about 1 per 6000 small pores and of radius 20–30 nm, apparently account for the transfer of macromolecules [19]. In general, water and solutes of molecular weight less than 2000 are absorbed from the peritoneal cavity via the blood system, larger molecules and particulate substances enter the lymphatics [16,19]. Lymphatics, present mainly on the diaphragmatic peritoneum, have also been found in the mesentery, where they form a network [16]. Proteins [20], red blood cells and tumour cells [20] and liposomes [21] are absorbed via lymphatic drainage.

Access to the peritoneal cavity can be obtained, in analogy with peritoneal dialysis for chronic renal failure, via a Tenckhoff catheter [22]. It is the best established and characterized device for repeated administration of drug-containing fluid [23]. Besides the fact that a large volume can be installed into the peritoneal cavity via the catheter, the fluid can also be withdrawn through it. This gives the possibility of changing the dwell time (the time the cytostatic drug stays in the peritoneal cavity), studying pharmacokinetics in the peritoneal cavity and examining the fluid cytologically to evaluate the effects of chemotherapy on the patient's neoplasm [24].

For effective intraperitoneal therapy, it is important that the fluid containing drug distributes well to the entire peritoneal contents. In patients with ovarian cancer, there are several factors that influence homogeneous distribution. Firstly, these patients have often had one or more laparotomies and perhaps also surgical debulking. As a result, adhesions are common. Secondly, multiple tumour masses may be present and adversely affect fluid distribution. For these reasons, peritoneal fluid dynamics should be considered in clinical trials of intraperitoneal therapy. In primates, Rosenshein *et al.* [25] showed that when small volumes were used, the fluid failed to distribute throughout the peritoneum. Uniform distribution was only seen when the fluid volume was sufficient to cause abdominal distension. Myers *et al.* [26] confirmed this finding: 1.8–2.0 l was sufficient to give uniform distribution in all but a few patients. Howell *et al.* [27] and Gyves *et al.* [28] obtained similar results. This technique is called the 'belly bath' [29]. A volume greater than 1500 ml is sufficient even in patients with bulky abdominal tumour or extensive adhesions resulting from previous laparotomies [23]. On the other hand, administration of 50–200 ml of fluid in man, even into pre-existing ascites, almost always leads to pooling at the site of installation. It makes little sense to treat widespread intra-abdominal disease with small volumes of fluid.

Peritoneal tumours

Cancer chemotherapy aims to eradicate clinically manifest and microscopic metastases. Poor drug penetration into solid tumours may be an important reason for missing this goal. Diminished access of chemotherapeutic agents may be related to altered vasculature or drug penetration barriers.

The tumour vasculature consists of vessels recruited from the pre-existing network of the host vasculature, a response to angiogenic factors released by cancer cells [30]. Although the tumour vasculature originates from the host vasculature, its organization may be different depending on the tumour type, growth rate and location. Macroscopically, the tumour vasculature can be classified in two idealized categories: peripheral and central. In tumours with peripheral vascularization, the centres are usually poorly perfused [31]. In those with central vascularization, one would expect the opposite. Microscopically, the tumour vasculature is highly heterogeneous and does not conform to standard organization (i.e. artery, arteriole, capillaries, postcapillary venule, venule, vein). A key difference between normal and tumour vessels is that the latter are dilated and tortuous [32]. In addition, ultrastructural studies of animal and human tumours have shown that many of the tumour vessels have wide interendothelial junctions, a large number of fenestrae and transendothelial channels, and discontinuous or no basal lamina [31]. These characteristics suggest that tumours should have high vascular permeability, a hypothesis confirmed by tissue-uptake studies which have found that the vascular permeability of tumours was significantly higher than of skin and muscle [31,33].

In addition to higher vascular permeability, increased interstitial pressure has also been demonstrated [34]. This may have severe consequences not only for fluid extravasation but also for the intravasation of molecules present in the interstitium. Because the transvascular transport of molecules such as cytostatic drugs occurs primarily by convection under normal conditions [31], a decrease in fluid extravasation would lead to a decrease in extravasation of drug [35]. On the other hand, cytostatic drugs in the interstitial tissue can be washed out via the vascular system due to the high interstitial pressure. Many low-molecular-weight conventional drugs have had minimal impact on solid tumours [36]. A key factor limiting their effectiveness in treatment has been the inadequate and nonuniform localization of these molecules in tumours [37]. Because

of the peculiarities of tumour microvascularization and the intratumoral physiological conditions, the maldistribution of cytostatic drugs in tumours is not surprising.

EXPERIMENTAL AND CLINICAL DATA

Tumour penetration by cytostatic drugs

For intraperitoneal therapy to be effective against intraperitoneal tumours, the drug must diffuse inwards from the periphery of the tumour mass. Of all the factors involved in intraperitoneal therapy, this is probably the least well-defined. Analysis of drug penetration into tumours involves not only assessment of diffusion rate but also pharmacokinetics and removal of drug by capillary blood flow [23]. All mathematical expressions describing diffusion have terms including the concentration gradient and the duration of drug exposure. Penetration by passive diffusion is most appropriately related to the integral of concentration × time from zero to infinity—i.e. area under the curve (AUC) for peritoneal fluid and plasma. The expression might relate to total tumour drug exposure and may be relevant to drug penetration [38], although this may not hold true for all drugs. Intracellular levels of doxorubicin and daunomycin in leukaemia cells have been measured after rapid (10 min) or prolonged (24 h) infusion [39]. Despite similarities in the plasma AUCs for rapid and prolonged infusions, the intracellular peak levels and AUCs were 2–3 times higher after prolonged infusion. Thus, for certain drugs, the temporal component assumes greater importance than 'concentration gradient' or 'peak level' in determining the degree of intracellular drug uptake by passive diffusion.

Few data are available describing intratumoral drug distribution after intraperitoneal administration [40–42]. At the Netherlands Cancer Institute, we have examined the ability of cisplatin to penetrate the peritoneal lining following intraperitoneal delivery: cytotoxic concentrations reached only to a depth of 1–3 mm from the peritoneal surface [41]. Figure 2 shows a three-dimensional distribution of the relative platinum concentrations in a frozen tumour section after intraperitoneal treatment with cisplatin. The highest platinum concentrations occurred at the periphery of the tumour. It was shown, however, in the same peritoneal tumour model in the rat that when intraperitoneal and intravenous administration were compared,

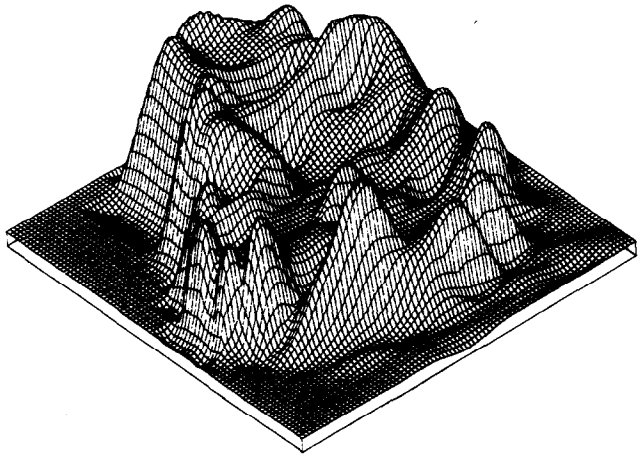

Fig. 2. Three-dimensional distribution plot of the relative platinum concentration (vertical axis) as a function of position in frozen tumour section. Platinum concentration was measured by proton induced X-ray emission [64].

Table 3. Tumour penetration by cytostatic drugs

Cytostatic drug	Tissue	Penetration depth	Ref.
Doxorubicin	Mouse ovarian tumour	4–6 cell layers	40
	Tumour spheroid (human lung tumour)	3–4 cell layers	38
4'-Deoxydoxorubicin	Tumour spheroid (human lung tumour)	6–7 cell layers	38
Methotrexate	Tumour spheroid (human osteosarcoma)	3–7 cell layers	48
5-Fluorouracil	Tumour spheroid (human glioma)	0.2 mm	49
Vinblastine	Tumour spheroid (human glioma)	3–4 cell layers	49
Mitoxantrone	Tumour spheroid (human neuroblastoma)	5–6 cell layers	*
Cisplatin	Brain tissue	0.8 mm	44
	Peritoneal tumour (human)	1–3 mm	41
	Peritoneal tumour (rat CC531)	1–2 mm	42, 43
	Peritoneal tumour (human)	2–2.5 mm	45
Carboplatin	Peritoneal tumour (rat CC531)	0.2–0.5 mm	46
Oxaliplatin	Peritoneal tumour (rat CC531)	1–2 mm	47

*Unpublished (Los *et al.*).

the pharmacokinetic advantage of the intraperitoneal installation of cisplatin was limited to 1–2 mm from the peritoneal surface. Based on these experimental observations, any advantage intraperitoneal cisplatin will have over intravenous administration will be limited to those clinical situations in which small-volume disease is present at the start of treatment. In ovarian carcinoma, this includes patients with negative second-look laparotomies following cisplatin-based systemic therapy [44] and patients with microscopic disease or small tumour nodules (probably under 0.5 cm). Morrison *et al.* [44] also concluded that the penetration depth in rat brain tissue was 0.8 mm in a linear diffusion reaction permeation model. The distribution of cisplatin in the rat was similar to those found in human necropsy samples of peritoneal tumours (i.e. penetration of 2–2.5 mm) [45].

The penetration of carboplatin is less than that of cisplatin. Not only does less carboplatin penetrate into peritoneal rat tumours (about 7 times less) but the penetration distance was also less after equimolar intraperitoneal treatment (0.5 mm for carboplatin compared with 2 mm for cisplatin). A lipophilic analogue, oxaliplatin, had a distribution similar to that of cisplatin, and since oxaliplatin is not cross-resistant with cisplatin, it could in theory be used in patients with cisplatin resistance [46,47].

For tumour penetration of different drugs, cisplatin is one of the most favourable drugs (Table 3). Ozols *et al.* [40] evaluated the intensity of intracellular fluorescence in mouse ovarian

tumours treated both intraperitoneally and intravenously with doxorubicin. Only the outer 4–6 cell layers in tumour masses were intensely fluorescent; deeper than this, little fluorescence was observed. Despite the high drug concentrations obtained within the peritoneal cavity, drug diffusion into tumour masses was minimal and had no advantage over intravenous treatment [40].

Kerr and Kaye [38] also demonstrated that the penetration capacity of doxorubicin in a spheroid tumour model was not more than several cell layers. The lipophilic analogue of doxorubicin, 4'-deoxydoxorubicin, penetrated more deeply with associated improvement of cytotoxic response [38]. We have studied the penetration of mitoxantrone *in vitro* in a similar spheroid model. Similar to doxorubicin, mitoxantrone did not penetrate more than several cell layers. The difference observed between cisplatin and the other drugs suggests variability of penetration depth into tumour nodules. Therefore measures aimed at improving drug penetration may be crucial in increasing the therapeutic efficacy of cytotoxic agents [38], although multiple administration at suitable intervals may cause 'peeling' of the tumour in increments. Over a longer period, drug-resistant phenotypes might emerge, eventually negating the possible benefits of high drug concentrations. Nodules of around 0.5 cm thickness would therefore be ideal for therapy, since there would be a good chance of eradicating them with one or a few therapy courses.

Clinical trials

Trials have been largely restricted to small numbers of patients in phase I studies. The few phase II studies with 5-fluorouracil (5-FU), methotrexate, doxorubicin, melphalan, cytarabine, mitoxantrone, cisplatin and carboplatin are presented in Table 4.

Intraperitoneal 5-FU has been used for several decades for controlling malignant tumour cells present in ascites [50]. Sugarbaker *et al.* [51] reported a prospective randomized trial of 66 patients with advanced primary colorectal cancer, each receiving 5-FU, either intravenously or intraperitoneally. No difference was found in survival or disease-free interval. In the intraperitoneal group, the frequency of first recurrence in the peritoneum was decreased. Recurrence in the peritoneal cavity alone, however, was only a small proportion of the total recurrence (Table 4).

Methotrexate is an attractive agent for intraperitoneal therapy [52,53]. Folinic acid, which crosses the peritoneal membrane poorly from the systemic circulation, may be administered systemically to limit toxicity [54], making it possible to maintain high concentrations of methotrexate in the peritoneal cavity for a long time. Howell compared intraperitoneal methotrexate with intravenous folinic acid and demonstrated 1 response in 18 patients with ovarian cancer [54]. Pain in the abdomen limited dose escalation of both these drugs.

The efficacy of intraperitoneal doxorubicin has been demonstrated *in vitro* and in animals [55]. Ozols *et al.* [56] then treated 10 patients with advanced ovarian carcinoma with doxorubicin and reported 3 responses. The dose-limiting toxicity, chemically induced peritonitis, makes doxorubicin impractical for intraperitoneal administration except in very low doses.

Pharmacokinetic analysis predicted an advantage for intraperitoneal administration of melphalan and a phase I study confirmed this prediction: 1 of 14 evaluable ovarian cancer patients had a complete response lasting more than 12 months [57]. 2 other responses were seen in gastrointestinal tumours.

Table 4. Clinical results of intraperitoneal chemotherapy: single-agent treatment

Drug	Dose (mg/m^2)*	Type of cancer	*n*	Responses (%)	Ref.
5-FU	1.3–2080 mg	Ovarian	5	20 (CR) 20 (PR)	79
	845–1170 mg	Ovarian	14	7 (PR)	51
	1040–1539 mg	GI	66	†	
	1 g	Colon	5	20 (PR)	28
Methotrexate	30	Ovarian	2	50 (PR)	53
	13.5–45 mg	4 Ovarian 1 Melanoma	5	0	52
Doxorubicin	10–50 mg	Ovarian	10	30 (PR)	56
Melphalan	30–90	Ovarian + GI	19	16 (PR)	57
	12–40	Ovarian	3	33 (PR)	81
Cytarabine	10, 100, 1000 μmol	Ovarian	10	20 (PR)	58
Mitoxantrone	10–40	Ovarian + GI	21	38 (PR)	61
	14	Ovarian	8	50 (PR)	62
Cisplatin	90–270	Ovarian	18	55 (PR)	65
	60–150	Ovarian	27	33 (CR)	64
	50	Ovarian	23	65 (PR)	82
	120–180	Ovarian	4	25 (CR) 50 (PR)	83
Carboplatin	200–650	Ovarian	27	15 (CR)	66
	200–500	Ovarian	22	18 (CR) 36 (PR)	67
	150–350	Ovarian	22	14 (CR) 9 (PR)	68

*Except where indicated.
†No difference vs. intravenous.
CR = histologically proven complete remission, PR = partial remission, includes also a negative cytology or a decrease in ascites. GI = gastrointestinal malignancies. IV = intravenous route.

Cytarabine has been studied both as a single agent and with other agents. King *et al.* [58] used it as a single agent and demonstrated 2 responses in 10 patients with advanced ovarian cancer. Mitoxantrone is a new cytostatic drug with similar antitumour activity to doxorubicin in the systemic treatment of epithelial ovarian cancer [59]. Phase I and II studies demonstrated pharmacological advantages for intraperitoneal compared with systemic treatment [60]. Clinical results, however, were disappointing [61,62].

Cisplatin is one of the most effective drugs available for the treatment of ovarian carcinoma [63,64]. When administered in hypertonic saline dialysate with systemic sodium thiosulphate, nephrotoxicity is reduced [65]. Results suggest that intraperitoneal cisplatin may be able to salvage patients with small-volume residual disease. Howell *et al.* [65] recorded 10 out of 18 patients who responded, while Ten Bokkel Huinink *et al.* [64] demonstrated that 30% of heavily pretreated patients achieved a pathologically documented complete remission after intraperitoneal cisplatin. Carboplatin is as active as cisplatin in patients with advanced ovarian cancer after intravenous therapy, but in phase I and II trials has proven significantly less toxic. Nevertheless, by the intraperitoneal route carboplatin is less active than cisplatin. Phase I and II studies indicated lower complete remission (CR) rates [65–68].

Table 5. Clinical results of intraperitoneal chemotherapy: multi-agent treatment

Drug	Dose (mg/m²)*	Type of cancer	*n*	Responses (%)	Ref.
Cisplatin +	100–200 mg/m²	Ovarian	31	3 (CR)	
Cytarabine + doxorubicin	10^{-3}–10^{4} mol/l	+ GI		28 (PR)	84
Cisplatin + cytarabine	100–200 mg/m² + 2000 mg	Ovarian + GI	52	31 (PR)	69
Cisplatin +	200 mg/m²	Ovarian	31	16 (CR)	71
cytarabine +	1200 mg/m²			10 (PR)	
bleomycin	2 U/m²				
Cisplatin + mitomycin	100 mg/m² 5–10 mg	Mesothelioma	11	45 (PR)	72
Cisplatin +	200 mg/m²	Ovarian	12	25 (CR)	73
etoposide	350 mg/m²			33 (PR)	
	200 mg/m²	Ovarian	13	69 (CR)	74
	350 mg/m²				
	100 mg/m²	Ovarian	57	21 (CR)	75
	200 mg/m²			19 (PR)	
Cisplatin +	90 mg/m²	Ovarian	21	43 (CR)	76
intravenous	600 mg/m²				
cyclophosphamide				15 (PR)	

*Except where indicated.

Combination studies (Table 5) with cisplatin and cytarabine plus or minus doxorubicin have been evaluated by Markman *et al.* [70]. Responses were noted in 21 of 56 patients with ovarian cancer, although the effect upon survival was not clear [14]. Nevertheless, combined trials with intraperitoneal cisplatin and cytarabine hold some promise, since total peritoneal drug exposure of cytarabine by this route was 300–1000 times greater than that in plasma. A phase II trial of intraperitoneal chemotherapy with cisplatin, cytarabine and bleomycin in 31 patients who had either failed or recurred after intravenous therapy with cisplatin demonstrated a response rate of 26%, of which 16% were pathologically documented as complete responses [71]. In malignant mesothelioma, Markman and Kelsen [72] concluded that intraperitoneal cisplatin-based therapy results in the short-term palliation of symptoms due to ascites production in patients with peritoneal disease and that an occasional patient experienced long-term local disease control.

The combination of cisplatin with etoposide intraperitoneally was effective for patients who had failed intravenous cisplatin-based chemotherapy. A study in San Diego demonstrated that 9 out of 13 patients achieved complete remission [73]. The same group also concluded that this combination was as effective as standard intravenous therapy in untreated stage III and IV ovarian cancer. Of the 12 patients attaining a clinical CR, 7 had a second-look laparotomy. 3 of these 7 were pathologic CRs, and 4 had microscopic disease only [74]. Reichman *et al.* [75] also emphasize the efficacy of the combination of cisplatin with etoposide since they found in refractory/recurrent ovarian cancer that the overall surgical response rate was 40% and the CR rate was 21%.

The combination of intraperitoneal cisplatin and intravenous cyclophosphamide was tested as first-line chemotherapy by Zambetti *et al.* [76]. Overall efficacy was good (15% partial response, 43% CR), although treatment failed in 8 out of the 21 patients evaluable for response (38%) and was not better than after cisplatin-based intravenous treatment. An explanation for the apparent discrepancy between these findings and the theoretical expectations of a better treatment outcome after intraperitoneal cisplatin is probably the inclusion of patients with tumour nodules up to 2 cm in diameter, since penetration of cisplatin into peritoneal tumours is limited to 1–2 mm [42, 43,45].

Conclusions

The clinical data indicate further improvement in the therapeutic effect in these patients who, by and large, had failed to achieve CR after optimal intravenous treatment. The Second International Conference on Intracavitary Chemotherapy [1] confirmed this, demonstrating in an overview of all reported studies a mean CR rate for all the different intraperitoneal treatments in patients with ovarian cancer of 10%. The studies included patients with bulky disease and heavily pretreated patients. In conclusion, the clinical data indicated that salvage intraperitoneal therapy could produce complete remissions and provide further impetus to improve treatment by this route.

With intraperitoneal chemotherapy in the clinic, stage and extent of residual disease, the choice of drug and adequate intratumoural drug distribution must be considered. Most of the patients described in these studies had minimal residual disease at the time of intraperitoneal treatment. Clinical studies have consistently demonstrated improved survival of patients without disease after second-look laparotomy compared with those with residual tumour [7,77]. Optimal tumour debulking and early stage are therefore the most important factors predicting outcome. If intraperitoneal therapy has a role, it will probably be as an adjuvant strategy, which may convert incomplete surgical or chemical 'debulking' to CR in the peritoneal space. Its role in eradicating liver micrometastases is not clear, nor is its use as a reservoir to provide prolonged exposure systemically.

Drug selection is probably the most important aspect of intraperitoneal chemotherapy. Cisplatin is one of the best choices (Tables 4 and 5). As predicted by pharmacological modeling [2], intraperitoneal installation of many commonly used chemotherapeutic agents produces local concentrations in the peritoneal cavity many times higher than those in plasma. The pharmacological advantage of this route is defined as the ratio of total drug exposure for the peritoneal cavity to that for plasma. This ratio varies from 4 for thiotepa to 1800 for thioguanine [78]. The major question, however, is whether the enormous pharmacological advantages can be translated into improved response rate, which depends on the penetration capacity of the drug. None of the drugs currently available for intraperitoneal therapy are very good at penetrating deeply into tumour from the surface. The best are cisplatin and oxaliplatin; cisplatin has the highest single-agent response rate (Tables 4 and 5). It is disappointing that carboplatin probably has less efficient penetration than cisplatin [46]. As a consequence of clinical trial data [66,67] the EORTC Gynaecological Group have instituted a randomised trial of intraperitoneal cisplatin after achieving a good response from first-line therapy in stage III/IV ovarian carcinoma.

PERSPECTIVES

Diminished access of chemotherapeutic agents to cells in tumours will result in a lack of total eradication of that tumour.

Improvement in intraperitoneal chemotherapy will therefore be based on the penetration of drugs into peritoneal tumours. Penetration of cytostatic drugs depends on the permeability of the tumour cell membrane, the lipophilicity of the drug itself and the drug concentration and dwell time in the peritoneal cavity.

The first direction might therefore be the development of new drugs with better penetration properties. Kerr and Kaye [38] demonstrated with a tumour spheroid model that lipophilic analogues of doxorubicin penetrated more deeply than the parent compound with associated improvement of cytotoxic response. Another possibility is to increase the permeability of tumour cell membranes. One way to achieve this is to increase the temperature in the region of the tumour. We demonstrated in the rat peritoneal tumour model that the combination of intraperitoneal cisplatin with regional hyperthermia increased the platinum concentration in peritoneal tumours four-fold [85]. The platinum distribution patterns in peritoneal tumours confirmed an improved penetration (the penetration depth increased on heating from 1–2 mm to 3–4 mm). Intraperitoneal cisplatin plus local heating might improve the therapeutic ratio.

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