Nano drug delivery systems for ovarian cancer therapy

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Abstract
Ovarian cancer is the second most common gynecologic cancer in Europe and the USA, and the most fatal gynecologic malignancy among all cancers with a mortality rate of 6%. The traditional treatment of ovarian cancer includes cytoreductive surgery and platinum-taxane combined chemotherapy. Although the response to the standard treatment scheme is promising at first, the disease often recurs and eventually treatment fails with the development of chemoresistance as the main cause of failure of treatment. The purpose of this brief review is to summarize the new strategies, especially in terms of nanotechnology, for the treatment of ovarian cancer.

Introduction
Ovarian cancer is the most lethal gynecologic cancer due to its high recurrence rate [1-3] even though it is one of the most sensitive tumors, even at advanced stage [4]. Today, it globally ranks fifth place among the causes of death for women [2,3]. The first-line treatment of ovarian cancer is cytoreductive surgery followed by platinum-based chemotherapy [2-8]. Despite improvements in the field of medicine, the reason for high mortality in ovarian cancer is late diagnosis because of nonspecific symptoms [9] (almost 75% [8,10] at stage III or later), and relapse of the disease [1-3]. The most significant reason for the recurrence of ovarian cancer is resistance to platinum-based chemotherapy in the majority of patients in progressive stages, although the initial success in treatment with agents such as cisplatin or carboplatin is more than 70% [3,11]. It is known that resistant cancer cells develop resistance to platinum compounds by reducing cell uptake, increasing elimination, inactivation/detoxification of drugs, and accelerating DNA repair [12-14]. Efforts are being made to develop new treatment options due to the frequency of platinum resistance [3,15]. For this purpose, various drug delivery and administration approaches have been developed such as the use of the intraperitoneal route, use of passive and/or active targeting nano drug delivery systems [16,17].

Nanotechnology can be a solution for obstacles of ovarian cancer treatment. When recent studies were reviewed, along with developments in nanobiological fields, nanotechnology was found to have extensively investigated for molecular imaging, drug delivery, treatment and tumor targeting. Particulate drug nanocarriers such as liposomes, niosomes, polymeric micelles, solid lipid nanoparticles and polymeric nanoparticles have unique features for interacting with tumor microenvironments and tumor targeting as their submicron size, functional surfaces, stability, possibility to encapsulate hydrophobic drugs, prolong the residence time in systemic circulation [18,19]. Generally, conventional chemotherapy applications result in rapid blood clearance, degradation, undesirable side effects rooting from drug distribution to healthy tissues, poor drug accumulation in tumor tissues due to poor penetration capacity and multidrug resistance (MDR) [20].

Nano drug delivery systems can be beneficial for the controlled delivery of chemotherapeutics by means of location and duration without undesirable side effects by overcoming several drug delivery barriers through passive or active targeting strategies [11,20].

The main goal of many nanostructuring applications is to protect the drug from rapid degradation after systemic application, to improve the pharmacokinetic behaviour of drugs by preventing rapid clearance of drugs by the reticulo-endothelial system (RES), to achieve therapeutic drug concentrations in the tumor site, to reduce side effects as much as possible by blocking drug delivery to normal tissues, to achieve more effective treatment by providing controlled release within the therapeutic window, to modulate the MDR mechanism by modifying drug uptake [20-22]. Additionally, a study indicated that nanocarriers can both enhance the sensitivity of tumor cells to chemotherapeutics and limit metastasis of the tumor [23]. Some examples of the passive and active targeted nano drug delivery systems can be seen in Table 1.

Passive targeting
Nano drug delivery systems for targeting tumors are based on the delivery of anti-tumor drugs within nanocarriers capable of targeting tumor tissues by taking advantage of the physiological and pathological characteristics of tumors [23]. The superiority of nanoparticulate systems in cancer treatment is mainly based on the enhanced permeability and retention (EPR) effect of the surrounding vessels of the tumor [23,24]. Increased accumulation of nanoparticles in tumor sites is due to the abnormal vasculature with a 200-800 nm pore size, whereas normal vessel endothelium has 5-10 nm pores. These wider pores result in the leakage of tumor vessels and reduced lymphatic drainage leading to an EPR effect and accumulation of nanoparticles in the tumor tissue [21,23].

Cai et al. developed a linear-dendritic copolymer system (referred to as telodendrimer) via peptide chemistry for the co-delivery of paclitaxel, a low dose hydrophobic drug, and cisplatin, a hydrophilic drug. The single-drug loaded telodendrimers displayed less cytotoxicity than free drugs due to the slow release profile; however, telodendrimers loaded with two drugs showed significantly higher cytotoxicity against...
Table 1. Nano drug delivery systems for ovarian cancer therapy

| Drug | Delivery System | Targeting ligand | Carrier material | Preparation method | Characteristics | Results | Ref. |
|------|----------------|------------------|-----------------|--------------------|-----------------|---------|------|
| Parthenolide / Doxorubicin | Micel | - | PSMA-b-PS PMSA-b-PBA | Self-Assembly | Micel size: 20-100 nm PDI: 0.03-0.25 Zeta potential: -40 mV/-50 mV Encapsulation efficiency: >70% for parthenolide | -Improved internalization, efficacy and higher cytotoxicity | [20] |
| Paclitaxel / Cyclophamine / Gossypol | Micel | - | PEG-b-PCL | Solvent evaporation | Micel size: 80-90 nm Loading efficiency: 9.4% | -Enhanced efficiency in 3-D cell culture -Dramatic reduction in tumor volumes | [32] |
| Cisplatin / Paclitaxel | Telo-dendrimer | - | (II)PEG₆₆(COOH)₆₆-L-CA₈ | Peptide chemistry | Particle size: 16.9 nm Loading efficiency: for paclitaxel 92% | -Higher cytotoxicity -Higher accumulation at the tumor site, antitumor activity -Improved pharmacokinetic | [25] |
| Genistein | Liposome | - | HSPC, DOPE, Cholesterol | Film hydration | Particle size: 159-407 nm | -Maximized membrane incorporation, pharmacological activity, bioavailability and pharmacokinetic | [33] |
| Irinotecan / Doxorubicin | Liposome | - | DSPC, Cholesterol | Thin film hydration, followed by extrusion | Encapsulation efficiency: >80% | -Improvement in therapeutic efficacy due to an increase in systemic drug exposure, with the maintenance of the synergistic molar drug ratio of 1:1 in circulation | [34] |
| Paclitaxel | Nano-crystal Hydrogel | - | Hyaluronic acid | Temperature induced crystallization | Particle size: 258 nm Zeta potential: -5.51 mV | -Greater cytotoxicity and antitumor effect microparticulate PTX gel and free drug -Extended survival of tumor-bearing mice | [30] |
| R547 | Micel | Transferrin | mPEG-PE | Lipid film hydration | Micel size: 13.2 - 15.5 nm Drug content: 0.789-0.815% | -Improved interaction of Tf-modified micelles with A2780 ovarian carcinoma cells -Higher in vitro cytotoxicity -Decreased in vivo tumor growth inhibition studies in A2780-tumor bearing mice -Improved pharmacokinetic | [19] |
| Paclitaxel | Nano-particle | Follicle-stimulating hormone polypeptide | PEG-PLA | Emulsion/solvent evaporation technique | Particle size: 127.5 nm Zeta potential: -35.3 mV Encapsulation efficiency: 41.37 % | -Improved cellular uptake -Higher drug concentrations in lymph nodes -Decreased tumor volume -Increased survival time | [26] |
| Shikonin | Nano-particle | TEM1/ endosialin-targeting antibody (Ab) | PLGA | Single/double emulsion solvent evaporation/ diffusion technique with sonication | Particle size: 120 - 250 nm Zeta potential: -35 mV Drug entrainment: 42 % | -Enhanced interaction with TEM1-positive MSI1 cells, -Significant cytotoxicity | [35] |
| siRNA | Nano-particle | Folic acid | Poly (ethylene glycol)-chitosan oligo-saccharide lactate (PEG-COL) | Ionic gelation | Particle size: 200 nm Zeta potential: 8.4 mV | -Suppression of ovarian cancer cell proliferation -Significant accumulation at the tumor site -Active targeting ability | [27] |
| Dorsaksel / gadolinium | Nano-emulsion | Folic acid | Egg lecithin DSPE-PEG₂₀₀ DTPA-PE | High-shear microfluidization | Particle size: 130-140 nm Zeta potential: -50 mV | -Significantly improved cytotoxicity -Extended period of accumulation at tumor site | [29] |

SKOV3 cells, indicating a strong synergism. Optimal cytotoxicity was observed at a 2:1 ratio of cisplatin:paclitaxel. In *in-vivo* fluorescence optical imaging studies, fluorescent dye encapsulated telodendrimers accumulated mainly at the SKOV-3 tumor xenograft, 4-fold higher than other organs; whereas free dye showed very weak tumor fluorescence. The pharmacokinetic behaviour of the free drug cisplatin was enhanced with slower clearance rates and higher plasma half-life. Furthermore, *in-vivo* anti-tumor efficacy studies indicated that the average tumor volume decrease was significantly higher for animal group treated with two drugs loaded telodendrimer group similar to *in-vitro* studies [25].
Active targeting

One of the key parameters for anticancer nanocarriers is targeting ligands in addition to size and surface properties [24]. In ovarian cancer, highly expressed cell-surface proteins include the folate receptor, EGF receptor (EGFR, HER2), luteinizing hormone receptor, claudins, mucins, and integrins [3].

Fan et al. developed a nanoparticle system targeting the follicle-stimulating hormone receptor (FSHR) loaded with paclitaxel to prevent lymphatic metastasis of ovarian cancer. Targeted nanoparticles showed improved cellular uptake into FSHR positive cells, NuTu-19, while there was no difference for non-targeted nanoparticles between FSHR positive and negative cells. In a model of ovarian cancer with lymphatic metastasis in rats, the drug concentration in lymph nodes for the animal group treated with targeted nanoparticles was observed to increase over time and was significantly higher than the free drug and non-targeted nanoparticle group. Moreover, the size and weight of the lymph nodes were reduced and average survival time was longer for the targeted nanoparticle group [26].

Since many genes involved in the regulation of proliferation and angiogenesis have been mutated during cancer, gene silencing via RNA interferences (RNAi) mediated by short interfering RNA (siRNA) is a great therapeutic target for cancer therapy. Hypoxic inducible factor-1a (HIF-1a) is an overexpressed protein in ovarian cancer and associated with cancer progression. Based on this information Li et al. developed tumor-targeting siRNA/folic acid–poly(ethylene glycol)–chitosan oligosaccharide lactate (FA–PEG–COL) nanoparticles for HIF-1a suppression and therefore inhibition of angiogenesis and tumor growth. In vitro gene silencing studies made via Western Blot and Real time PCR demonstrated that siRNA delivery by FA–PEG–COL nanoparticles significantly reduced both protein and mRNA levels of HIF-1a, leading to a strong suppression of cell proliferation in human ovarian cancer cells. When fluorescent dye loaded FA–PEG–COL nanoparticles iv administered to nude mice bearing OV18#2 human ovarian cancer cells, significant accumulation at the tumor site was seen at 3 h post injection with subsequent increase at the 12 and 24 h time while significant liver accumulation was observed with COL nanoparticles treated animal group, indicating the active targeting ability of FA–PEG–COL nanoparticles [27].

Because of its multi-functional properties nanotechnology allows co-delivery of targeting ligands, drugs and imaging agents, which enables therapeutic, diagnostic and real-time traceable drug delivery goals to be achieved at the same time. This approach is called nanotheranostic [28]. By taking advantage of this superior property of nanotechnology Ganta et al. developed a folate targeted gadolinium decorated theranostic nanoemulsion of docetaxel for overcoming drug resistance and resensitization. Am J Obstet Gynecol 191: 1552-1572. [Crossref]

Conclusion

The use of nano drug delivery systems for ovarian cancer therapy is gaining more and more importance day by day due to their excellent properties and promising results. There are lots of nano-sized drug delivery systems designed for diagnosis and therapy under preclinical and clinical development and will be marketed a lot more in the near future.

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