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Review Article

Nanooncology in ovarian cancer treatment

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Summary

In the following review, the authors present various methods of using nanoparticles in the therapy of ovarian cancer. Nanoparticles have been shown to prolong the half-time of various chemotheurapeutics, have a lower toxicity, and increase chemosensitivity. It is their hope that this article will widen the discussion within the scientific community on the use of nanotheurapeutics in oncology.

Key words: Nanoparticles; Ovarian cancer; Chemotherapy; Nanotherapeutics; Oncology.

Introduction

Currently, ovarian cancer is the deadliest gynecologic malignancy in the United States, with an expected 21,980 cases to be diagnosed in 2014, and 14,270 expected deaths [1]. Given the asymptomatic nature of ovarian carcinoma in its early stages, this malignancy is most commonly diagnosed in the late stages, attributing to its poor prognosis. Thus there is a growing need to evaluate more effective methods of irradicating ovarian carcinoma, while also diminishing the toxic side effects seen with treatment. There are many ways to achieve better distribution and longer halftime of cytostatic drugs. Those might involve the use of liposomes, micelles, and other structures as vectors for therapeutic substances. These nanovectors tend to range in size from ten to 100 nm [2, 3]. The encapsulation of currently used therapeutics in nanostructures might lead to lower toxicity.

Nanotherapeutics can be transported to the cell either in a passive or active manner. Below are presented the various groups into which nanotherapeutics may be classified:

Liposomal and micellar nanotherapeutics - Doxil

The PEGylated form of liposomal doxorubicin, known under the tradename of Doxil, is widely used in platinum-resistant patients [4]. It has a much longer halftime in this form, and has been shown to have a lesser toxicity when compared to the non-liposomal form. Due to the clinical success of this PEGylated form, clinical trials are currently being performed to discover the efficacy of other chemotherapeutic compounds (Table 1).

Nanocarriers bound with noble metals – gold nanoparticles (AuNPs)

Xiong *et al.* used 20 nm nanoparticles of gold which were tested on cell lines of ovarian cancer: A2780, OVCAR5, and SKOV3-ip [5]. These particles have reduced expression of markers ALDH1, CD44, CD133, Sox2, MDR1, and ABCG2 that are typical for stem cells. Moreover, they stopped activation of the Akt and NF-κB pathways, which play a key role in chemoresistance. The cells after 24 hours

Table 1. —

Form	Therapeutic	Name	Phase and registration number
Liposomal lurotecan	Lurotecan	OSI-211	Phase II, NCT00010179
Paclitaxel bound with albumin	Paclitaxel	ABI-007	Phase II, NCT00466986
Nanocarries administered intravenously	Paclitaxel	Nanotax	Phase I, NCT00666991
Polymer conjugate	Inhibotor topoizomerazy I	NKTR-102	Phase II, NCT00806156103
Polymer based cyclodextrin	Kamptotecin	CRLX101	Phase I, NCT00333502
25 kDa polymer based on hydroxypropylometacrylamide	Oxaliplatin analogue	AP5346	Phase II, NCT00415298

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were exposed to cisplatin, and a higher chemosensitivity was observed.

Nanoparticles using siRNA silencing – siRNA MDR1

The discovery of RNA interference mechanisms was awarded the Nobel Prize in 2006 to Andrew Z. Fire and Craig C. Mello. Trials of gene silencing were conducted in the area of oncology. A potential target is the multi drug resistance (MDR)1 gene and glycoprotein P. Yanga *et al.* tested 173 nm particle built from hyaluronic acid HA-PEI/HA-PEG/MDR1 siRNA [6, 7]. The administration of this particle in the murine model, together with paclitaxel treatment, has revealed lower expression of glycoprotein P and increased cell apoptosis. Similar tests were made with nanoparticles where its siRNA was targeted against survivin [8].

Immunonanoparticles - NPs–Tx–HER

Nanoparticle Nps–Tx–HER, with a size of about 273 nm, is a particle covered with anti-HER2 antibody (trastuzumab) with paclitaxel inside [9]. At the University of Geneva, Cirstoiu-Hapca was injected intraperitoneally the SKOV-3 cell line, which overexpresses HER2 in mice model. In this study, chemosensitivity of paclitaxel alone was compared with its nano form. A ten times larger concentration of therapeutic was shown after the use of the nanoparticle.

Magneto-electric nanoparticles

Guduru's team from Florida International University's Center for Personalized NanoMedicine tested 30 nm CoFe2O4@BaTiO3 MEN (magneto-electric nanoparticle) filled with paclitaxel (PTX) [10]. After the use of a magnetic field of 30 ersteds on the SKOV-3 cell line (ovarian carcinoma) and HOMEC cell line (control), the transfer of particles was made only to cancer cells. The authors proposed a new term of nano-electroporation for this method. In their article, they also presented data that the transfer of the therapeutic dose is five times greater than that in vectors based on antibodies. Other research with the use of 40 nm nanoparticles with docetaxel on SKOV-3 cell line was made by Huang *et al.* [11]. In Vilnius, Lithuania, cobalt-ferrite nanoparticles (Co-SPIONs) were created and tested against the A2780 ovarian cancer cell line. The compound was found to be non-cytotoxic, but could be utilized in magnetic resonance imaging [12]

Reactive oxygen species (ROS) - induced nanotherapy based on the combinatorial effect of phototherapy and gene suppression

A study performed at the Oregon State University Department of Pharmaceutical Sciences recently examined an approach to combine intraoperatively targeted photodynamic therapy (PDT) with gene suppression, specifically of the DJ-1 protein, which induces malignant cells' ROS defence mechanism [13]. Dedrimer-based nanocompounds for the malignancy-targeted delivery of near infrared photosensitizer of phthalocyanine (Pc) and DJ-1 suppressor, DJ-1siRNA were created. Sizes of the nanoplatforms fell within the range of 10-200 nm, which prevents the elimination by the kidneys (> 10 nm), destruction via macrophages (< 200 nm), and optimized tumor-targeting delivery via the enhanced permeability and retention effect (< 200 nm). In order to achieve cancer specificity with the nanoplatforms, luteinizing hormone-releasing hormone (LHRH) peptides were included with the platforms, which interacted with the LHRH receptors overexpressed in ovarian carcinoma. For in vitro studies, two LHRH-positive ovarian cancer lines were utilized, ES2 and A2780/AD. ES2 has a lower basal level of DJ-1 protein when compared with A2780/AD, and greater response to treatment with the nanocompound was seen in A2780/AD cells. In vivo studies were then performed where mice were subcutaneously injected with A2780/AD ovarian cancer cells, and, once the tumor had grown to a size of 40 mm^3, PPI-siRNA nanoplatform loaded with DJ-1 siRNA was given via intravenous route. Twenty-four hours later, an injection of PPI-Pc was administered, after which tumors and controls were exposed for ten minutes to one dose of light via a 690-nm laser diode. On the 15^{th} day post-treatment, a reduction in tumor size was seen in both PDT and the nanocompound therapy. However, tumors treated solely via PDT began to regrow on the 16^{th} day after discontinuation of treatment. Combination therapy showed no evidence of cancer recurrence within the 25^{th} day follow-up period. Use of a nanoplatform to deliver tumor-targeting therapy was also shown to decrease treatment side effects due to the lack of drug leaching into systemic circulation.

Discussion

Presented above were only some examples of nanotherapeutics. It needs to be remembered, however, that most of the research was performed only in vitro and on some of ovarian cancer cell lines. Personalized medicine and nanotherapeutics are still in their early research phases.

In addition to their therapeutic use, some nanocarriers and microstructures were also developed that aid in imaging. For example, microparticles (2.5 up to 4.5 microns) based on perflutren may be used during ultrasound examinations [14, 15]. Also, an iron-based nanocompound has been shown to assist in T1 magnetic resonance imaging [16].

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