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].

Nanotechnology-based 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

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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 / Cyclopamine / 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	-	(III)PEG^{5K} (COOH)$_8$-L-CA$_8$	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 Zeta potential : -19.4 / -22.6 mV Encapsulation efficiency : 73.5 - 93.1%	-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	[19]
Paclitaxel	Nano-particle	Follicle-stimulating hormone polypeptide	PEG-PLA	Emulsion/solvent evaporation technique	Particle size: 127.5 nm Zeta potential: -35.3 mV Entrapping 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 entrapment :42 %	-Enhanced interaction with TEM1-positive MS1 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]
Dosetaksel / gadolinium	Nano-emulsion	Folic acid	Egg lecithin DSPE-PEG$_{2000}$ 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 nanocarries 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 OVK18#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 efflux transporters which are one of the chemoresistance mechanisms of ovarian cancer and tracing drug distribution. According to cellular uptake studies theranostic nanoemulsion uptake into folate receptor positive SKOV3 ovarian cancer cell line was time dependent and higher than nontargeted nanoparticles. MTT studies demonstrated that IC_{50} value of chemoresistant SKOV3TR decreased 270-fold compared to free drug. Magnetic resonance imaging study made thanks to gadolinium showed that folate targeted theranostic nanoparticles accumulated over the period of 24 hour at tumor site [29].

Intraperitoneal chemotherapy

Intraperitoneal (i.p) chemotherapy in other words the infusion of chemotherapeutic agents directly into the peritoneum is a promising option for ovarian cancer therapy due to spread of the disease to the peritoneal cavity [7,30,31]. Although there are some common drawbacks about i.p administration such as complications related to i.p infusion, including abdominal pain, intolerance to a high level of drug, and discomfort related to the catheter implantation, i.p chemotherapy can be beneficial to maintain an effective local drug concentration for a prolonged period and maximize the locoregional effects on residual tumors [30]. Another problem about i.p chemotherapy is rapid clearance of small molecule drugs from peritoneal cavity and necessity of frequent dosing [30]. In order to increase the residence time of the chemotherapeutics in the peritoneal cavity controlled release drug carriers, such as microparticles, hydrogels and bioadhesive nanoparticels [31].

Sun *et al.* developed a system comprising of in-situ crosslinkable hydrogel depot containing paclitaxel nanocrystals (PNC). PNC with 258 ± 28.1 nm particle size and −5.51 ± 0.42 mV zeta potential was produced by anti-solvent and temperature induced crystallization method while hyaluronic acid gel was produced by crosslinking HA-adipic acid dihydrazide (HA-ADH) and HA-aldehyde (HA-CHO) in situ. PNC were more cytotoxic than microparticulate PTX in SKOV3 cell culture due to cellular PTX retention. After single dose intraperitoneal administration *in vivo* studies demonstrated that PNC-gel was more toxic than microparticulate PTX gel and extended survival of tumor-bearing mice because of greater antitumor effect than microparticulate PTX gel and free drug [30] (Table 1).

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.

Funding

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