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The Role of Nanotechnology-Based Photodynamic Therapy in the Treatment of Ovarian Cancer

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Abstract

Ovarian cancer is one of the most dangerous and deadly cancers in women. This cancer progresses very quickly and metastasizes to the peritoneal cavity and pelvis. It is called silent death because 75% of patients who refer to hospitals are diagnosed at advanced stages of the disease. Transvaginal ultrasonography, Cancer antigen (CA125, Doppler imaging, Human kallikrein 10 (hK10), lysophosphatidic acid (LPA), computerized tomography scans, cytology and / or biopsy are used to diagnose ovarian cancer. Surgery and chemotherapy are also among common treatments used for the treatment of ovarian cancer. However, these traditional therapies have a variety of side effects, including nausea, vomiting, peripheral neuropathy, neurotoxicity. Nanotechnology with its unique features can overcome these limitations and problems. Nanoparticles can use modern therapies, such as nanotechnology-based photodynamic therapy, nanotechnology-based gene therapy, nanotechnology-based radiotherapy and radiofrequency therapy, and nanotechnology-based cancer theranostic that can helps in the treatment of cancer. Nanotechnology-based photodynamic therapy is considered one of the most effective, safe, and novel methods in cancer treatment. The use of nanoparticles as photosensitizers can overcome many of the limitations of traditional therapies. Nanoparticles can be targeted to specific sites, controllable, in some cases, used in a way to produce ROS. The use of nanotechnology can attenuate toxicity in target sites and greatly reduce injuries to normal cells.

Keywords: Ovarian cancer; Nanotechnology; Photodynamic therapy, Nanoparticles, Photosensitizers

1 Introduction

Ovarian cancer is the most common cause of mortality in adult women (1). Numerous studies have shown that ovarian cancer takes more victims than breast cancer. According to a study conducted by the American Cancer Society, the mortality rate from ovarian cancer was about 69%, while such a rate was about 19% fir breast cancer. Some genetic and epigenetic changes may occur in the body to transform a normal ovarian cell to a cancer cell. Some researchers believe that ovarian cancer is the result of a mutation in the gene on chromosome 17q, known as BRCA1. It is estimated that mutations in this gene may increase the risk of ovarian cancer by 30% in individuals who are over 60 years old. The origin of ovarian cancer may be the surfaces of the ovary, the fallopian tube, or the mesothelium-lined peritoneal cavity. Ovarian cancer mainly affects postmenopausal women and is a deadly cancer. The cure rate for this cancer is 30%. This may be due to the fact that most patients only refer to medical centers when the disease progresses to advanced stages with extensive metastatic lesions in the peritoneal cavity (2-5).

In general, ovarian cancer accounts for 4% of all cases of cancer in women. In addition, gynecologic malignancies are the leading cause of death in females. Ovarian cancer is mostly asymptomatic at the early stages, indicating why most of patients are diagnosed at advanced stages of the disease when hospitalized in medical centers (6). Ovarian cancer is ranked as the second gynecological cancer in terms of the incidence among women (7, 8). Cancer cells grow rapidly in ovarian cancer, which is a very aggressive cancer that quickly metastasizes to other tissues and organs. One major difference between this cancer and other types of cancer is that unlike other types of cancer, caused by vascular dissemination, ovarian cancer rarely spreads through the angiogenesis process. In addition, it may involve pelvic and / or para-aortic lymph nodes. Patients with ovarian cancer have locally advanced disease in the pelvis, with contiguous extension to or encasement of the reproductive organs (uterus, fallopian tube, tube, ovaries) and the sigmoid colon (7, 9). Another type of tissue change occurring during ovarian cancer is the transformation of the omentum. During the disease, the omentum, a soft 20 × 15× 2-cm fat pad which covers the abdominal cavity and bowel, transforms and this causes obstruction of the stomach and the small and large bowel and cause severe pain to the patient (10).

2 Risk factors

Some risk factors include: (a) several lines of evidence suggest that certain drugs and chemicals may increase gonadotropins by increasing estrogen degradation in the liver or directly stimulating their production by the pituitary gland. Pelvic irradiation, exposure of follicles to chemicals or toxic metabolites, or ovarian infections such as mumps are other risk factors of the disease development (11). (b) The long-term use of estrogen-only replacement therapy (particularly for 10 or more years) (12). (c) Women with susceptibility genes such as BRCAl (13-18). (d) Women who have had first-degree relatives with ovarian cancer (19-22). (e) In general, the incidence of ovarian cancer is increased with age. According to some studies, the incidence is higher in individuals who have over 60 years old. It is also very rare to occur before 40 years

old (23). (f) Some findings suggest the significance of geographic and ethnic variations in the incidence of ovarian cancer. Studies showed that Caucasian women in industrialized countries such as the North America and Europe have a higher incidence of ovarian cancer than others (24). (g) Some studies have reported a dietary effect on the development of ovarian cancer. These studies have shown that Western diet, which is high in meats and low in vegetables may have a role in the incidence of ovarian cancer. Studies have also shown that whole-grain food, low-fat milk, calcium or lactose, vegetable, significantly reduced the risk of ovarian cancer (25). (h) Smoking and tobacco are also linked to ovarian cancer and increase the risk of cancer (26, 27). (i) Exposure to talc or asbestos has been demonstrated that cause or make individuals probe to develop ovarian cancer. These substances cause chronic inflammation in the ovarian epithelium. Inflammation is capable of producing oxidants that can cause direct damage to DNA and lead to increased proliferation of cancer cells, enhancing the risk of mutagenesis (28).

3 Diagnosis

3.1 Screening

If ovarian cancer is diagnosed at the early stages of the disease, the chance of recovery is increased. Nowadays, ultrasound, which is a non-invasive procedure, is used for screening the human body (29-32).

3.2 Transvaginal ultrasonography

This imaging method measures the ovarian size and estimates the internal ovarian structure, volume, septum thickness and papillary formation (33).

3.3 Doppler imaging

This imaging method is a complementary method for improving the sensitivity of transvaginal ultrasound assessment and evaluation of angiogenesis in ovarian tumors (34, 35).

3.4 Cancer antigen (CA125)

This cancer antigen (CA125) is overexpressed in nearly 82% of women with ovarian cancer compared with healthy women (36).

3.5 Lysophosphatidic acid (LPA)

In this examination, the serum concentration of LPA is measured and it has been shown that more than 90% of female patients with ovarian cancer exhibit increased levels of this molecule in their serum samples (37).

3.6 Human kallikrein 10 (hK10)

This enzyme is a secreted serine protease highly expressed in ovarian tissues and considered a novel biomarker for ovarian cancer. The serum level of hK10 is a strong and independent prognostic marker for ovarian cancer (38).

4 Conventional treatments

In general, conventional treatments are routinely applied for patients with ovarian cancer depending on the stage of the disease. The first line therapy is surgery followed by chemotherapy and in some cases radiotherapy. In the case of initial responses, secondary therapy might be needed to complete the treatment course (39, 40).

4.1 Surgical treatment

The surgical procedure is the commonest invasive therapeutic strategy used for patients with ovarian cancer. This surgery includes: total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal cytology. These procedures are performed by trained gynecological specialists or oncologists. If the surgery process accomplished, it brings the best chance for the overall survival of patients. Laparotomy is a surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity. It seems that the laparoscopic removal of ovarian cysts is best strategy only in patients with benign cysts (41-49). The main purpose of cytoreductive surgery is to remove the entire tumor, which may have metastasized to the pelvic and abdominal cavities, i.e., “optimum cytoreduction,” in order to increase the efficacy of additional adjuvant therapy (40). In fact, surgery can reduce the number of tumor cells and subsequently the size of tumors (50).

4.2 Chemotherapy

Several studies show that women who have not successful surgery exhibit poor prognosis in which the 5-year survival rate is about 0-5%. Therefore, due to the low efficacy of surgery alone, chemotherapy can be combined with conventional therapies. Chemotherapy is usually prescribed following the surgical procedures. Chemotherapy prevents the disease progress and improve the overall survival of patients with cancer (51-54). Chemotherapeutic agents are intravenously administered to patients with ovarian cancer and prescribed in 5-8 sessions. Ovarian tumors tend to be chemo-sensitive and confine themselves to the surface of the peritoneal cavity. These features have made them a suitable target for intraperitoneal (IP) chemotherapy. A group of studies have shown that intraperitoneal chemotherapy improves overall survival of patients with cancer (55). The most common drug used for the treatment of ovarian cancer is platinum (56). Nowadays, combination chemotherapy is used as a current regimen for the treatment of advanced ovarian cancer. Various chemotherapeutic agents, such as paclitaxel, topotecan, gemcitabine, oral etoposide, olaparib, cyclophosphamide, chlorambucil, melphalan, thiotepa, treosulfan, and encapsulated doxorubicin are prescribed in combination with carboplatin or cisplatin (39, 40, 57, 58)

4.3 Some side effects of common treatments for ovarian cancer

Many patients with ovarian cancer experience recurrence, despite responding well to primary chemotherapy. Whether a patient undergoes second or third course of chemotherapy mainly depends on the emergence of side effects of drugs used. The most common side effect reported in patients with ovarian cancer is chemotherapy-induced nausea and vomiting (CINV) (59). In addition, chemotherapy may cause neurotoxicity in the peripheral and central nervous system, resulting in cognitive deficits, encephalopathy, dementia, or even coma the adverse effects may limit the dosage and usage of chemotherapeutic agents. Bone marrow toxicity is another well-known adverse effects in response to chemotherapy; however, this problem could be partially attenuated by the administration of growth factors or bone marrow transplantation (60). Also, some drugs used for the treatment of ovarian cancer, such as a combination of doxorubicin hydrochloride and cisplatin, may increase the risk of leukemia when used in relatively high doses (39). Generally, an increase in the survival of patients is the major goal of chemotherapy, a decrease in clinical symptoms and

preservation of the quality of life are also critical issues that should be taken into account. Reports indicated that chemotherapy can cause nausea, vomiting, hair loss, cognitive dysfunction, fatigue, changes in sexual desire, and a reduction in the quality of life (61).

5 Applications of nanotechnology in ovarian cancer

Nanotechnology is an interdisciplinary field and provide extraordinary opportunities for biological sciences. One of its beneficial use is the treatment of cancer, which has received much attention due to the growing number of patients. In fact, nanotechnology provides early diagnosis, prediction, prevention, personalized therapy, and targeted therapy. Some researchers believe that nanotechnology paved the way for the treatment of various types of cancer. Some of features have distinguished nanotechnology from other scientific approaches that include: (a) nanosystems and nanostructures can be can be used both as a diagnostic and a therapeutic factor at the same time; (b) drugs are capable of being targeted for specific cells or tissues without causing adverse effects on normal cells/tissues; and (c) nanosystems are able to carry several therapeutic molecules and therefore provide a platform for combination therapy to overcome drug-resistance. Nanotechnology has opened new therapeutic windows for cancer treatment. Some of these new approaches include nanotechnology-based photodynamic therapy, nanotechnology-based gene therapy, nanotechnology-based radiotherapy and radiofrequency therapy, nanotechnology-based cancer theranostic (62-72).

5.1 Nanotechnology-based photodynamic therapy

One of the new and relatively widely used fields of nanotechnology is photodynamic therapy. In this area, the basis of treatment is the use of photosensitizers. In this method, light with a certain wavelength is emitted to photosensitizers. Light radiation activates photosensitizers, which subsequently activates the release of radical oxygen species. The released radical oxygen species can induce cell death in tumor cells and diminish the rate of angiogenesis. This therapeutic approach could be performed locally or systemically. Since this method does not suppress the immune system of humans, it can be carried out repeatedly by physicians. This method could also act as complementary therapy in addition to surgery, chemotherapy, or radiotherapy (73, 74). Table 1 shows some of the nanostructures used in photodynamic therapy in ovarian cancer, as well as other nanoparticles used for diagnostic and therapeutic purposes.

Table 1: Shows some of the nanostructures used in photodynamic therapy

Nano particle	Function	Reference
Hypericin-loaded nanoparticles	Hy-loaded NPs are used for photo dynamic therapy against NuTu-19 cancer cells. Nanoencapsulation of Hy in PLA improves the treatment outcome and needs lower doses of drugs.	(75)
Nanocomplex–anti-HER2 conjugates	Gold nanoshell-based complex- anti-HER2 conjugates (nanocomplex) binds specifically to OVCAR3 cells. These multiple nanostructures are stimulated by near-IR light to induce cell death in ovarian cancer cells through photothermal cancer therapy.	(76)
SPION-PG-Lys8 / Ce6	These types of nanostructures exert anti-proliferative activity against SKOV3 ovarian cancer cells through photodynamic therapy and the production of reactive oxygen species (ROS).	(77)
(ZnO-MTAP)	Zinc oxide (ZnO) nanoparticles conjugated to porphyrin via PDT and subsequently the release of reactive oxygen species (ROS) are able to induce selective cytotoxicity against OVCAR-3 in ovarian cancer. These nanostructures induce cell death in a dose-dependent manner	(78)
Fe_3O_4@SiO_2@APTES@PPa (FSAP)	Magnetic iron oxide modified pyropheophorbide-a fluorescence nanoparticles, Fe_3O_4@SiO_2@APTES@PPa (FSAP) are used against ovarian cancer cells (SKOV-3). Upon PDT, nanoparticles induce the generation of ROS in cancer cells	(79)
Composite Conjugated Polymer/Fullerene Nanoparticles	These nanostructures hold promising results in the treatment of a variety of cancer cells, including: MDA-MB-231 (human breast cancer), A549 (human lung cancer), and OVCAR3 (human ovarian cancer). These nanoparticles become activate upon PDT.	(80)
Dendrimer-based nanoplatforms	Dendrimer-based nanoplatforms are utilized for cancer-targeted delivery of near-infrared photosensitizers, phthalocyanine, and DJ-1 siRNA. These nanostructure is used activated via PDT to suppress the DJ-1 protein, one of the key players in resistance of cancer cells to ROS.	(81)
Core–shell–shell upconversion nanoparticles (UCNPs) [NaGdF4:Yb/Nd@NaGdF4: Yb/Er@NaGdF4]	UCNPs can be used as a theranostic agent. This nanostructure can be used for the combination therapy with Pt and PDT against cisplatin resistance.	(82)
Polymeric micelles	Polymeric micelles of P123 and F127 significantly enhance photodynamic effect with Photofrin II® and efficiently deliver photosensitizer in SKOV-3 and MCF-7/WT cells. PDT with Photofrin II® loaded in polymeric micelles induces with low hemolytic impact.	(83)
Folic Acid-Conjugated, SERS-Labeled Silver Nanotriangles	Due to having both multimodal optical imaging and SERS detection with hyperthermia capabilities through site specificity, this nanostructure can be introduced as an excellent candidate for personalized medicine.	(84)
Hy-loaded NPs of polylactic acid	This nanosystems serves Hy as a natural photosensitizer. Since Hy has a hydrophobic nature, polylactic acid polymers are employed to solve this problem.	(85)

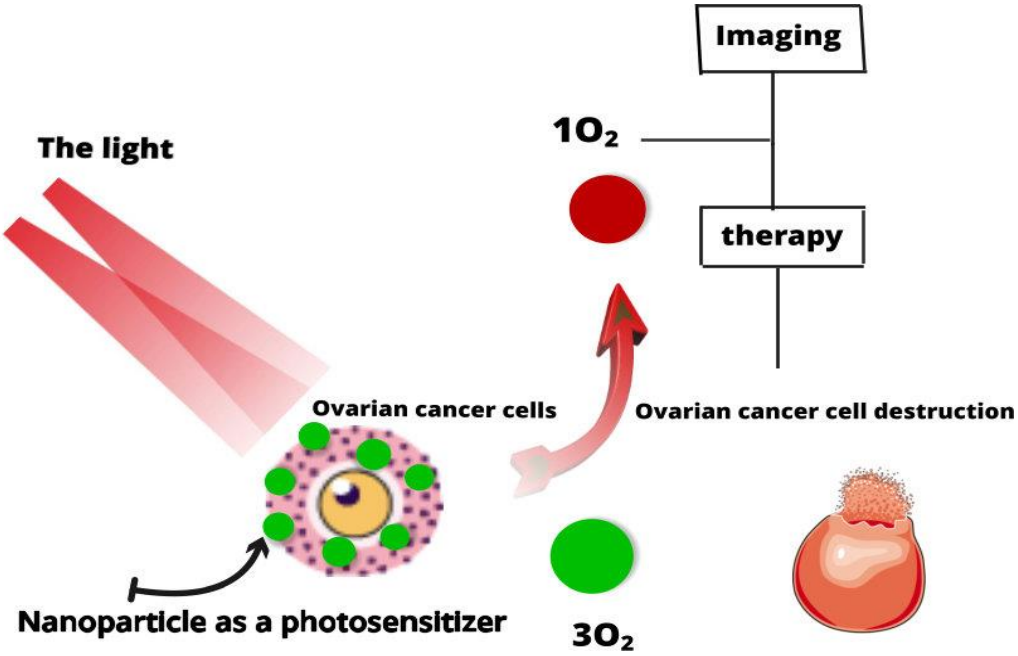

Figure 1: Shows the role of nanoparticles as photosensitizers in the treatment of ovarian cancer

In general, photodynamic therapy (PDT) is a promising therapeutic strategy for cancer treatment in which a specific wavelength of light is transmitted to a photosensitizer, energy transfer cascades, leading to cytotoxicity in cancer cells (Figure 1). Photosensitizers stimulate the production of reactive oxygen species, eventually leading to apoptotic and necrotic cell death by affecting various cellular components. The use of this therapeutic mechanism for the treatment of cancer cells is a safe and new method in selective destruction of tumors with minimal systemic toxicity and side effects on normal cells. Creating a successful and desirable PDT requires the accurate selection of the desired tissue and the efficient transfer of photosensitizers, the photoactivating light and to establish dosimetric correlation of light and drug parameters to PDT-induced tumor response. Nanotechnology offers promising solutions for tumor selection and control of photosensitizer bio-distribution. The feasibility of various designs can also allow incorporating the imaging agents and providing the light delivery and dosimetric components (86-95). The use of nanoparticles and nanostructures in PDT has several advantages including excellent colloidal stability, effective and desirable protection against enzymes and hydrolysis of encapsulated drugs, and controlled release of the drug, In addition, in some cases, it is possible to directly stimulate nanoparticles to produce reactive oxygen species(up-conversion nanoparticles, quantum dots, self-lighting nanoparticles), and, most importantly, the sizes to which they are able to be accumulated in cancer cells using the enhanced permeability and retention (EPR) effect of tumor tissues. The use of nanoparticles as PS can overcome many of the limitations of conventional PDT therapy (96-100).

6 Conclusion

Ovarian cancer is one of the deadliest cancer affecting the female gender. Conventional treatments can cause side effects for patients, and, in some cases, may result in recurrence. Nanotechnology has also provided solutions for the treatment of ovarian cancer. One of these solutions is nanotechnology-based PDT. In this method, nanoparticles act as photosensitizers. Nanostructures can reduce the need for conventional therapies and enhance targeted therapy, leading to decreased toxicity of chemotherapeutic agents and decreased rates of damages to normal cells. Thus, it can be concluded that nanotechnology-based PDT can be used as a promising strategy for the treatment of ovarian cancer.

Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

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