Recent advances in drug delivery strategies for treatment of ovarian cancer

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Introduction: Ovarian cancer is associated with the highest mortality rate of all gynecological malignancies, due in part to inadequate treatment strategies and the asymptomatic nature of the disease. Current standard of care includes surgery and systemic chemotherapy. However, this approach can result in toxicities and eventual disease relapse, due to the emergence of multidrug resistance. Drug delivery systems (DDS) have shown promise in overcoming many of the limitations facing conventional treatment regimens.
Areas covered: This review provides an overview of recent advances in DDS strategies for the treatment ovarian cancers. Nano-sized systems, including nanoparticles, micelles, liposomes and drug conjugates; microspheres; implants and injectable depots are discussed. The advantages, limitations and clinical potential of these strategies are also outlined.
Expert opinion: Nano-sized DDS enable passive targeting to tumors due to their size, and further improvements in tumor localization can be made using targeting moieties. Microspheres, implants and injectable depots have been investigated for peritoneal localized and sustained therapy. Overall, the benefits of using DDS for ovarian cancer therapy include higher drug levels at the diseased site, circumvention of drug resistance mechanisms, minimization of non-specific toxicities, improvements in solubility of poorly soluble drugs and elimination of toxicities associated with conventionally used pharmaceutical excipients.

Keywords: conjugates, drug delivery, implants, injectable depots, liposomes, micelles, microspheres, nanoparticles, nanosystems, ovarian cancer

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1. Introduction

Ovarian cancer is the fifth leading cause of cancer death in women and is associated with high morbidity and mortality rates as most patients are diagnosed with advanced stage disease [1]. In the 1970s, platinum-based chemotherapy was introduced, addition of taxanes followed in the late 80s and more recently the potential benefits of using intraperitoneal (i.p.) chemotherapy has been highlighted in several Phase III clinical trials [2]. Currently, first-line therapy includes cytoreductive surgery followed by intravenous (i.v.) chemotherapy with carboplatin and paclitaxel. Although most patients achieve complete clinical response following this standard treatment regimen, over 85% eventually relapse due to the emergence of multidrug resistance (MDR) [3].

As the peritoneal cavity is the site of disease both at diagnosis and relapse, i.p. chemotherapy has been explored. Although promising clinical results have been observed [4], the use of i.p. chemotherapy has remained limited due to local toxicities and complications associated with indwelling catheters. Improvements in the 5-year survival rates for women with ovarian cancer have been seen over the past

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Article highlights.

- Ovarian cancer has the highest mortality of all gynecological malignancies due to poor screening techniques and inadequate treatment strategies.
- The major driving force for the development of drug delivery systems (DDS) for ovarian cancer treatment has been to achieve greater drug concentrations at tumor sites, to overcome drug resistance and to minimize toxicities to healthy tissues.
- Nano-sized systems including nanoparticles, micelles, liposomes and drug conjugates have been investigated.
- Due to their size, nano-sized DDS (NDDS) can passively accumulate in solid tumors (i.e., enhanced permeation and retention (EPR) effect). To further improve accumulation at tumor sites, targeting moieties have been conjugated to the surface of NDDS (i.e., active targeting). Use of NDDS may not be appropriate for residual disease following cytoreductive surgery.
- Microspheres, implants and injectable depots DSS have been used as localized chemotherapy strategies. These systems have the potential to provide sustained drug release over extended periods in the peritoneal cavity, the site of ovarian cancer. Prolonged drug exposure has been shown to increase tumor responsiveness to chemotherapeutics in various ovarian cancer models.
- The clinical translation of DDS has been limited for use in the treatment of ovarian cancer. Nano-sized systems suffer from rapid clearance and require frequent dosing, material component issues have been documented for microspheres and implants can be invasive and require surgical expertise for implantation.
- DDS can potentially bypass transport barriers, leading to higher therapeutic drug concentrations at diseased sites. NDDS are ideal for intravenous (i.v.) administration due to their size, while intraperitoneal (i.p.) administration is more appropriate for microspheres, implants and injectable depots.
- The use of depot DDS for i.p. administration of chemotherapy seems promising and integration of imaging may facilitate patient-specific placement of the delivery system.

This box summarizes key points contained in the article.

few decades [5]. However, these gains have been rather modest, prompting the need to develop new treatment strategies.

Drug delivery systems (DDS) have been investigated to improve therapeutic outcomes in ovarian cancer. The primary goals have been to attain greater drug concentrations at diseased sites, to bypass drug resistance and to minimize toxicities to healthy tissues. DDS can also address issues associated with anticancer agents such as poor aqueous solubility, low target-site specificity and rapid clearance [6]; as well as, circumvent problems linked to pharmaceutical excipients that are commonly used as formulation vehicles [7,8]. A number of drugs relying on advanced DDS have entered clinical development for use in the treatment of ovarian cancer, and one has reached the market as a second-line therapy (**Table 1**). The following review outlines recent research and advances in DDS for the treatment of ovarian cancer, specifically focusing on DDS that have yielded significant therapeutic effects in animal models. Nano-sized systems, microspheres, implants and injectable depots will be discussed (**Figure 1**), and the advantages, limitations and clinical potential of these systems will be highlighted (**Table 2**). This review only focuses on delivery of small molecules and not biological therapeutics such as proteins, monoclonal antibodies and small interfering RNA (siRNA).

2. Ovarian cancer

2.1 Classification, pathogenesis and risk factors

Ovarian cancer is cancerous growth arising from different parts of the ovary. Patients typically present with non-specific symptoms at early stages, and due to the lack of effective screening methods, most are diagnosed with disseminated disease. It is predicted that in 2011 there will be approximately 25,000 new cases of ovarian cancer in North America, resulting in about 15,000 deaths [9,10]. Over 90% of ovarian cancers are believed to develop on the ovarian epithelium, while the remainder arise from germ or stromal cells [11]. This review is focused on epithelial-derived ovarian cancers, which represent the major and most lethal forms of the disease. Epithelial ovarian cancers exhibit a variety of tumor morphologies and clinical manifestations. The most common histological subtypes are serous, endometrioid, mucinous and clear cell [12]. The majority of epithelial ovarian cancers have been classified as serous, which can be further divided into high- and low-grade tumors [13]. The high-grade tumors are chemosensitive while low-grade tumors are slow growing and chemoresistant [14]. There are key differences in incidence, tumor behavior and clinical outcome between each subtype. High-grade serous carcinomas tend to be aggressive disease that spread rapidly throughout the peritoneal cavity, while endometrioid and mucinous carcinomas are typically low-grade disease, confined to the ovary [14,15]. Tumor subtypes can also strongly impact clinical response. For example, late-stage serous tumors are initially highly responsive while clear cell tumors are resistant [12].

Although family history poses a significant risk towards ovarian cancer development, only 5% of ovarian cancer patients are genetically predisposed to the disease [16]. Ovulation requires rupture and subsequent repair of the ovarian epithelium, and a repeated pattern of disruption and repair is thought to encourage abnormalities in the cells composing this epithelial lining [17]. Thus, phenomena that increase the frequency of ovulation, such as nulliparity, menopause and increasing age are associated with increased risk, whereas factors such as oral contraceptive use and pregnancy, which decrease the overall frequency of ovulation, are associated with reduced risk [18].

Based on the various known risk factors, several theories have been proposed to explain the pathogenesis of ovarian cancer. One hypothesis suggests that repeated damage and repair of the ovarian epithelium resulting from ovulation

Table 1. DDS that have entered clinical trials for ovarian cancer therapy.

Name	Delivery system	Compound	Clinical stage	Ref.
DOXIL®	Liposome	Doxorubicin	Approved	[159]
OPAXIO™	Drug conjugate	Paclitaxel	Phase III	[160]
CT-2106	Drug conjugate	Camptothecin	Phase II	[160]
Genexol-PM	Block copolymer micelle	Paclitaxel	Phase II (recruiting)	-
Paclimer®	Microsphere	Paclitaxel	Failed in Phase I	[163]

DDS: Drug delivery systems.

may encourage malignant transformation of epithelial cells [19]. Inflammation resulting from this and other processes occurring in the vicinity of the ovaries has also been implicated in disease development [17]. Various hormones are suggested to play a role in carcinogenesis, such as steroids produced post-ovulation, and androgens that rise in levels in postmenopausal women [20,22]. Further, estrogen hormones are hypothesized to stimulate gonadotropin hormones, promoting the entrapment of epithelial cells in ovarian inclusion cysts, where malignancy can develop [21]. None of these theories, however, explain all of the associated risk factors, and therefore it is likely that a combination of various factors leads to this disease. Recent evidence suggests that a number of ovarian cancers arise from the fallopian tube and metastasize to the ovary [23]. For example, the distal fallopian tube has been identified as a source of high-grade serous ovarian cancers [24,25].

2.2 Clinical presentation and diagnosis

Clinical symptoms of epithelial ovarian cancer are nonspecific and include bloating, constipation, fatigue, nausea, pelvic or abdominal pain, urinary urgency or frequency, difficulty eating and early satiety [26]. Current screening methods include pelvic examinations, measurement of serum CA-125 levels and transvaginal pelvic ultrasonography [27]. Although serum CA-125 levels are elevated in more than 80% of patients with advanced epithelial ovarian cancer, this measurement alone is neither sufficiently sensitive nor specific enough to be diagnostic [28]. Elevated serum CA-125 levels may be associated with various conditions, such as, pregnancy, pelvic inflammatory disease and other diseases [28]. Furthermore, CA-125 levels are elevated in less than 50% of the cases in early stage ovarian cancers, underscoring the lack of sensitivity to diagnose at a curable stage [29]. CA-125 is, therefore, not a useful diagnostic serum biomarker. At present, surgery is needed to accurately diagnose and stage the disease.

The disease is staged during debulking surgery, from stage I, where growth is limited to the ovaries, through to stage IV characterized by distant metastases to the liver or outside the peritoneal cavity [30]. Ovarian cancer can metastasize from the ovaries in different manners. Firstly, by directly invading adjacent organs like the peritoneum, uterus, and rectum after bypassing the ovarian capsule [31]. Another way is for individual cancer cells to enter nearby lymph nodes, thereby spreading via the lymphatic system. This is a common process in advanced disease, but only occurs at a frequency of 20% in early stage disease [31]. Alternatively, cancer cells can seed from the primary tumor, circulate throughout the peritoneal cavity with the assistance of movement-promoting events such as peristalsis and respiration, and re-implant in various tissues in the peritoneal cavity [31]. At the time of diagnosis, almost 70% of cases present with distant metastasis [31]. When ovarian cancer is diagnosed at stages I or II, long-term (> 10 years) survival rates range from 80 – 95%; however, for over 75% of patients for whom diagnosis occurs at stages III or IV, long-term survival drops to below 30% [5]. The presence of distant metastases at the time of diagnosis largely accounts for the high death rate of patients with this disease.

2.3 Surgery and chemotherapy

The standard first-line management of advanced stage (III or IV) ovarian cancer consists of surgical staging, operative tumor debulking, followed by six cycles of i.v. chemotherapy with platinum (i.e., carboplatin) and taxane (i.e., paclitaxel) drugs administered every 3 weeks [5]. The median survival of these patients is about 2 years, with less than 30% surviving 5 years after diagnosis [32]. Cytoreductive surgery leads to increased patient survival due to several beneficial effects including that i) the removal of resistant cancer cell populations can promote sensitivity to anticancer agents; ii) the removal of large tumor masses can result in a reduction in devascularized tumor beds, allowing greater drug delivery to the remaining cancer cells and iii) the lower-volume disease that remains may require lower drug doses with increased chance of response [33]. The concept of cytoreductive surgery for ovarian cancer was first proposed in 1934 by Meigs [34]. In 1975, Griffiths demonstrated that patient survival depends on the extent of residual disease after primary surgery [35]. Studies by Hoskins *et al.* have demonstrated that the smaller the residual disease, the better the survival outcome, with patients left with no gross residual disease having the most favorable prognosis [36].

The first evidence supporting the role of chemotherapy in the management of ovarian cancer was reported for the alkylating agents cyclophosphamide and melphalan [2]. In the 1970s, the observation of improved patient progression following treatment with alkylating agents (i.e., cisplatin) led

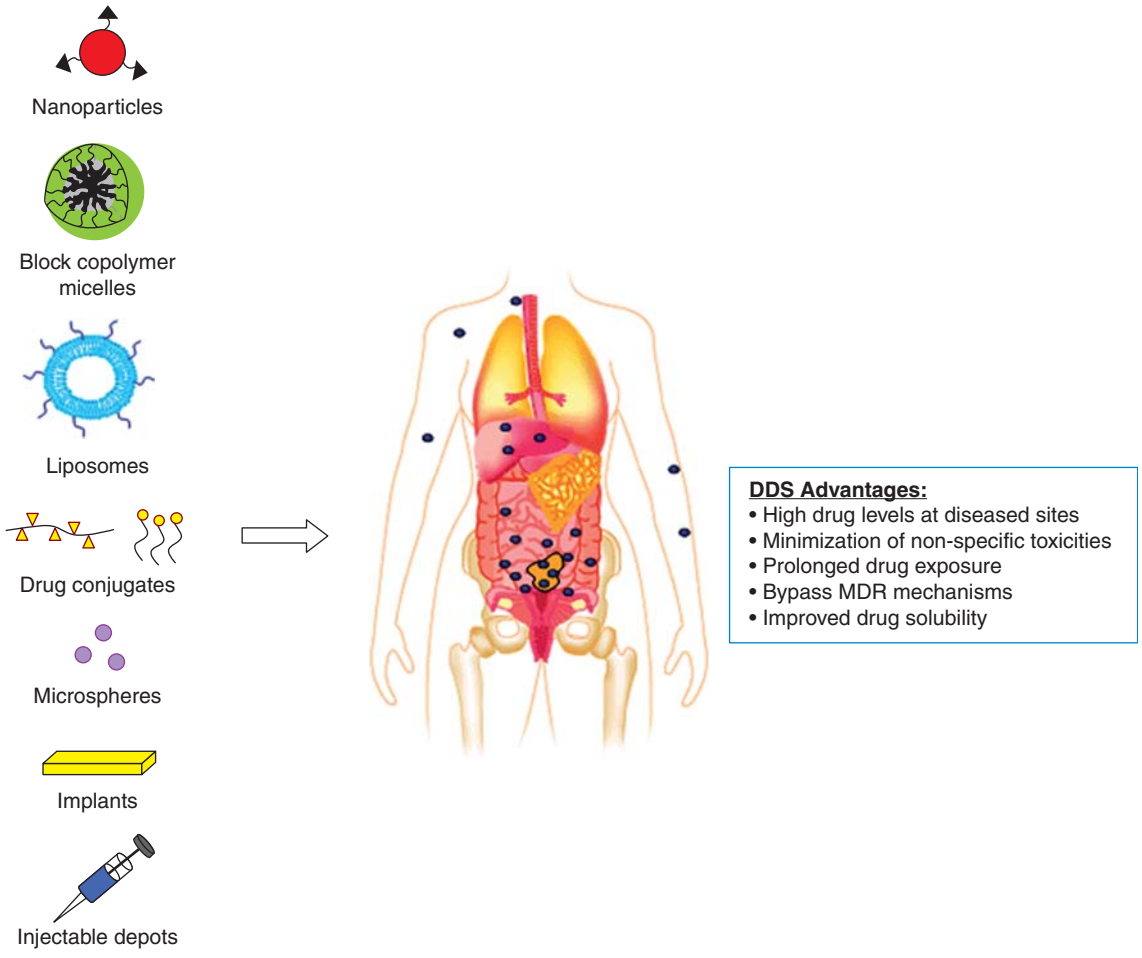

Figure 1. Drug delivery systems (DDS) that have been investigated for ovarian cancer therapy. Nanoparticles, micelles, liposomes, drug conjugates, microspheres, implants and injectable depots have been investigated as DDS for ovarian cancer therapy. The main advantages associated with using DDS over conventional chemotherapy include achieving higher therapeutic drug concentrations in tumors and ascites, decreased non-specific toxicities, increased drug exposure to cancer cells, circumvention of drug resistance and improvements in drug solubility.

to the incorporation of this agent as a component of first-line therapy. In order to improve tolerability, other platinum agents were evaluated and carboplatin was found to be associated with fewer side effects than cisplatin, in particular emesis, nephrotoxicity and neurotoxicity, and showed equal efficacy in several randomized trials [37-40]. Following the introduction of platinum-based agents into standard chemotherapy, paclitaxel incorporation became another landmark in the management of ovarian cancer. Paclitaxel combined with cisplatin resulted in an improved outcome compared with one of the standard chemotherapy strategies used at that time (cisplatin plus cyclophosphamide) in a randomized Phase III trial [41]. Studies have shown that toxicity can be lessened and modified by replacing carboplatin for cisplatin and docetaxel for paclitaxel, respectively [42-44]. However, studies to-date have yet to demonstrate a better i.v. chemotherapy approach to the platinum and taxane combination in terms of improving overall survival.

Over the past several years, a number of strategies have been explored in Phase III trials and smaller randomized trials to improve the clinical outcome beyond what is achievable with the current standard of care. One approach has been to double the duration of platinum treatment periods from 5 – 6 cycles to 10 – 12 cycles [45-47]. Another strategy has been to increase the platinum dose intensity [48-50]. Other studies have looked at high-dose chemotherapy regimens [51-53]. Finally, the effects of adding a third anticancer agent to the platinum and taxane regimen have been explored [54-56]. These approaches have failed to reveal any significant impact on either progression-free or overall survival compared with standard of care. Furthermore, greater toxicity was observed when the number of dosing cycles was increased,

Table 2. Advantages and limitations of DDS investigated for ovarian cancer therapy.

System	Advantages	Limitations
Nano-sized systems	Passive targeting due to size Active targeting Ease of administration	Small size may lead to rapid clearance and limited half-life Frequent dosing required May not be applicable for residual disease following cytoreductive surgery
Microspheres	Prolonged release profile Several formulations have reached the market for other cancers	Peritoneal adhesions Limited tumor penetration
Implants and injectable depots	Localized delivery Sustained drug release Lower systemic toxicity Facilitates delivery of drugs with short half-life Increased bioavailability by decreasing first-pass hepatic metabolism Enhanced effect for cell cycle-specific drugs Reduced dose dumping	Invasive Surgical expertise needed for implantation and removal Limited tumor penetration Viscosity issues if injectable

DDS: Drug delivery systems.

the dosing concentrations were intensified or when a third agent was used.

2.4 Intraperitoneal chemotherapy

i.p. chemotherapy has been explored due to promising clinical results in patients with optimally debulked advanced ovarian cancer [57-59]. The rationale for i.p. chemotherapy is to eliminate residual disease by achieving higher drug concentrations for longer periods directly in the peritoneal cavity while reducing systemic toxicities [60]. The peritoneal cavity is the site of ovarian cancer presentation or recurrence, and tumors remain confined to the peritoneal cavity for most of their natural history [26]. Consequently, the delivery of anticancer agents directly into the peritoneal cavity is a logical approach. Drugs administered via the i.p. route can reach tumors through direct penetration from the peritoneal cavity and via systemic recirculation [61]. In fact, anticancer agents including carboplatin and paclitaxel present several advantages when administered via the i.p. route, including a higher local concentration, prolonged tumor exposure and reduced systemic toxicities [61]. The pharmacokinetic advantage, defined as the ratio of peritoneal AUC (area under the curve) to plasma AUC, has been reported to be 12, 18, 181 and 1000 following i.p. administration of cisplatin [62], carboplatin [63], docetaxel [64] and paclitaxel [65], respectively, and this has also been observed with other anticancer agents [60].

To date, there have been three randomized controlled Phase III trials of first-line i.p. chemotherapy in conjunction with surgical cytoreduction [57-59]. These studies have become the basis for recommending i.p. chemotherapy as a standard treatment for selected patients with ovarian cancer. In the first trial conducted by Alberts *et al.* [57], patients with stage III ovarian cancer and residual disease ≤ 2 cm received i.v. cisplatin and i.v. cyclophosphamide (i.v. group) or i.p. cisplatin and i.v. cyclophosphamide (i.p. group) on day 1 of every 3 weeks for six cycles. Overall survival was 41 months for the i.v. group and 49 months for the i.p. group. Grade three and four toxicities were lower in the i.p. group. The second study by Markman *et al.* [59] randomized patients with stage III ovarian cancer and residual disease ≤ 1 cm to receive i.v. chemotherapy with paclitaxel followed by cisplatin, administered every 3 weeks for six cycles. The i.p. group consisted of i.v. carboplatin every 4 weeks for two cycles followed by i.v. paclitaxel and i.p. cisplatin every 3 weeks for six cycles. The i.p. group showed improvement in both progression-free survival (27.9 vs 22.2 months) and overall survival (63.2 vs 52.2 months). Grade three and four toxicities including leukopenia were higher in the i.p. group and were thought to be caused by the high doses of carboplatin and increased number of treatment cycles. The third trial, by Armstrong *et al.* [58] randomized patients with stage III ovarian cancer and residual disease ≤ 1 cm to receive i.v. paclitaxel followed by i.v. cisplatin every 3 weeks for six cycles. For the i.p. arm, patients received i.v. paclitaxel followed by i.p. cisplatin then i.p. paclitaxel every 3 weeks for six cycles. The i.p. group showed favorable outcomes in progression-free survival (23.8 vs 18.3 months) and overall survival (66.9 vs 49.5 months), although the i.p. arm had more toxicities, including leukopenia, neurotoxicity and gastrointestinal disturbances. Only 42% of patients were able to complete the full six cycles of i.p. chemotherapy.

A follow-up study observed that the initially lower quality of life in patients receiving i.p. chemotherapy was improved to baseline after 1 year [66]. Overall, these studies have

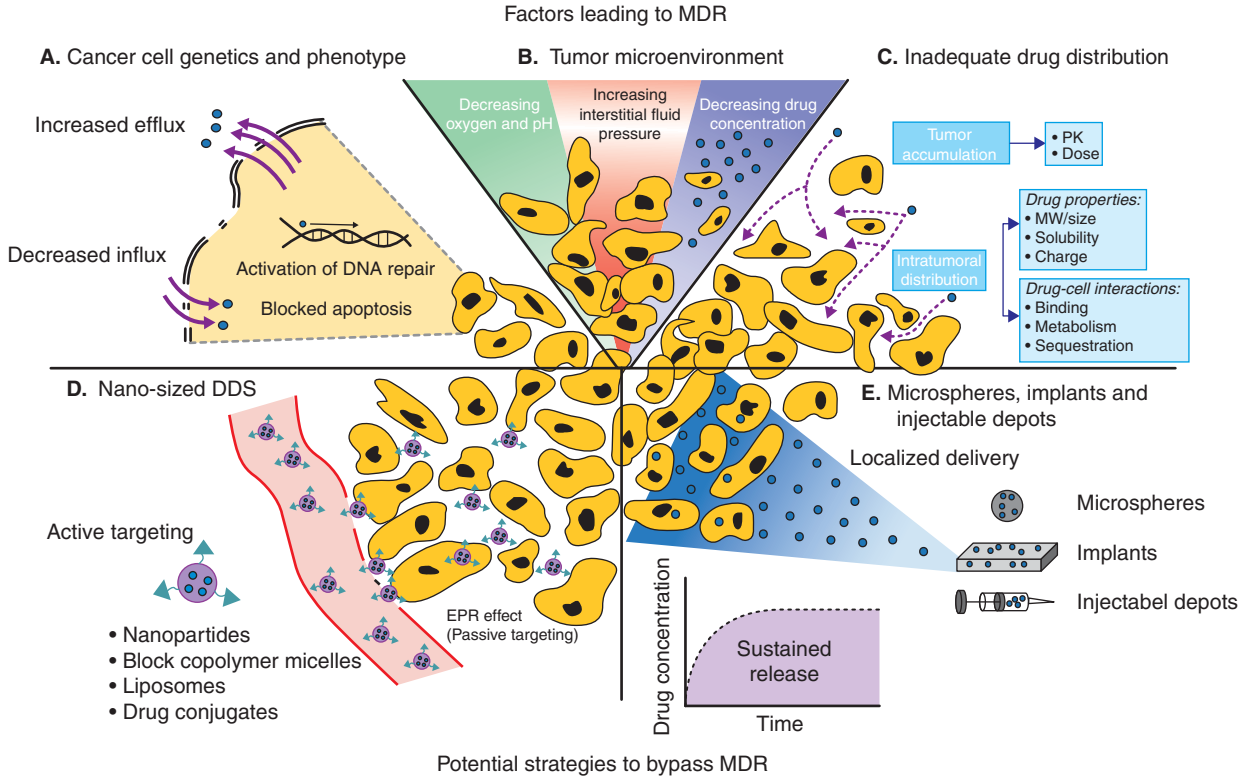

Figure 2. Factors leading to multidrug resistance (MDR) in ovarian cancer and strategies investigated to overcome them using drug delivery systems (DDS). One of the leading causes of treatment failure in ovarian cancer is the onset of resistant disease. Factors leading to MDR can be divided into three broad categories: cancer cell genetics and phenotype; tumor microenvironment and inadequate drug exposure. **(A)** Cancer cell genetics and phenotype changes leading to MDR can arise from mutation or amplification of genes encoding ATP-dependent drug efflux transporters modifications in drug metabolism, alterations in cell cycle, increase in DNA damage repair mechanisms and changes in the apoptotic signaling pathway. **(B)** Tumor microenvironment properties such as hypoxic regions, low extracellular pH, heterogeneous vascular density and blood flow and increased interstitial fluid pressure can cause MDR. **(C)** Inadequate drug distribution due to dose, pharmacokinetics, drug properties and drug–cell interactions can also lead to MDR. The DDS that can be utilized to overcome MDR include (D) nano-sized DDS or (E) implants, injectable depots and microspheres. (D) Due to their size, NDDS can passively accumulate in tumors (i.e., EPR effect), which can be enhanced by attachment of targeting moieties onto the surface of NDDS (i.e., active targeting). **(E)** Implants, injectable depots and microspheres used locally can by-pass MDR mechanisms via sustained prolonged drug delivery.

Panels (**A**) [77] (**B**) and (**C**) [180] are adapted with permission from Nature Publishing Group.

demonstrated that i.p. chemotherapy can lead to improved overall survival of 12 – 16 months in patients with optimally debulked advanced ovarian cancer. Based on the last Phase III trial by Armstrong and collaborators in 2006, the US National Cancer Institute issued a 'Clinical Announcement' informing patients, oncologists and the public, on the impact and benefits of i.p. chemotherapy for advanced ovarian cancer therapy [67]. The most commonly used i.p. regimen is derived from the Armstrong report previously mentioned: i.v. paclitaxel on day 1, i.p. cisplatin on day 2 and i.p. paclitaxel on day 8, based on a 28-day cycle [68].

Despite the survival benefit, the use of i.p. chemotherapy has been limited by various complications including local toxicities (e.g., intestinal toxicity, abdominal pain) and infection, bowel perforation and mechanical malfunctions due to prolonged use of an indwelling i.p. catheter [69,70]. These problems have led to the inability of a majority of patients (up to 70%) to complete all treatment cycles [71] and the reluctance of oncologists to adopt i.p. chemotherapy [72]. DDS administered via the i.p. route may circumvent issues currently associated with i.p. chemotherapy administered via catheters, resulting in improvements in patient survival.

2.5 Multidrug resistance

One of the leading causes of chemotherapy failure in ovarian cancer is the development of MDR. MDR is a phenomenon by which cancer cells develop the ability to survive in the

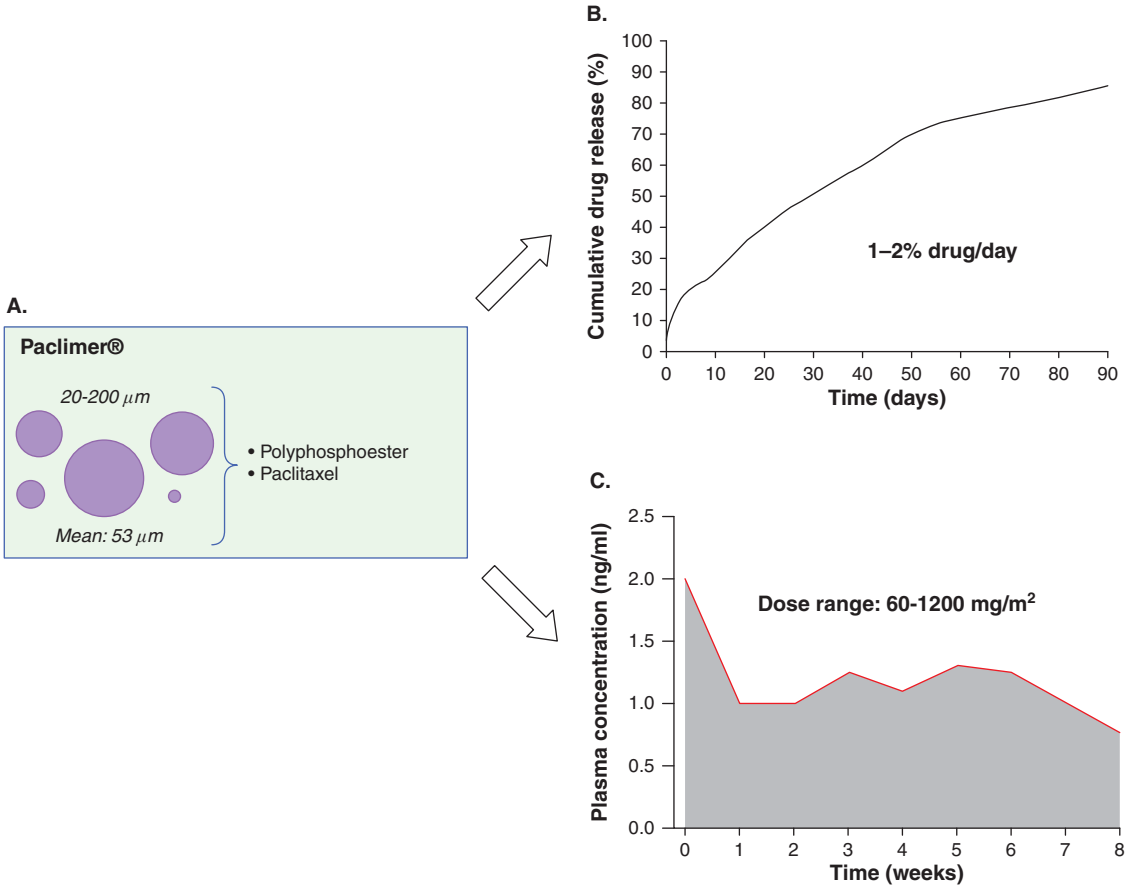

Figure 3. Paclimer® drug delivery system. (A) Paclimer is a microsphere formulation composed of a polyphosphoester polymer loaded with paclitaxel. **(B)** *In vitro*, the release rate of paclitaxel from Paclimer is reported to be about 1 – 2% drug per day, with over 80% released by 90 days. **(C)** In a Phase I clinical trial, it was reported that sustained paclitaxel plasma levels were achieved over an 8-week period at all doses tested except 60 mg/m^2 which showed no detectable plasma drug levels.
Panel (**B**) is adapted with permission from the American Association for Cancer Research [162].
Panel (**C**) is adapted with permission from Elsevier [163].

presence of structurally and functionally different anticancer agents [73]. The current chemotherapy dosing regimen of intermittent i.v. infusions results in onset of chemoresistant disease 2 years following initiation of treatment [74]. Possible reasons for the onset of MDR include (**Figure 2**): i) cancer cell genetics and phenotype; ii) tumor microenvironment and iii) inadequate drug exposure. The mutation and/or amplification of genes encoding ATP-dependent drug efflux transporters have been widely documented as key contributors to MDR [75]. Drug efflux transporters, when overexpressed, have been shown to cause the development of cellular resistance to a broad spectrum of hydrophobic anticancer agents [76]. Another cellular mechanism involved in MDR is the decreased uptake of water-soluble drugs such as platinum agents which require transporters to enter cells [75]. Furthermore, modifications in drug metabolism, alterations in cell cycle, enhanced DNA damage repair mechanisms and changes in apoptotic signaling pathways have also been identified as sources of cancer cell-specific mechanisms of MDR [77,78].

Drug resistance can also develop as a result of the tumor microenvironment including hypoxic regions, low extracellular pH, heterogeneous vascular density and blood flow and increased interstitial fluid pressure [79-84]. These physiological properties have been shown to result in limited drug penetration, heterogeneous distribution of drug and regions with slowly proliferating cells that are less chemosensitive. As well, inadequate drug exposure at tumor sites can lead to MDR. This may result from an insufficient therapeutic dose reaching the tumor, short drug residence time and/or drug metabolism and excretion [32]. Different approaches to overcome MDR have been pursued including the use of drug efflux transporter inhibitors, synthesis of more active drug analogs and development of prodrugs [85]. Some investigators have explored using DDS such as nanoparticles to improve the effectiveness of chemotherapy in resistant disease [86-90], while others have shown

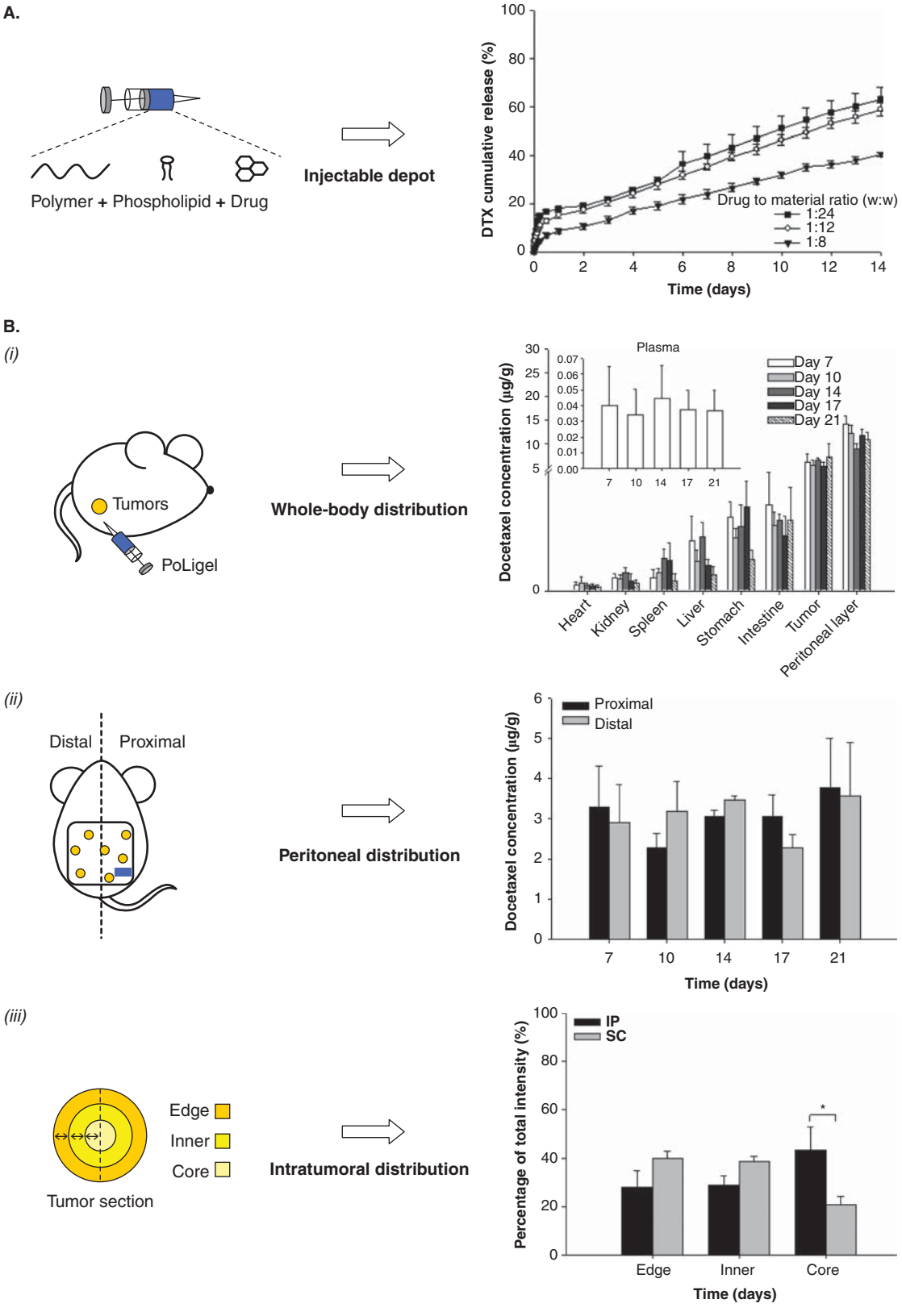

Figure 4. An injectable depot drug delivery system for localized and sustained chemotherapy of ovarian cancer (continued).

that extending drug exposure time using localized DDS can increase tumor responsiveness (**Figure 2**) [91-95].

3. Advanced drug delivery strategies for treatment of ovarian cancer

To date, a number of DDS have been designed to improve the therapeutic index of cancer drugs for treatment of ovarian cancer. The majority of these DDS have either been put forward to address solubility issues or overcome transport barriers. As an example, the taxanes paclitaxel and docetaxel are highly lipophilic with poor aqueous solubility [96]. For this reason, the non-ionic surfactants Cremophor EL and Polysorbate 80 are currently used as formulation vehicles for Paclitaxel (Taxol®, Bristol-Myers Squibb, Montreal, QC, Canada) and Docetaxel (Taxotere®, Sanofi-Aventis, Laval, QC, Canada), respectively. These surfactants have been associated with hypersensitivity and neurotoxicity and can influence drug distribution at the whole-body and cellular levels [97,98]. DDS have been put forward to improve solubility and circumvent issues associated with these excipients.

Furthermore, DDS have also been developed to bypass systemic and peritoneal transport barriers in order to achieve higher therapeutic drug concentrations at diseased sites. Nano-sized DDS (NDDS) are ideal for i.v. administration as they can take advantage of the enhanced permeation and retention (EPR) effect [99]. The EPR effect occurs as a result of leaky vasculature and impaired lymphatic clearance within tumors, which leads to preferential NDDS extravasation and retention at tumor sites [100]. Once administered i.v., NDDS can reduce systemic drug exposure, increase tumor accumulation and bypass MDR mechanisms [101]. On the other hand, i.p. administration is more suitable for microspheres, implants and injectable depots. These DDS have the potential to provide sustained drug release over extended periods in the peritoneal cavity. Prolonged drug exposure has been shown to increase tumor responsiveness to chemotherapeutics in various ovarian cancer models [91-95]. Sustained and localized delivery may also improve intratumoral drug distribution and penetration [102] and allow for circumvention of MDR [95,103,104]. The following sections highlight DDS developed for ovarian cancer therapy and discuss the advantages and limitations associated with each.

3.1 NDDS: nanoparticles, block copolymer micelles, liposomes and drug conjugates

NDDS such as nanoparticles [105-113], block copolymer micelles [114-121], liposomes [122-125] and drugs conjugated to peptides [126,127], small molecules [128] or polymers [129-137] have been investigated for ovarian cancer therapy. These systems can be defined as drug carriers that are in the '1 – 100 nm range in at least one dimension', a scale at which unique physical, chemical and biological properties emerge that can be used to develop novel technologies and products [138]. Anticancer agents can be loaded in the NDDS by encapsulation or conjugation [139]. In terms of biocompatibility, material components such as block copolymers used to prepare NDDS are less toxic alternatives to solubilize free drug compared with excipients such as non-ionic surfactants [140]. After systemic administration, NDDS have been shown to increase drug accumulation at solid tumor sites via passive targeting which relies on the EPR effect. The NDDS have an extended circulation lifetime following i.v. administration in comparison with free drugs [141-143]. This can result in an increase in tumor accumulation via the EPR effect, and in turn, increase efficacy [144]. NDDS and their material components have been shown to overcome MDR mechanisms by directing endocytosis-mediated cellular internalization of drug [101,145] and/or interacting directly with efflux pumps [146-148]. In an attempt to further increase the therapeutic index of drug-loaded NDDS for ovarian cancer, scientists have pursued active targeting by functionalizing the NDDS surface with moieties that recognize targets expressed on or near cancer cells [149-152]. Active targeting may also aid in bypassing MDR mechanisms, resulting in an increase in cellular accumulation of drug [153]. Another approach used to overcome MDR using NDDS has been combination drug delivery, whereby drugs with different mechanisms of action are co-delivered [111,113]. However, NDDS do not provide a means to increase the peritoneal residence time of the drug significantly. Following i.p. administration, NDDS are typically cleared rapidly from the peritoneal cavity through absorption into the lymphatic drainage [154-156]. As the goal of i.p. administration is to increase the residence time of drug in the peritoneal cavity, NDDS may not be suitable for this route of delivery.

Of the limited number of DDS evaluated in clinical trials for the treatment of ovarian cancer, most have been nano-sized systems. Genexol-PM is a formulation developed by

Figure 4. An injectable depot drug delivery system for localized and sustained chemotherapy of ovarian cancer. (A) The injectable depot is composed of polymer and phospholipids and loaded with docetaxel. A sustained drug release profile is achieved and release rate can be tuned by changing drug to material ratio [94]. **(B)** Favorable drug distribution is seen at the whole-body, peritoneal and intratumoral levels following i.p. administration of the formulation [102]. (i) Sustained concentrations of drug are attained in plasma, tissue and tumors over a 3-week period. (ii) Homogeneous drug distribution is achieved in the peritoneal cavity as seen by similar drug levels in tumors proximal and distal to the formulation site of injection. (iii) At the intratumoral level, drug is distributed more to the core of i.p. tumors when compared with s.c. tumors following i.p. administration of the formulation.
Graphs in panels (**A**) and (**B**) are reproduced with permission from Elsevier: [94] and [102], respectively.

Samyang Corporation in Korea, that consists of poly(ethylene glycol)-*b*-poly(L-lactide) block copolymer micelles loaded with paclitaxel. Genexol-PM has been shown to increase the tumor accumulation of drug and result in significant improvements in efficacy in comparison with Taxol in a murine model of ovarian cancer [157]. A subsequent Phase I study of Genexol-PM in patients with advanced, refractory malignancies including lung, breast and ovarian showed that Genexol-PM permits the administration of a higher dose of paclitaxel compared with Taxol without additional toxicity [158]. Currently, ovarian cancer patients are being recruited for a Phase II clinical trial to evaluate Genexol-PM in combination with carboplatin for first-line treatment. DOXIL®, a liposome formulation of doxorubicin has been approved for treatment of refractory Kaposi's sarcoma, ovarian cancer and recurrent breast cancer [159]. OPAXIO™ (Cell Therapeutics Inc., Seattle, WA, USA) is a polymer–drug conjugate system that includes paclitaxel linked to polyglutamate. This polymer–drug conjugate is currently being evaluated as monthly maintenance therapy in a Phase III clinical trial in ovarian cancer patients who have achieved a complete response following standard first-line chemotherapy [160]. A similar formulation from Cell Therapeutics Inc. (camptothecin conjugated to polyglutamate) was investigated in a Phase II open-label study as a single agent in patients with advanced metastatic ovarian cancer who had failed one prior platinum- and taxane-based regimen [160].

3.2 Microspheres

Microsphere DDS, typically between 1 and 1000 µm in size, have been explored for delivery of a range of cancer therapies. Indeed, a number of microsphere formulations composed of the biodegradable copolymer poly(D,L-lactide-*co*-glycolide) have been approved for prostate cancer therapy and have been reviewed elsewhere [161]. Paclimer®, a poly (phosphoester) microsphere formulation of paclitaxel, with a sustained *in vitro* release profile (1 – 2% per day) over a 90-day period [162], was investigated by Armstrong *et al.* in a Phase I clinical trial (**Figure 3**) [163]. Patients with recurrent ovarian cancer were treated with Paclimer every 8 weeks for two cycles via the i.p. route. It was reported that sustained plasma levels of paclitaxel were achieved throughout the 8-week period. However, biocompatibility issues associated with the microspheres were observed, including visible residual polymer filaments 7 months post-treatment. Beyond providing sustained plasma levels, microspheres may be used to increase the peritoneal residence time for drugs. Compared with NDDS, microspheres have been shown to have longer peritoneal retention following i.p. administration [156]. Consequently, microspheres have the potential to be utilized as a means to provide sustained plasma and peritoneal drug levels combined with localized drug exposure when delivered via the i.p. route. To date, only a limited number of preclinical studies have investigated microsphere formulations for i.p. chemotherapy in ovarian cancer models [156,164,165].

3.3 Implants and injectable depots

Implantable and injectable depot DDS have been investigated for localized and sustained delivery of anticancer agents [166]. Examples of such systems investigated in clinical trials include the injectable depot OncoGel™ for esophageal and brain cancers [167] and implantable Gliadel® wafers for brain cancer [168,169]. The i.p. implantable and injectable depot systems may be the most promising approach for treatment of ovarian cancers, given that the disease is located primarily within the peritoneal cavity during its natural history. Advantages associated with these DDS for ovarian cancer are higher drug concentrations at the disease site, extended drug exposure which may be particularly beneficial for cell cycle-specific anticancer agents, and lower systemic toxicity. Yet, implantable and injectable depot DDS face a number of drawbacks that have limited their implementation in the clinical setting. One challenge is achieving homogeneous distribution of drug in the peritoneal cavity following release from the delivery system. In addition, metastatic regions outside of the peritoneal cavity may not be reached with a localized approach. However, the sustained plasma levels provided by some implantable and injectable depot DDS may be effective at treating metastatic disease. The extent of tumor drug penetration may be low compared with i.v. chemotherapy as local drug exposure from the periphery of tumors may not provide sufficient intratumoral drug distribution. Yet once again if the DDS results in sustained plasma levels the systemic circulation may provide an additional route for drug entry into tumor nodules. Difficulties in precise implantation in the peritoneal cavity may arise, requiring a high level of surgical expertise. Finally, the viscosity of injectable depots may lead to issues. It has been reported that low viscosity injectable systems may fail to provide a delayed drug release profile while high viscosity injectables may be difficult to administer [170].

Yang *et al.* have incorporated docetaxel into an injectable thermosensitive mixed micelle gel [171]. The impact of site of administration (i.e., intratumoral, peritumoral and subcutaneous) of the gel on efficacy in a subcutaneous SKOV-3 murine model of ovarian cancer was investigated. Intratumoral administration resulted in the lowest tumor growth rate and was 4.2-, 2.6- and 1.7-fold lower than that in the non-treated control, subcutaneous and peritumoral groups, respectively. Grant *et al.* designed an implantable chitosan–phospholipid film that provided sustained i.p. delivery of paclitaxel for the treatment of ovarian cancer [172]. Implantation of the films in the peritoneal cavities of healthy mice revealed no signs of toxicities over a 4-week period [173]. Treatment with the chitosan–phospholipid film containing paclitaxel resulted in complete tumor inhibition in a murine xenograft model of human ovarian cancer, whereas only 47% inhibition was observed in animals given equivalent

bolus i.p. doses of paclitaxel [92]. Intermittent doses of paclitaxel also resulted in a pronounced induction of the *mdr1* gene, which plays a significant role in MDR, while sustained delivery of paclitaxel via the films did not result in *mdr1* induction [104].

To avoid the need for surgical implantation, Grant *et al.* [174] and more recently Zahedi *et al.* [94] (**Figure 4**) developed injectable chitosan–phospholipid depots (PoLigel) for paclitaxel and docetaxel delivery, respectively. No signs of toxicity or inflammation were detected on administration of drug-free or drug-loaded formulations [94,175]. The PoLigel has been shown to result in a homogeneous distribution of docetaxel within the peritoneal cavity of healthy CD-1 mice without the need for fluid co-administration [94,176]. As well, compared with i.p. administration of Taxotere in healthy CD-1 mice, the PoLigel provides sustained peritoneal drug levels [176]. Sustained concentrations of docetaxel were observed in plasma, tissue, tumor and ascites in murine models of ovarian cancer over a 3-week period [102]. Recent work by De Souza *et al.* has shown that sustained docetaxel therapy via the PoLigel is considerably more efficacious than intermittent therapy, resulting in a greater decrease in tumor burden and ascites fluid accumulation [91]. Immunostaining revealed that sustained dosing increases tumor cell death while reducing angiogenesis and cell proliferation in ovarian tumors to a greater extent than intermittent dosing. In a recent study, sustained administration of docetaxel in combination with cepharanthine, a potent drug efflux transporter inhibitor, was examined using the injectable chitosan–phospholipid formulation [95]. Sustained combination treatment was more than twice as efficacious as intermittent docetaxel therapy administered as Taxotere in the murine HEYA8-MDR ovarian cancer orthotopic model. Moreover, sustained monotherapy with docetaxel resulted in a 76% reduction in tumor burden compared to control, while intermittent treatment with Taxotere only resulted in a 36% decrease in tumor burden.

4. Conclusion

At this time, the survival rates for ovarian cancer patients with advanced stage disease are low due to non-specific early symptoms and inadequate treatment strategies. The standard i.v. chemotherapy approach has proven to be ineffective as a result of low therapeutic drug levels reaching the diseased sites and high toxicities affecting normal tissues. Furthermore, this course of therapy eventually leads to the onset of untreatable drug-resistant disease. DDS have emerged as potential viable treatment strategies for this disease. Overall, the benefits of using DDS for ovarian cancer therapy include higher drug levels at the diseased site, circumvention of drug resistance mechanisms, minimization of non-specific toxicities, improvements in solubility of poorly soluble drugs and elimination of toxicities associated with conventionally used pharmaceutical excipients.

5. Expert opinion

The effective administration of stand-alone small molecule anticancer agents currently faces problems such as undesirable biodistribution, low target-site specificity and rapid clearance. DDS can be used to overcome these obstacles and a handful have reached clinical trials or have been approved for ovarian cancer therapy. Unexpected toxicity is an important consideration when developing DDS. Material components used to prepare DDS must be rigorously tested for safety and biocompatibility to prevent toxicity issues when these reach the clinic. For instance, i.p. administered DDS may result in gastrointestinal toxicity both from high local concentrations of drug and material components [163,170]. Physicochemical properties of NDDS such as size, shape and surface properties can influence their toxicity, and can therefore be optimized to reduce the possibility of adverse reactions [101]. These factors should be taken into careful consideration when developing DDS for ovarian cancer therapy. The administration route, specifically drug administration via the i.p. route, may add an enhanced therapeutic effect for ovarian cancer therapy owing to higher local drug concentrations at tumor sites, prolonged drug exposure to the tumors and lower systemic toxicities. Three pivotal Phase III studies have shown the potential benefits associated with i.p. chemotherapy. Furthermore, it has been shown that altering the chemotherapy dosing schedule can greatly influence and improve efficacy outcomes. For example, by increasing the frequency of treatments, it is possible to reduce tumor repopulation rates, decrease MDR and improve efficacy [177]. Consequently, lengthening the time that chemotherapeutics are retained within the peritoneal cavity may be advantageous for the treatment of ovarian cancer. Hydrophilic drugs such as platinum agents are cleared more rapidly than bulky hydrophobic drugs such as taxanes from the peritoneal cavity following i.p. administration [60]. As well, drugs in free form are eventually absorbed through peritoneal capillaries into the systemic circulation, followed by quick elimination [178]. NDDS can have prolonged peritoneal residence time compared with free drug; but, are typically cleared within 2 days through absorption into the lymphatic circulation [155]. The presence of active targeting moieties at the surface of NDDS may result in an increase in their retention within the peritoneal cavity and further enhance the uptake of NDDS into cancer cells. However, to date studies comparing the peritoneal retention of targeted and non-targeted NDDS following i.p. administration have not been conducted. Microspheres have been shown to lead to further improvements in peritoneal retention of drugs in comparison with NDDS [156]. Incorporation of free drugs or NDDS into implants and injectable depots can increase their peritoneal retention times to several weeks [94,101,170]. Significant improvements in efficacy outcomes in multiple models of ovarian cancer using localized chemotherapy via i.p. implants and

injectable depots have been observed. However, there are significant hurdles associated with adoption of such technologies into the clinic. Despite the fact that studies in murine models have confirmed homogeneous distribution of drug within the peritoneal cavity and good tumor penetration, this may not be indicative of results in humans. Physiological differences exist between mice and humans that must be taken into account for successful clinical translation. Another key issue facing widespread adoption of administration of DDS via the i.p. route is the surgical skill and expertise required for accurate placement of these systems. Imaging modalities have recently proven to be valuable in non-invasively guiding intratumoral and peritumoral implantation of delivery systems [171,172]. Recently, a folate receptor-α-targeted optical fluorescent agent was used for intraoperative image-guided staging and cytoreductive surgery in ovarian cancer patients [179]. Image-guided surgery and drug delivery have gained widespread interest in recent years. The integration of imaging in drug delivery for ovarian cancer will move us toward the implementation of personalized medicine and better management of this deadly disease.

Declaration of interest

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