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Enhancing delivery of small molecule and cell-based therapies for ovarian cancer using advanced delivery strategies

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Abstract

Ovarian cancer is the most lethal gynecological malignancy with a global five-year survival rate of 30-50%. First-line treatment involves cytoreductive surgery and administration of platinum-based small molecules and paclitaxel. These therapies were traditionally administered via intravenous infusion, although intraperitoneal delivery has also been investigated. Initial clinical trials of intraperitoneal administration for ovarian cancer indicated significant improvements in overall

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survival compared to intravenous delivery, but this result is not consistent across all studies performed. Recently cell-based immunotherapy has been of interest for ovarian cancer. Direct intraperitoneal delivery of cell-based immunotherapies might prompt local immunoregulatory mechanisms to act synergistically with the delivered immunotherapy. Based on this theory, pre-clinical *in vivo* studies have delivered these cell-based immunotherapies via the intraperitoneal route, with promising results. However, successful intraperitoneal delivery of cell-based immunotherapy and clinical adoption of this technique will depend on overcoming challenges of intraperitoneal delivery and finding the optimal combinations of dose, therapeutic and delivery route. We review the potential advantages and disadvantages of intraperitoneal delivery of cell-based immunotherapy for ovarian cancer and the pre-clinical and clinical work performed so far. Potential advanced delivery strategies, which might improve the efficacy and adoption of intraperitoneal delivery of therapy for ovarian cancer, are also outlined.

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Intraperitoneal administration of therapy for ovarian cancer holds promise for improved patient outcomes, however, results have been inconsistent to date which may be due to poor delivery strategies. This review focuses on intraperitoneal delivery of small molecules and cell-based immunotherapies and potential advanced delivery strategies are outlined which might improve the adoption of intraperitoneal delivery of therapy for ovarian cancer.

Keywords:

ovarian cancer; intraperitoneal delivery; immunotherapy; chemotherapy; advanced drug delivery

Table of Contents Keyword:

Advanced therapy delivery

1. Introduction

1.1 Overview of ovarian cancer

Ovarian cancer, the most lethal of the gynecological malignancies, refers to a histologically diverse range of tumor types [1]. 90% of ovarian cancers diagnosed are carcinomas. These can be divided into five distinct subtypes: high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma and low-grade serous carcinoma (LGSC) [2]. The remainder are of stromal or germ cell origin or cannot be classified [3]. The exact pathogenesis of ovarian cancer is not completely understood, but specific genetic mutations associated with each subtype have been identified [3–5].

Diagnosis of ovarian cancer is often made at an advanced stage with 75% of ovarian cancer diagnoses made at Stage III-IV or later [6–8]. This is mainly because initial symptoms of ovarian cancer such as abdominal pain and distention are non-specific and may be misdiagnosed as irritable bowel syndrome [7, 9, 10]. The National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis of ovarian cancer state that women who are symptomatic should have serum CA-125 measured, and be sent for further investigation

if the level is >35 units/mL [9, 11]. CA-125 can also be useful for non-invasive monitoring of a patient's response to chemotherapy [11]. Transvaginal ultrasonography (TVUS) may also be used to aid diagnosis, but significant enlargement of the ovary is required for this technique to work [4, 11].

Ovarian cancer should be staged, as part of the diagnostic process, in line with the guidelines of the International Federation of Gynecology and Obstetrics (FIGO) [2]. Cancer which is confined to the ovaries or fallopian tubes is designated as stage I [2]. As the cancer spreads to other pelvic organs, it is classified as stage II. Stage III represents the stage where diagnosis most commonly occurs [2]. At this stage the cancer has spread to the abdomen. The presence of metastasis above the diaphragm or parenchymal metastasis signifies stage IV ovarian cancer [2]. Progression of cancer in the peritoneum is caused by cancer cells becoming detached from the original tumor and diffusing through the peritoneal fluid, while distant metastasis normally occurs via the lymphatic system and less commonly through the vasculature [5]. Cancer cells diffusing through the peritoneal fluid are thought to travel as spheroids as opposed to single cells, which might make them more resistant to chemotherapy than single cells [5].

1.2 Incidence, morbidity and mortality of ovarian cancer

239,000 new cases of ovarian cancer are diagnosed globally each year with an estimated 152,000 deaths [3, 12]. The median age at diagnosis is 63 years [4, 13]. In general, the incidence is higher in developed, urban regions and the global incidence rate has not changed significantly since 1973 [3, 8, 12, 14]. A family history of ovarian cancer or genetic mutations in the *BRCA1* and *BRCA2* genes increase the risk of ovarian cancer [3, 15].

Ovarian cancer is the 5th highest cause of cancer mortality, with an overall five-year survival rate of 30-50% globally [3, 12, 16]. 75% of patients diagnosed with ovarian cancer present with advanced stage disease [1, 5, 8, 17]. Cancer stage at diagnosis strongly impacts survival. Women diagnosed at stage I have a five-year survival rate of > 80% compared to just 42% if diagnosed at stage III [8, 16–19].

Outside of survival, ovarian cancer also has an impact on patients' quality of life and significantly increases rates of depression and anxiety compared to healthy women [20, 21].

2 Treatment of ovarian cancer

Management of patients with ovarian cancer requires input from a multidisciplinary team of surgeons, oncologists, and histopathologists [4]. Histology of ovarian tumors is particularly important as profiling the tumor type can aid decision making on therapy and help predict survival [4]. Most women will be treated with a combination of chemotherapy and cytoreductive surgery.

2.1 Cytoreductive surgery

The British Gynecological Cancer Society (BGCS) stipulate that all women diagnosed with ovarian cancer should be considered for cytoreductive/tumor debulking surgery [22]. The aim of cytoreductive surgery is to remove as much of the tumor tissue as possible. Optimal

cytoreduction involves removing all visible evidence of the cancer and is the strongest predictor of overall survival [23–26]. The proportion of patients in whom optimal surgical cytoreduction is achieved varies from 46–84% and may reduce with increasing age [27–29]. Where sub-optimal cytoreduction occurs, and residual tumor tissue remains following debulking, this is usually found on the diaphragm or in the pelvic region, including on the bladder, rectum or sigmoid colon [23]. Secondary cytoreductive surgery can be performed where a woman experiences a relapse of ovarian cancer [30, 31]. Hyperthermic intraperitoneal chemotherapy (HIPEC) (discussed in Section 3.1.2), may be administered at the time of cytoreductive surgery [32].

While complete cytoreduction followed by chemotherapy has been shown to significantly improve survival compared to chemotherapy alone in women with platinum-sensitive ovarian cancer (overall survival 60.7 months versus 46.2 months), cytoreductive surgery can be associated with significant morbidity for the patient [33]. 33–37% of patients report morbidity 30 days following surgery [27–29, 34]. Age, overall health status, peritoneal cancer index, extent of surgery and surgical hypothermia all impact on the development and severity of post-operative complications following surgical cytoreduction [25, 27, 29, 33, 35, 36]. However, even when the risk of morbidity is high, combining cytoreductive surgery with chemotherapy can improve overall outcomes [29].

A further benefit of cytoreductive surgery is that reducing the tumor volume may result in the remaining cancer cells being converted into a growth phase where they are more sensitive to chemotherapeutics [37]. These residual cancer stem cells are generally resistant to therapy and left behind following surgery, however, surgery prompting them to adopt a proliferative phenotype might reduce their resistance to chemotherapy, improving overall treatment outcomes [38, 39]. Chemotherapy delivered via the intraperitoneal route may have difficulty penetrating the tumor as it is not being transported in the bloodstream. Cytoreductive surgery removes macroscopic tumors allowing IP chemotherapy to be considered.

2.2 Traditional chemotherapeutics

Platinum-based treatment regimens have represented the gold standard of therapy for over 40 years [4, 40]. Three approved platinum-based chemotherapeutics exist: cisplatin, carboplatin and oxaliplatin [41, 42]. Platinum-based drugs remain intact in the bloodstream and enter cells via copper transporters [41]. Once inside the cell, platinum-based molecules bind to nuclear DNA. This binding causes unwinding of the DNA and subsequent prevention of replication and cell death via apoptosis [41–43]. Resistance to platinum-based therapies can occur as a result of accelerated degradation of the molecule, reduced cellular uptake or development of mechanisms of DNA repair to overcome the effects of platinum-therapy [41–43]. Similar to most other chemotherapeutics platinum-based agents are not selective for cancer cells and thus, can cause side-effects which are most apparent in fast-growing tissues [41]. Nephrotoxicity is a serious and common side-effect of cisplatin and most centres have adopted specific hydration protocols around platinum drug dosing to prevent nephrotoxicity [44]. Oxaliplatin and carboplatin are less nephrotoxic than cisplatin but are also associated with ototoxicity, neurotoxicity and neutropenia [45–48]. Carboplatin is now

most often used in chemotherapy protocols for ovarian cancer and is dosed to an Area Under the Curve (AUC) of 4-7.5 depending on the protocol [48]. In most regions, first line therapy involves combination of paclitaxel with platinum-based agents [49, 50].

Paclitaxel, exerts a cytotoxic effect by binding to polymerised tubulin and stabilising microtubules to dissociation [51]. The addition of paclitaxel to platinum-based regimens has been shown to improve progression-free survival and thus, regimens using this combination represent first-line therapy in most regions worldwide [4, 49, 50]. Paclitaxel, used in combination with carboplatin, is usually given weekly at a dose of 80 mg/m² IV or three-weekly at 175 mg/m² IV [48]. Paclitaxel is associated with side-effects such as alopecia, arthralgia, myalgia, cardiac conduction abnormalities and tissue necrosis if extravasated and rarely cardiac conduction abnormalities [48].

Response to this first line treatment and time to relapse is used to classify patients as platinum-refractory, platinum resistant or platinum sensitive [52]. Up to 14% of patients are classified as platinum-refractory, with disease progression during initial treatment [52]. Among patients who respond to initial platinum-based chemotherapy, 75% go on to experience an ovarian cancer relapse. This relapse is classified as platinum resistant if it occurs within 6 months after last platinum treatment and platinum sensitive if more than 6 months after treatment [52]. Women with platinum resistant disease generally have a response rate to second-line treatments of less than 20% [4, 52].

More recently anti-vascular endothelial growth factor (VEGF) treatments have been investigated for ovarian cancer [53]. Bevacizumab is a monoclonal antibody which can inhibit the effects of VEGF, cutting off the essential blood supply to the tumor [53]. The addition of bevacizumab to standard chemotherapy regimens has been shown to significantly improve overall survival ($p=0.0447$) compared to standard chemotherapy alone in recurrent ovarian cancer. However, the addition of bevacizumab is associated with a 10% increase in reported adverse events [54]. Maintenance bevacizumab can increase progression-free survival and improve outcomes for patients with stage IV disease, large volume ascites or where optimal tumor debulking was not possible [22].

Mutations in the *BRCA1* or *BRCA2* genes interfere with normal DNA repair pathways. Poly (ADP-ribose) polymerase (PARP) enzymes become important in cases of *BRCA1* or *BRCA2* mutations as they become one of the main mechanisms of DNA repair [4, 55, 56]. These PARP enzymes allow cancer cells to repair their DNA, facilitating cell proliferation and disease progression [4]. Inhibiting the PARP enzymes, prevents DNA repair and subsequently prevents cell proliferation [55, 56]. Olaparib, rucaparib and niraparib are currently approved by the FDA for the treatment of ovarian cancer [55, 57]. These agents can significantly improve progression-free survival in the post-platinum maintenance setting [55, 58]. Germline and somatic genetic testing help identify patients most likely to benefit from these agents [57, 58].

2.3 Immunotherapy

Immunotherapy involves harnessing the innate ability of immune cells to kill cancer cells [59, 60]. Normally, the immune system can detect cells in the body which are aberrantly

proliferating and kill them before tumor formation occurs [59–61]. However, cancer cells have developed mechanisms to evade this immune response [59–61]. There are five broad categories of immunotherapy currently being investigated as anti-cancer agents [62]. These categories are: cell-based immunotherapy, immunomodulators, vaccines, antibody-based targeted therapies and oncolytic viruses [62, 63]. The first molecule licensed as an immunotherapy for cancer treatment was interferon- α for hairy cell leukaemia in 1986 [63]. In April 2010, sipuleucel-T was approved as immunotherapy for prostate cancer [64]. In 2017 two engineered T cell therapies were approved [63]. Tisagenleucel was approved for B cell acute lymphocytic leukaemia and non-Hodgkin's lymphoma while axicabtagene ciloleucel was approved for large B cell lymphoma [63].

Ovarian cancer has been identified as a cancer that might respond well to immunotherapy [60, 65, 66]. This is because ovarian cancers express tumor associated antigens and peptide major histocompatibility complexes (MHCs) which can be recognised by cytotoxic T lymphocytes [60, 65, 66]. Furthermore, infiltration of CD57⁺ natural killer (NK) cells into tumors in women with HGSC has been associated with improved overall survival, indicating the important role of immune cells in ovarian cancer [67]. Despite the huge promise of immunotherapy, there are several issues that still need to be addressed. Many patients do not respond to this type of therapy and autoimmune reactions can occur in some patients. Delivery and infiltration into solid tumors has proved challenging [63]. Advanced delivery strategies for immunotherapy have the potential to significantly enhance its efficacy against solid tumors and cost-benefit ratio, allowing the full potential of immunotherapy to be realised [63, 68, 69]. Such strategies should aim to evenly distribute the therapeutic agent to the target region and prolong its residence time there, while also considering ease of placement and insertion, potential for development of adhesions, patient comfort and effect on the therapy. These aspects will be discussed in subsequent sections of this review.

Several advanced delivery strategies for immunotherapies have been suggested including: nanoparticle-mediated delivery [70], intratumoral injection [71], implantable scaffolds [72–74], injectable hydrogels [75], transdermal delivery [70] or local delivery [63, 68]. Recently it has been established that the intraperitoneal (IP) route of delivery may be beneficial for immunotherapy targeting peritoneal cancers [76, 77]. Catumaxomab, is a monoclonal antibody-based immunotherapy that has been licensed for IP infusion in patients with malignant ascites [78]. Herein we will focus specifically on cell-based immunotherapies using T cells and NK cells. Extensive work has been focussed on improving the potency of these cell types and improving their homing to and specificity for cancer cells. However, while direct delivery of these therapies to the peritoneum might prompt local immunoregulatory mechanisms, augmenting the overall response to the delivered therapy, the tumor microenvironment is generally considered hostile to immunotherapies such as T cells and NK cells [77, 79]. Studies of CAR T cells in various tumor types in rodents have shown inactivation of the CAR T cells within the tumor microenvironment via a variety of mechanisms including activation of regulatory T cells and inhibitory cytokines. This has resulted in various groups investigating both the exact processes within the tumor microenvironment and CAR T cells which can overcome these inactivation mechanisms [79–82]. Established and investigational treatments for ovarian cancer have been reviewed extensively elsewhere [60, 61, 65, 66, 83–85]. Herein we will focus on reviewing IP delivery

of T cells and NK cells for ovarian cancer and recommendations for improving delivery. We will first review the theoretical pharmacokinetic advantages of IP delivery of therapy, before reviewing the results of clinical trials where small molecule chemotherapeutics were delivered IP and then will review current pre-clinical work and clinical trials on IP delivery of T cells and NK cells.

3 Intraperitoneal delivery of cancer therapeutics

Intravenous delivery represents the standard delivery method for platinum-based therapies, paclitaxel and bevacizumab. The bioavailability of any molecule delivered via the intravenous route is, by definition, 100%, with bioavailability values for other routes of administration being calculated based on this [86]. Disadvantages of the IV route include first-pass metabolism and systemic distribution of the drug where it can cause off-target effects. Thus, the dose chosen for IV administration must balance achieving a therapeutically effective dose at the intended site of action with avoiding systemic side-effects [87]. IP delivery of therapy might reduce systemic side-effects. Studies reported in the literature have recorded nausea, vomiting, fatigue, neuropathy and abdominal pain as the most common side-effects of IP chemotherapy, regardless of the therapeutic agent (cisplatin, carboplatin or paclitaxel) used [88]. A Cochrane Review of IP chemotherapy using various regimens reported that, compared to IV therapy, the incidence of serious gastrointestinal effects, pain, fever and infection was increased with IP therapy while the incidence of ototoxicity was reduced [89]. However, the frequency of these side-effects depends on the individual drug used with significantly more grade 3 nausea and vomiting, neuropathy and neutropenia reported with cisplatin compared with carboplatin [90]. The dose of the chemotherapeutic used will also impact the severity of the local toxicity. IP doses of chemotherapeutics vary depending on the regimen used. IP doses of paclitaxel 60 mg/m², carboplatin to an Area Under the Curve (AUC) of 6 and cisplatin 100 mg/m² have been stated in the literature, but these can be adapted based on the specific regimen and other factors such as renal function [91]. A summary of delivery routes for ovarian cancer is shown in Figure 1.

The different physicochemical properties of the therapies to be delivered, as shown in Figure 2, makes achieving optimal IP delivery challenging. Thus, IP delivery of traditional chemotherapeutics and novel immunotherapies is the focus of this review.

3.1 Intraperitoneal delivery

The peritoneum covers the abdominopelvic organs posteriorly and anteriorly the abdominal wall [87]. IP delivery of therapy for ovarian cancer is of particular interest as ovarian cancer commonly remains within the abdomen at the time of initial diagnosis [5, 92]. IP delivery of therapy for ovarian cancer was first proposed and investigated by Dedrick and colleagues in 1978 [93]. They proposed that because peritoneal clearance of certain molecules had been shown to occur at a slower rate than clearance from the systemic circulation, direct intraperitoneal delivery of chemotherapy for ovarian cancer might improve concentrations at the target site, provide sustained effects and reduce systemic toxicity [93].

The pharmacokinetic benefit of IP delivery, in terms of increased peritoneal concentration of the delivered drug, has been extensively studied for commonly administered therapies [94–96]. However, this pharmacokinetic benefit may not necessarily be associated with a pharmacodynamic benefit. Poor tumor vascularization and adhesions can prevent the therapy from reaching the desired site negating the increased concentrations achieved [37]. Furthermore, IP chemotherapy is not suitable in women with macroscopic residual disease post-cytoreductive surgery [92]. Dedrick and colleagues suggested four guidelines to be followed for IP delivery of chemotherapeutics: (1) Tumors should have a small diameter to facilitate penetration of the chemotherapeutic, (2) the therapy should be delivered in a large volume of liquid, sufficient to cover the peritoneal surface, (3) if combining medicines, hepatic and renal clearance of both should be considered and (4) plasma clearance of the drug in question should be high compared to peritoneal clearance [93].

Based on this reasoning it is now widely accepted that direct delivery of chemotherapy into the peritoneum removes the issue of dilution in the systemic circulation and thus the bioavailability of the delivered therapeutic is improved, with a higher concentration at the target site [5, 87, 97]. Furthermore, reduced systemic exposure might reduce harmful and uncomfortable side-effects [92, 96].

3.1.1 IP chemotherapy delivered via an implanted peritoneal catheter—Three pivotal trials on IP cisplatin have been performed. In 1996, Alberts and colleagues reported on a phase III trial (GOG 114) comparing IP and IV cisplatin in 546 women with stage III ovarian cancer [98]. All women underwent initial cytoreductive surgery and received concurrent IV cyclophosphamide along with the IP or IV cisplatin [98]. Alberts and colleagues reported a significantly improved median survival in the IP cisplatin group of 49 months, compared to 41 months in the IV cisplatin group [98]. Significantly improved overall survival with the use of IP cisplatin in combination with IV paclitaxel compared to IV paclitaxel and IV cisplatin was also reported by Markman and colleagues in another large phase III study in 2001 although the patients receiving IP cisplatin also received two doses of IV carboplatin [99]. In 2006 Armstrong and colleagues reported on GOG 172 with 415 women with optimally cytoreduced stage III ovarian cancer, treated with either IV paclitaxel and IV cisplatin or IV paclitaxel followed by IP cisplatin and IP paclitaxel [100]. Both progression-free survival and median overall survival were significantly improved in the group that received IP cisplatin and paclitaxel.

In 2015 the GOG published the long-term follow-up of the pivotal phase III GOG 114 Alberts and GOG 172 Armstrong studies. Patients who had received IP chemotherapy, delivered via an implanted IP catheter, had a significantly reduced risk of death ($p < 0.002$), with an average 10 months extended survival following IP therapy compared to IV therapy [92]. A retrospective review of GOG 172 also showed significantly improved overall survival in women with ovarian cancer who had a *BRCA1* mutation compared to those with normal *BRCA1* expression [101].

Many of the studies in IP chemotherapy employ different treatment regimens and randomisation strategies making the true value of IP delivery difficult to determine [97]. Other barriers to the adoption of IP chemotherapy as standard for women with ovarian

cancer include: catheter blockage issues, catheter placement issues, inconvenience and higher local toxicity compared to IV therapy [92]. In GOG 172, Armstrong and colleagues reported that only 42% of women completed all six assigned cycles of IP chemotherapy [100]. While the primary reason for this was catheter-related issues, significantly more adverse events were reported in the patients receiving IP therapy. Specifically women receiving IP therapy experienced severe or life-threatening pain, fatigue, hematologic, gastrointestinal, metabolic, or neurologic toxicities significantly more than patients in the IV chemotherapy group [100]. In discussing these adverse events Armstrong and colleagues note that these may be mitigated by reducing the dose administered IP, changing the regimen to only administer one drug IP instead of two and standardising the port used and the timing and technique for insertion [100]. Based on these toxicity concerns, the BGCS guidelines currently recommend that IP chemotherapy should only be used within clinical trials [22]. Considering that one of the main reasons for discontinuation of IP chemotherapy in GOG 172 was catheter-related issues, innovations in catheter design should be prioritised to facilitate better delivery of therapy and potentially reduce discontinuation rates [100].

3.1.2 IP chemotherapy delivered intraoperatively—Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is an alternative to implantation of an IP catheter and is performed during cytoreductive surgery. The hyperthermic element was introduced based on the logic that the use of hyperthermia might improve drug penetration into tumors and enhance cell killing [36, 87, 102]. Despite direct administration to the peritoneum, systemic toxicity still occurs in 4–27% of patients treated with HIPEC [36]. Thus, eliciting the risk-benefit of HIPEC versus IV chemotherapy in ovarian cancer is important.

Deraco and colleagues performed studies mainly focussed on the combination of HIPEC with cytoreductive surgery in four Italian cancer centres [37, 102]. Cisplatin and doxorubicin were used as the chemotherapeutic agents for HIPEC and were both delivered concurrently over 90 minutes. The volume of liquid was between 4 and 6 litres [102]. Deraco and colleagues determined that this procedure was safe with severe morbidity in 15.2% of patients and an operative mortality of less than 4% [102].

Combination of HIPEC with interval debulking has also been shown to improve outcomes in women with ovarian cancer. Van Driel and colleagues performed a phase III multicentre trial of interval debulking surgery with or without cisplatin HIPEC administration [103]. Disease recurrence was significantly ($p=0.003$) reduced in the group that received HIPEC [103]. At four-year follow-up significantly fewer patients had died in the HIPEC group ($p=0.02$) [103]. The proportion of patients experiencing adverse events wasn't significantly different between the two groups [103].

Few randomised controlled trials investigating the benefits of HIPEC exist. Many of the available studies included heterogenous patient populations with conflicting results [103–106]. There are many variables with HIPEC, drug used, dose, contact time, temperature and the effect of these needs to be fully established [104]. Furthermore, HIPEC requires a longer time in the operating room, both for the surgical staff and the patient and the costs and risks of prolonged anaesthesia need to be considered [104].

3.2 Protocol for Peritoneal Perfusion - HIPEC

Peritoneal perfusion can be performed using either open- or closed-abdomen techniques as shown in Figure 3. Heart-lung pumps were initially used for perfusion therapy, but specialised machines which facilitate hyperthermic perfusion have now been developed [37, 102]. RanD produce the “Performer HT” for the delivery of hyperthermic treatments in surgical oncology [107]. This device allows perfusion of liquid containing chemotherapeutics through the peritoneum. Temperature controllers are present on both the inlets and outlets and extra temperature probes can be attached if desired [107]. Protocols vary slightly between institutions, but the following represent the general protocols used.

Open-abdomen perfusion [103]: Silicone inflow drain placed centrally in the abdomen, drainage tubes placed in the sub-hepatic, sub-diaphragmatic left and small pelvis. An elevated rim is formed around the abdominal cavity using towel clips and tie wraps. Temperature sensors are placed beside the inflow system. The abdomen remains open during perfusion. The surgeon can adjust the bowel loops during perfusion and should watch the process to ensure the entire area is covered with perfusate. Temperature should be maintained at 40-41°C throughout. Perfusion lasts for 90 minutes after which the drains are allowed to empty to remove all liquid from the peritoneal cavity. Temperature probes are removed and the abdomen is closed.

Closed-abdomen technique [108, 109]: Catheters and temperature probes are placed as per the open-abdomen technique, the skin is then closed and the chemotherapeutic is infused. Manual external agitation of the abdomen is performed throughout the perfusion time of approximately 90 minutes to distribute the infused liquid throughout the peritoneum. When the infusion is complete the temporary closures in the abdomen are reopened, the catheters are removed and the abdomen is closed in the normal post-surgical fashion. Advantages of closed perfusion over open perfusion include easier maintenance of abdominal temperature and reduced exposure of healthcare staff to the chemotherapeutic.

3.3 Protocol for IP chemotherapy – implanted catheter

Patients receiving multiple cycles of IP chemotherapy will have a port and catheter inserted which is used for the infusions of chemotherapy (Figure 3 (B)). Patients will be in a supine or semi-Fowler position for administration of therapy and are often advised to move from side-to-side every 15 minutes for one hour after the infusion finishes. Chemotherapy is administered through this port and catheter in 1 litre of warm isotonic saline. A second litre of saline may be administered as tolerated. Once all fluids have been administered the port and catheter are flushed to prevent blockage and a compression dressing is placed over the port for several hours in case infusion fluid might leak out [110, 111].

The semi-permanent ports used attach to Tenckhoff catheters which remain inserted in the peritoneum for the duration of the therapy [96]. Normally, approximately 10 cm of catheter will be present in the peritoneal cavity [110]. IP catheters currently used are either fenestrated or single-lumen catheters [111]. Catheter-related complications represent one of the main reasons for cessation of IP chemotherapy and occur in 3-34% of patients [110, 112].

Ivy and colleagues determined that the rate of complications was not significantly different with fenestrated compared to single-lumen catheters [110]. Such catheters, originally designed for dialysis, might increase the risk of bowel complications and the Dacron cuff on Tenckhoff catheters can erode into the peritoneum causing further complications [111]. The catheter material may also impact the rate of complications. Makhija and colleagues reported a reduction in complications with silicone catheters compared to polyurethane catheters used in an earlier study by Davidson et al. [113–115]. Changing the catheter material from polyurethane to silicone reduced rate of complications from 17.6% to 10%. This included a reduction in catheter malfunction from 8.8% to 6.3% and a reduction in infection from 5.3% to 3.7% with polyurethane compared to silicone respectively [113–115]. The size of the semi-permanent port used depends on the thickness of the subcutaneous adipose tissue, but should be as small as possible for patient comfort [111].

Catheter-related issues play a role in reducing the desirability of IP chemotherapy administration. Significant innovation in medical device design and drug delivery could overcome this issue, making IP chemotherapy more effective and tolerable for the patient.

3.4 Intraperitoneal delivery of cell-based immunotherapy

Most pre-clinical work and clinical trials on IP delivery of therapy for ovarian cancer refer to the administration of small molecule therapeutics. However, some work on IP delivery of T cells and NK cells for ovarian cancer has been reported and is reviewed here.

3.4.1 T cells—T cells are a subset of immune system cells that recognise specific MHC/peptide complexes on the surface of pathogenic or cancer cells [116, 117]. Activation of T cells via this pathway results in the production of death ligands and/or release of cytotoxic cytoplasmic granules which kill the target cell [118]. Most T cell-based immunotherapies reported recently are functionalised to improve their ability to detect and kill specific cancer cells. As shown in Table 1, T cells delivered via IP injection have been functionalised with many different cell surface ligands targeted to tumor associated antigens and have shown promising results in mouse models. Tumor associated antigens studied in ovarian cancer to date include HER-2/neu, MAGE-A1, folate binding protein (FBP), p53, NY-ESO-1, EpCAM and CA-125 [119]. The individual ovarian tumor associated antigens are not reviewed specifically in this article, but have been studied extensively in multiple publications [120–124].

Ang and colleagues produced chimeric antigen receptor T (CAR T) cells for peritoneal cancers [125]. The T cells were designed specifically to recognise the epithelial cell adhesion molecule (EpCAM) which is expressed on peritoneal cancer cells [125]. These anti-EpCAM CAR T cells were tested in mice with peritoneal tumors formed by the ovarian cancer cell line SKOV3. 1×10^7 T cells were injected into the mice IP twice weekly for three weeks starting 8 days following initial injection of tumor cells [125]. As shown in Figure 4A IP injection of these anti-EpCAM CAR T cells reduced tumor burden as seen on BLI compared to mice treated with PBS alone. The anti-EpCAM CAR T cells also significantly improved survival in NSG mice injected with 0.5×10^7 human HRT-18G rectal cancer cells compared to control mice injected with saline alone [125]. Han et al. produced

CAR T cells specifically targeted to HER-2 overexpressing cancer cells and delivered them IP in a mouse model of peritoneal cancer using NCI-N87 and MKN-28 gastric cancer cells [76]. 1×10^7 cells were administered IP on day 7 and day 10 following tumor cell injection (3×10^6 NCI-N87 IP) and mice were monitored until day 90 [76]. IP administration of these CAR T cells significantly delayed tumor growth and prolonged survival compared to untreated controls. The authors suggested that this localised delivery of CAR T cells might improve delivery to the tumor locations and reduce off-target effects [76]. The authors hypothesised that these CAR T cells would also be useful in HER-2 overexpressing ovarian cancers and successfully showed the potential for this on SKOV3 ovarian cancer cells *in vitro* [76]. Koneru and colleagues developed a CAR T cell capable of binding to the MUC-16^{ecto} antigen which is commonly overexpressed on ovarian cancer cells [79]. Mice were injected with 2.5×10^6 CAR T cells either IP or IV two weeks after injection of 1×10^7 SKOV3 ovarian cancer cells. Regardless of the route of administration CAR T cells significantly improved mouse survival compared to no treatment. CAR T cells delivered IP significantly improved mouse survival compared to CAR T cells delivered IV [79]. However, the authors of this study noted that while IP administration of therapy might be advantageous for patients, IV administration confers the benefit of delivered T cells possibly homing more quickly to sites of distant metastasis [79]. On the basis of these pre-clinical studies, CAR T cells seem effective in reducing tumor growth and extending survival, and IP delivery may confer survival advantages compared to IV delivery.

Based on this potential benefit of locoregional delivery of T cells, Stephan and colleagues developed a biomaterial scaffold for local delivery of T cells either prior to or following tumor resection [72]. These alginate scaffolds were modified with a synthetic collagen-mimetic peptide, which slowed T cell migration, preventing rapid egress of cells from the scaffold [72]. The scaffolds were also loaded with silica microparticles to allow controlled release of normal stimulatory signals. Stephan and colleagues tested the T cell-loaded scaffolds in a mouse model of breast cancer following tumor resection [72]. They reported that T cells injected systemically had no effect on preventing tumor growth, cells injected directly to the tumor site provided a temporary reduction in tumor growth and a 4 day (significant) survival advantage compared to no treatment. However, T cells implanted in the alginate scaffold completely prevented tumor relapse [72]. A similar system of T cell-loaded scaffolds implanted at the target site may be of value in ovarian or other peritoneal cancers. This was shown by Coon and colleagues who delivered 10×10^6 CAR T cells targeted to receptor tyrosine kinase-like orphan receptor ROR1 to NSG mice 8 weeks following injection of 1×10^6 OVCAR-3 ovarian cancer cells into the mouse diaphragm [126]. The CAR T cells were delivered either via IV injection, direct injection into the tumor or on bioactive thin films composed of nitinol. The nitinol thin films completely eradicated the tumors in 70% of the mice and improved survival by 2.7 times compared to untreated mice, see Figure 4B [126].

3.4.2 Natural Killer (NK) cells—Natural killer cells have advantages over T cells in that they do not need to bind to a specific cell surface receptor on the target cell and importantly they do not cause graft-versus-host disease [61]. This means they have the potential to be used as an “off-the-shelf” cancer therapy. Similar to T cells, there are many

reports of pre-clinical work on the delivery of NK cells via IP injection for ovarian cancer in small animal models, these are discussed here and summarised in Table 2.

Geller and colleagues delivered NK cells to the mouse peritoneum. The NK cells were obtained from healthy human donors and enriched by depletion of CD3⁺ and CD19⁺ prior to activation with Interleukin 2 (IL-2) [127]. Irradiated NSG mice were injected with MA-148 ovarian cancer cells four days prior to IP injection of 20×10^6 of the aforementioned NK cells [127]. Mice received injections of either IL-2 or IL-15 during the study. Tumor burden was monitored using bioluminescent imaging (BLI) [127]. It was noted by the authors, that previous to this study, the long-term survival and anti-tumor activity of peripheral blood NK cells delivered IP had never been determined [127]. Geller and colleagues demonstrated stable engraftment of the IP delivered NK cells and an anti-tumor effect. This anti-tumor effect reduced tumor burden to levels similar to those in the control group of mice with no tumor cells, indicating the potential revolutionary effect of IP delivery of NK cells on ovarian cancer treatment [127]. Interestingly, Geller and colleagues also reported that NK cells delivered IP were able to traffic to the systemic circulation, and so, might be able to reach distant sites of metastasis if required [127].

Following on from this Hermanson and colleagues investigated IP injection of NK cells from two different sources to determine an optimal NK cell product as shown in Figure 5A [128]. The NK cell types used were isolated from peripheral blood (PB-NK cells) or derived from induced pluripotent stem cells (iPSC). Four days after injection of MA-148 ovarian cancer cells into NSG mice, 20×10^6 PB-NK cells or iPSC-derived NK cells were injected IP. Mice received IL-2 to promote NK cell survival and proliferation. BLI was used to monitor tumor burden and both cell types significantly reduced the tumor burden over the five week study [128]. Similar to the previous study, the NK cells were able to traffic to the systemic circulation. The NK cells also significantly reduced tumor burden in NSG mice where tumor formation was as a result of a different ovarian cancer cell type, A1847 [128]. Hermanson and colleagues then went on to investigate the effect of repeated NK cell dosing on tumor burden (Figure 5B). NSG mice were again injected with MA148 ovarian cancer cells, and three doses of PB-NK cells or iPSC-derived NK cells were administered IP on day 0 (four days after MA148 injection), day 7 and day 14 [128]. Repeated dosing significantly improved mouse overall survival and tumor burden compared to untreated controls although this was not compared statistically to the effects of a single dose [128]. The interest in IP delivery of NK cells has been such that Hermanson and colleagues have developed a protocol for performing mouse studies with IP injections of NK cells for treatment of ovarian cancer [129]. In this protocol they suggest that NK cells, treated with IL-2 to aid proliferation, can persist in the peritoneal cavity for up to 28 days post-injection [129].

Similar to the production of CAR T cells, CAR NK cells have also been produced with surface ligands specific to receptors on the target cancer cells [130, 131]. Genetic modification of primary NK cells to produce CAR NKs is less efficient than genetic modification of T cells [131]. However, iPSCs can produce NK cells and can be efficiently modified to produce specific CARs, thus allowing the production of CAR NK cells to be comparable to that of CAR T cells in terms of efficiency [131]. An example of a potential “CAR” is TNF-related apoptosis-inducing ligand (TRAIL), discovered in 1995. TRAIL can

induce apoptosis in cancer cells with relatively good specificity. However, the half-life of recombinant TRAIL is too short to allow any therapeutic value [130]. Song and colleagues have produced NK cells expressing a glycosylated TRAIL fusion protein [130]. Song et al. tested these modified NK cells in mice injected with LS174T colorectal cancer cells. Mice received 5×10^6 NK cells IP or IV twice a week for two weeks [130]. Song et al. reported that NK cells injected IP effectively infiltrated peritoneal tumors, while NK cells delivered IV did not [130]. The NK cells delivered IP successfully stopped tumor growth and increased tumor cell apoptosis in the mice [130]. Similar TRAIL-modified NK cells may be of use in ovarian cancer.

Based on such positive results in mice some clinical trials investigating the effect of IP delivery of NK cells have been initiated. One phase I Dutch study is currently recruiting patients to test IP infusion of *ex vivo*-cultured allogeneic NK cells for recurrent ovarian cancer. Twelve patients will be involved in this study and all will undergo laparoscopy for catheter placement in the peritoneal cavity [133]. Another study involves IP delivery of adaptive NK cells to women with ovarian cancer. This phase I study is designed to determine the maximum tolerated dose of NK cells delivered via an IP catheter, with doses to be administered ranging from 1×10^7 cells/kg to potentially 10×10^7 cells/kg [134]. Clinical trials involving IP delivery of T cells or NK cells for ovarian cancer are summarised in Table 3.

As new therapies for ovarian cancer are investigated, IP delivery may play an even more important role. IP delivery of immunotherapy may have benefits beyond simply increasing the concentration of the therapy at the target site. IP delivery of NK cells might activate local immunoregulatory mechanisms which could increase the cytotoxicity of NK cell-based therapy and subsequently improve patient outcomes [96]. Advanced delivery strategies for IP administration of chemotherapeutics should be investigated to facilitate IP delivery of such therapies.

3.5 Limitations of IP delivery of cancer therapeutics

Complications of IP delivery, which may be due to the drug or the route of administration, can include: abdominal discomfort, respiratory distress, and gastrointestinal symptoms such as nausea and diarrhoea [96, 141]. A number of contraindications to IP chemotherapy also exist including: presence of extensive adhesions, peritoneal infection or other peritoneal contamination or inability to undergo cytoreductive surgery [111]. Thus, IP chemotherapy is not suitable for all patients. Generally, the dose used is calculated based on body surface area (BSA) as for IV administration [87]. However, this may not be completely accurate as females have an estimated 10% larger peritoneum than males [87]. Placement of peritoneal catheters as well as the time required for therapy administration can result in increased time in hospital for patients which is inconvenient [96]. While there is much evidence that peritoneal exposure to a drug is substantially increased following IP administration some other pharmacokinetic questions are still unanswered. Drug penetration into the tumor may be reduced or affected by the reduction in delivery of drug to the tumor via capillary flow [96, 142]. This penetration issue is less of a problem where patients have microscopic or small macroscopic disease [96]. Clinical studies using IP delivery of cisplatin have

suggested the residual tumor volume may need to be much smaller than 0.5 cm to improve overall survival [96].

Another issue to widespread adoption of IP chemotherapy is that most clinical trials have been performed with IP cisplatin, while carboplatin is the IV platinum agent of choice due to its much better side-effect profile [96]. One recent review assessed the long-term survival of 271 women with stage IIIC or IV ovarian cancer. Patients in the IP group all received IV paclitaxel with either IP cisplatin and paclitaxel, or IP carboplatin and paclitaxel. Overall survival at five years was 73% in those who received IP therapy compared to 44% with IV therapy. However, when variables such as more aggressive treatment and the degree of cytoreduction were accounted for, there was no significant difference between overall survival in the IP and IV groups [143]. More recently, Walker and colleagues studied progression-free survival in women receiving one of the following treatment regimens: IV paclitaxel and IV carboplatin, IV paclitaxel with IP carboplatin, or IV paclitaxel with IP cisplatin and IP paclitaxel. All women were also given bevacizumab [144]. Median progression-free survival in a total of 1560 patients, was not significantly different with IP cisplatin or IP carboplatin compared to IV carboplatin. Grade 3 infections were significantly worse in the groups that got IP treatments compared to the group who did not. Based on the results, the authors recommended the use of IV carboplatin instead of IP carboplatin except where patients have a homologous repair deficiency and no gross residual disease [144]. Much like the other studies referred to herein, the authors noted that a different regimen and different IP doses might provide better results than IV therapy.

Another limitation to IP therapy delivery of therapy, either via HIPEC or implanted IP port, is local toxicity. Initial trials of cisplatin delivered via IP port had conflicting results in terms of toxicity. Alberts and colleagues reported more side-effects in patients receiving only IV and no IP chemotherapy, while Markman and Armstrong observed more adverse events in the groups receiving IP chemotherapy [98–100]. As research into IP chemotherapy progresses, the interplay between the drug used, the dose and the route of administration and their effect on toxicity will need to be investigated.

4 Advanced delivery solutions

Molecules with a molecular weight < 20 kDa are rapidly cleared from the peritoneum, with rat studies indicating complete clearance of docetaxel and paclitaxel in less than 24 hours [145]. Sustained release formulations, formulated as microparticles might overcome this issue of rapid clearance and increase the residence time of the drug at the target site [146]. This strategy has been investigated in pre-clinical studies. Tsai and colleagues delivered paclitaxel to the peritoneum in gelatin microparticles and reported that the paclitaxel was retained in the peritoneum for significantly longer following microparticle delivery compared to delivery of paclitaxel nanoparticles or free paclitaxel [146]. Sustained release of paclitaxel was also achieved by Grant and colleagues from paclitaxel-loaded nanoparticles on a chitosan and egg phosphatidylcholine film [147]. Sustained release of paclitaxel from the nanoparticle-loaded film was recorded for four months *in vitro* and the bioactivity of the released paclitaxel was confirmed on *in vitro* testing against SKOV-3 ovarian cancer cells [147]. These paclitaxel-loaded nanoparticles in the chitosan and egg phosphatidylcholine

film were then tested *in vivo* in a mouse model of ovarian cancer [148]. Mice with the nanoparticle-loaded film (60 mg/kg paclitaxel) implanted had significantly increased survival times and a significant reduction in tumour proliferation, weight and bioluminescence signal (from the SKOV-3 cancer cells) compared to mice treated with paclitaxel as an IP bolus injection (60 mg/kg) [148]. Electrospun polydioxanone nanoyarns have also been loaded with paclitaxel to achieve sustained paclitaxel release [149]. Varying the packing density of the nanoyarns allowed modulation of the paclitaxel release rate which might allow patient specific dosing to be achieved. *In vivo* sustained release of paclitaxel was achieved for 60 days in mice [149]. In a mouse model of ovarian cancer using ID8-VEGF cancer cells, the paclitaxel nanoyarns (20 mg/kg paclitaxel) achieved complete removal of the tumors compared to IP paclitaxel (20 mg/kg) on day 35 post-tumor cell injection (day 27 post-treatment start) [150]. Such a system might reduce the frequency of dosing required and improve patient quality of life.

Incorporating nanoparticles in a hydrogel might increase their residence time in the peritoneum [151]. This has been trialled by Yeo and colleagues who delivered Hyaluronic Acid – Poly (lactic-co-glycolic acid) nanoparticles to a rabbit peritoneum and observed that the nanoparticles remained in the peritoneum for seven days [151]. In this instance, Yeo et al. investigated the ability of the particles to reduce adhesions but a similar approach could be used for chemotherapeutic delivery. While many injectable depots and micro and nanoparticles have been investigated for ovarian cancer, none have yet received FDA approval [152].

In terms of medical device innovation for peritoneal delivery, Solass and colleagues, developed a device, similar to a nebuliser, to improve peritoneal dispersion and penetration of chemotherapeutics into tumor tissue [142]. The device, driven by mechanical pressure to spray therapeutic into the abdominal cavity, was tested on pigs using methylene blue in place of a therapeutic agent. The developed device improved peritoneal dispersion of the methylene blue compared to administration via peritoneal lavage [142]. This device was similar to an intraperitoneal nebuliser developed by Alkhamesi and colleagues which was tested in a rodent peritoneal tumor model [153]. Nebulised heparin and hyaluronan inhibited macroscopic tumor growth and the procedures were completed without complications [153]. A clinical trial of pressurized intraperitoneal aerosol chemotherapy has been performed in patients with peritoneal metastasis of gastric cancer [154]. Patients had a trocar inserted in the operating room, ascites was removed via suction and the chemotherapeutic was aerosolised into the abdomen. Although the results of this trial were inconclusive, the authors noted that the reduced toxicity of the chemotherapeutics compared to IV delivery and the reduced invasiveness compared to other procedures means this delivery method could benefit from further investigation [154].

Further device innovation was performed by Ye and colleagues who developed a delivery device for IP administration of cisplatin [155]. The device design was based on *in vitro* work by the group that demonstrated that sustained low doses of cisplatin produced better killing of ovarian cancer cells than intermittent dosing [156]. The devices used were fabricated from poly-L-lactic acid and consisted of a spherical chamber and cap. The cap had a circular orifice with a diameter of 180 μm , chosen to control cisplatin release based on its solubility

and diffusivity [155]. The devices were loaded with 5 mg cisplatin powder. The device was tested in mice, using weekly IP bolus injections (5 mg/kg) as a control. Treatment started 14 days after SKOV3 ovarian cancer cell implantation. The device released cisplatin continuously over 42 days with an approximate release rate of 1 µg/hour [155]. Both IP injection and cisplatin delivery using the device significantly reduced tumor burden compared to the untreated control. There was no significant difference in tumor mass or tumor burden between the IP bolus injection and micro-device groups [155].

Whyte et al. and members our team have developed a refillable reservoir device and tested this for cell delivery to the heart wall in a rodent model of myocardial infarction [157]. This device, consisting of a porous semi-permeable membrane for therapy delivery and a non-porous backing layer, was suggested to be suitable for site-specific delivery of multiple types of therapy to a variety of tissue types and anatomical locations. The device can be attached, via a catheter to an access port to allow delivery of therapy at intervals [157]. We have recently designed and manufactured similar devices for local, repeated delivery of therapy for use in large animal models that are easily translated to human studies [158].

Another device which might provide inspiration for drug delivery in ovarian cancer, is the Hepatic Arterial Infusion (HAI) pump used for delivery of chemotherapy in colorectal cancer that has metastasised to the liver. This pump is placed subcutaneously in the abdominal wall at the time of tumor resection [159]. The catheter tip is placed in the gastroduodenal artery to allow direct drug delivery to this site. The pump is normally left in place until two-year follow-up [159]. HAI pumps which do not require a battery have now been developed and their size has been reducing over the last 30 years to make the pumps more acceptable to patients [160]. A device similar to these could be useful for delivery of therapy to specific sites following tumor resection, allowing targeted delivery of therapy and potentially reducing the systemic and pan-peritoneal side-effects of cancer therapy.

4.1 Design requirements for improved catheters

The ideal IP drug delivery system would provide a prolonged, homogeneous distribution of the therapeutic agent throughout the peritoneum. In general, delivery of large fluid volumes would be preferred as small volumes of liquid do not move freely in the peritoneum and thus do not achieve adequate dispersion [161, 162]. Penetration of the therapeutic agent into the tumor should also be considered for patients with macroscopic disease, however, this may be less urgent as most patients have cytoreductive surgery as part of their treatment regimen [142]. Padmakumar and colleagues, in their review of sustained release implantable devices for intraperitoneal chemotherapy suggested that the ideal drug delivery system would be an implantable depot, fixed in the abdomen. This system should provide pulsed delivery of chemotherapy to the tumor site [152]. The four main design requirements for improved peritoneal therapy delivery device are therapy distribution, implantation/placement timing, prevention of adhesions and biocompatibility.

Therapy distribution—Prior to cytoreductive surgery the average size of tumors has been reported as 6.7 cm [28]. Following surgery, tumors should be < 1 cm. Dramatic changes occur in the abdomen during surgery with the removal, not just of tumors, but also

potentially the reproductive organs, omentum, appendix and bowel resection [28]. While distributing the therapy to the tumor sites, pan-peritoneal cytotoxicity, where the chemotherapeutic has an effect on the healthy tissue causing local toxicity, should be avoided [145]. Thus, any new medical device for IP delivery should deliver the therapy to the target site without affecting healthy tissue.

Implantation/placement timing—Ideally any device or port to be inserted or implanted would be placed at the time of cytoreductive surgery to prevent additional morbidity from a second surgery [111]. This would also be important in preventing adhesions which can lead to further patient morbidity [111]. This is complicated by the fact that complete diagnosis and staging usually occurs during cytoreductive surgery and so the patient may have to be pre-emptively counselled regarding insertion of an IP port or device at the time of surgery [111].

Prevention of adhesions—Adhesions are bands of tissue that form between surfaces in the peritoneum [145]. Adhesions generally occur due to abdominal traumas such as surgery or infection [163, 164]. These abnormal bands of tissue can cause chronic abdominal pain and bowel obstruction associated with significant mortality [145, 165]. In the future prevention of adhesions may be achieved by administration of anti-inflammatory, anti-proliferative or proteolytic agents [163, 165, 166]. Hydrogel-based physical barriers have also been used to protect areas of damage in the abdomen and prevent formation of adhesions [163–166].

Biocompatibility—Any suggested drug delivery device or catheter system should be biocompatible in the peritoneum [167]. Defrere and colleagues assessed the intraperitoneal biocompatibility of three polymers which could potentially be used as peritoneal therapy delivery devices [167]. The three polymers investigated were polydimethylsiloxane (PDMS), poly(ethylene-co-vinyl acetate) (PEVA) and poly(hydroxyethyl methacrylate) (polyHEMA). Biocompatibility was studied for 3 and 6 months in the peritoneal cavity of rats, rabbits and rhesus monkeys [167]. Inflammation was monitored by blood levels of C-reactive protein (CRP) and fibrinogen and implants were removed at the end of the study, macroscopically examined and subjected to histology. No major inflammatory response was observed to any of the polymers on blood sample analysis [167]. Although a fibrous capsule was observed with all implants, foreign body giant cells were not present, however, the authors did note, this capsule might affect drug delivery to the peritoneum [167]. Such a foreign body response is common with implanted biomaterials [167]. Much investigation has been directed towards reducing this fibrotic response including coating implants with biocompatible polymers, using actuation to prevent or disrupt capsule formation, use of angiogenic agents or corticosteroids or tailoring the material properties to reduce fibrous capsule formation [168–175]. These factors may need to be incorporated into any potential peritoneal therapy delivery device.

5 Conclusions and expert outlook

Ovarian cancer is the most lethal gynecological malignancy and there is an urgent clinical need for improved treatment agents and modalities. Intraperitoneal delivery of chemotherapy

has a theoretical pharmacokinetic advantage for the treatment of ovarian cancer. However, clinical trials investigating the effect of IP delivery of chemotherapy have delivered conflicting results in terms of overall and progression-free survival. This may be due, at least in part, to poor delivery strategies. Various publications have indicated that targeted, repeated delivery of therapy to the tumor site using a catheter than can be easily inserted and unblocked is essential. This may be even more important with the development of new therapeutics such as cell-based immunotherapy where locoregional delivery might prompt local immunoregulatory mechanisms to act synergistically with the delivered immunotherapy. Thus, improved IP delivery strategies are critically important. Microparticles which have been successfully employed for sustained delivery of therapy in prostate cancer, may not be suitable for cell delivery and so approaches may need to be device-based. Any developed cell delivery system should consider ease of placement and insertion, potential for development of adhesions, patient comfort and effect on the therapy. The combination of advanced cell-based immunotherapy and an optimised delivery system might substantially improve therapy delivery in ovarian cancer and has the potential to significantly improve patient outcomes for this lethal gynecological malignancy.

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Abbreviations

AUC	Area Under the Curve
BGCS	British Gynecological Cancer Society
BLI	Bioluminescent Imaging
BSA	Body Surface Area
CAR T cell	Chimeric Antigen Receptor T cell
EMA	European Medicines Agency
EpCAM	Epithelial Cell Adhesion Molecule
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GOG	Gynecologic Oncology Group
HGSC	High Grade Serous Carcinoma
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
IP	Intraperitoneal
iPSC	Induced Pluripotent Stem Cell
IV	Intravenous
LGSC	Low Grade Serous Carcinoma
MHC	Major Histocompatibility Complex
NICE	The National Institute for Health and Care Excellence
NK cell	Natural killer cell
PARP inhibitors	Poly (ADP-ribose) polymerase inhibitors
PB-NK	Peripheral Blood Natural Killer cell
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
TVUS	Transvaginal Ultrasonography
VEGF	Vascular Endothelial Growth Factor

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Figure 1:
A schematic illustration of intravenous, intraperitoneal and targeted intraperitoneal delivery of therapy for ovarian cancer.

Figure 2:
The various types of therapies that might require intraperitoneal delivery for the treatment of ovarian cancer.

Figure 3:
Intraperitoneal administration of chemotherapy using either (A) peritoneal perfusion or (B) an implanted peritoneal catheter.

Figure 4:

A) Bioluminescent imaging of female NSG mice bearing Luc⁺ SKOV-3 ovarian tumors. Mice were given either Phosphate Buffered Saline (PBS), 1×10^7 anti-CD19 RNA CAR-T cells IP or 1×10^7 anti-EpCAM RNA CAR-T cells IP twice weekly for three weeks starting on Day 8 after tumor cell injection. Day 8 represents the baseline for each mouse prior to treatment. (i) Tumor burden is visibly reduced in the group receiving anti-EpCAM RNA CAR-T cells at day 29. (ii) Tumor burden is plotted over time by bioluminescent imaging where each mouse is represented by one line and doses were administered at timepoints

indicated by arrows. Adapted under the terms of the CC by 3.0 license [125], Copyright 2020. B) NSG mice with Luc⁺ OVCAR-3 ovarian cancer cells implanted in the diaphragm. Eight weeks following implantation, cancer was evident throughout the abdomen. Mice received 10×10^6 CAR T cells recognising ROR1 (receptor tyrosine kinase-like orphan receptor) on day 0, either via IV injection, local injection into the tumor, or delivery on bioactive nitinol thin films (TFN). Tumor burden was monitored via bioluminescent imaging. Survival was recorded for each mouse. CAR T cells on TFN micromeshes completely eradicated detectable tumors in 70% of mice. Survival time of mice treated with TFN micromeshes was, on average 80 days, this was 2.7-fold longer than untreated mice. Adapted with permission [126], Copyright 2020, Springer Nature.

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A) Intraperitoneal delivery of NK cells **B) Repeated intraperitoneal delivery of NK cells** **Figure 5:**

A) Mice were injected with 2×10^5 Luc⁺ MA148 ovarian cancer cells on day -4. Bioluminescent imaging shows tumor burden on day -1 before IP injection with 20×10^6 Peripheral Blood NK cells activated overnight with IL-2 (Overnight PB-NK), PB-NK cells activated with clone 9.mbIL-21 artificial antigen-presenting cells (aAPC PB-NK) or induced pluripotent stem cell-derived NK cells (iPS-NK). All NK cell treated groups had a significant reduction in tumor burden compared to no treatment ($p < 0.0001$). iPS-NK cells significantly reduced tumor burden compared to aAPC PB-NK cells ($p = 0.014$). B)

Investigation of the effect of repeated dosing – mice were injected with either aAPC PB-NK cells or iPS-NK cells on Days 0, 7 and 14. Both treatment agents significantly reduced tumor burden compared to no treatment ($p < 0.0001$). Adapted with permission [128], Copyright 2020, John Wiley and Sons.

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Table 1

Overview of mouse studies investigating intraperitoneal injection of T cells for treatment of peritoneal cancer. CAR: Chimeric antigen receptor. DNA: Deoxyribonucleic acid. EpCAM: Epithelial cell adhesion molecule. HER: Human epidermal growth factor receptor. IP: Intraperitoneal. IV: Intravenous. NSG: NOD *scid* gamma. RNA: Ribonucleic acid. ROR1: Receptor tyrosine kinase like orphan receptor 1. VEGF: Vascular endothelial growth factor.

Mouse strain	Tumor cell dose, type and route of administration	T cell dose, type and route of administration	Outcome	Ref.
NSG	1 x 10 ⁷ SKOV3, IP	Day 8 post tumor cell injection. One injection of 1 x 10 ⁷ anti-EpCAM DNA CAR, IP.	Significant improvement in survival compared to mice receiving saline or a non-targeted T cell.	[125]
NSG	1 x 10 ⁷ SKOV3, IP	Day 8 post tumor cell injection. 1 x 10 ⁷ anti-EpCAM RNA CAR injected IP twice per week for three weeks.	Significant improvement in survival compared to mice receiving saline or a non-targeted T cell.	[125]
SCID-Beige	1 x 10 ⁷ SKOV3, IP	Day 14 post tumor cell injection. 2.5 x 10 ⁶ 4H11-28z/IL-12 CAR T cells (anti-MUC ¹⁶ T cells), IP.	Significantly improved survival with IP CAR T cells compared to mice treated with IV CAR T cells.	[79]
C57BL/6	5 x 10 ⁶ ID8-VEGF, IP	Day 56 post tumor cell injection. IP implantation of 7 x 10 ⁶ NKG2D CAR T cells in an alginate scaffold.	Significantly better T cell proliferation when delivered in an alginate scaffold compared to direct injection. Significantly better survival when cells delivered via alginate scaffold compared to standard IP injection.	[72]
NSG	1 x 10 ⁶ OVCAR-3, into the diaphragm	8 weeks post tumor cell injection. Delivery of 10 x 10 ⁶ CAR T cells recognising ROR1 IV, directly into the tumor, or on a bioactive nitinol thin film.	CAR T cells delivered on the nitinol film eradicated tumors in 70% of mice and improved survival by 2.7-fold compared to untreated mice.	[126]

Table 2

Pre-clinical studies investigating the effect of intraperitoneal delivery of Natural Killer (NK) cells for ovarian cancer. CAR4 targets Mesothelin. GSK: Glycogen synthase kinase. IP: intraperitoneal. NSG: NOD *scid* gamma.

Mouse strain	Tumor cell dose, type and route of administration	NK cell dose, type and route of administration	Outcome	Ref.
NSG	2 x 10 ⁵ MA-148, IP	Day 4 post tumor cell injection. 20 x 10 ⁶ peripheral blood NK cells, IP.	NK cells delivered IP can circulate to the periphery and secondary lymphoid organs. IP delivery of NK cells led to stable peritoneal engraftment and significant disease regression.	[127]
NSG	2 x 10 ⁵ MA-148 or A1847, IP	Day 4 post tumor cell injection. 20 x 10 ⁶ peripheral blood or induced pluripotent stem cell derived NK cells, IP.	NK cells from both sources significantly reduced tumor burden compared to no treatment in mice with tumors formed by either MA-148 or A1847 cells.	[128]
NSG	2 x 10 ⁵ MA-148, IP	Day 4, 11 and 18 post tumor cell injection. 20 x 10 ⁶ peripheral blood or induced pluripotent stem cell derived NK cells, IP.	Significant reduction in tumor burden and survival by NK cell types from both sources compared to no treatment.	[128]
NSG	2 x 10 ⁵ A1847, IP	Day 4 post tumor cell injection. 1.5 x 10 ⁷ peripheral blood NK cells, induced pluripotent stem cell derived NK cells, T-CAR(meso)-iPSC-NK cells, or CAR4(meso)-iPSC-NK cells, IP.	CAR4(meso)-iPSC-NK cells produced the greatest reduction in tumor burden of all groups. Addition of the CAR4 significantly improved outcomes compared to iPSC-NK cells with no CAR.	[131]
NSG	1 x 10 ⁵ SKOV3, IP	Day 5 post tumor cell injection. 2.5 x 10 ⁶ CD57 ⁺ enriched NK cells, IP, pre-cultured <i>ex vivo</i> overnight or for seven days in the presence of the GSK3 inhibitor CHIR99021. Some mice received 100 µg Herceptin IP in combination with NK cells.	Significant reduction in tumor burden occurred only in the group treated with Herceptin and NK cells cultured <i>ex vivo</i> with the GSK3 inhibitor for 7 days.	[132]

Table 3

Active clinical trials of T cells or NK cells delivered via IP injection for ovarian cancer.

Treatment	Stage	Primary Outcome	Ref.
Autologous PRGN-3005 UltraCAR-T cells via IP or IV injection.	Phase I	Adverse events up to 12 months after infusion, maximum tolerated dose.	[135]
Intradermal injection of alpha-type-1 polarised dendritic cell vaccine 2 weeks before day 0, on day 0 and day 28. IP injection of cytotoxic T lymphocytes over 15-30 minutes on day 0.	Phase I/IIa	Incidence of adverse events, dose limiting toxicities, change in immune response, persistence of cytotoxic T lymphocytes.	[136]
IV decitabine daily on days -8 to -6, cyclophosphamide IV on days -4 and -3, and genetically engineered NY-ESO-1-specific T lymphocytes IV and IP on day 0.	Phase I	Safety and tolerability of the treatment regimen.	[137]
IP or IV infusion of 4H11-28z/fIL-12/EFGRt T cells with or without prior treatment with IV cyclophosphamide on day -2 or -4. Four T cell doses will be used ranging from $3 \times 10^5/\text{kg}$ to $1 \times 10^7/\text{kg}$.	Phase I	Maximum tolerated dose.	[77]
IP infusion of TALL-104 MHC unrestricted T cells.	Phase II	Efficacy of repeated administration of TALL-104.	[138]
IP infusion of UCB-NK cells with or without cyclophosphamide/fludarabine chemotherapy.	Phase I	Incidence of adverse events.	[133]
IP infusion of donor NK cells and IL-2 after a preparative regimen of cyclophosphamide and fludarabine. INCB024360 twice daily for 90 days, starting 2 days before the NK cell infusion.	Phase I	Maximum tolerated dose.	[139]
IP infusion of 1×10^7 - 10×10^7 FATE-NK100 cells in 100 ml of 5% human serum albumin.	Phase I	Maximum tolerated dose of FATE-NK100. Results in 9 patients to-date show the therapy is safe, with a clinical benefit in 3 of 9 patients treated.	[134, 140]