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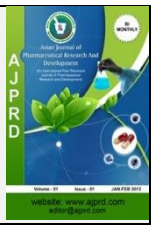

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Research Article

Ovarian Cancer: Current Scenario, Treatment and Novel Strategies for Management

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ABSTRACT

Ovarian cancer is the leading gynaecological cancer among women globally and leads to death with 5-year survival rate of metastatic form of ovarian cancer as only 20-30%. Detection of disease at an early stage is very difficult and no screening test are available for detection of OC in general population. For effective management of ovarian cancer chemotherapy, surgery, hormone therapy and radiation therapy are often used alone or in combination depending on the stage and severity of ovarian cancer. This mini-review describes about facts and figures as well as current diagnosis and treatment methods available for ovarian cancer. The manuscript will also cover a brief description of recent research of developing novel strategies such as liposomal drug delivery carriers in management of cancer.

Keywords: Cancer, ovarian cancer, diagnosis, treatment, nanoformulation, liposomes, drug delivery carrier

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INTRODUCTION

Cancer is defined as uncontrolled growth of body's own cells. Such cells become un-associated with the cell death pathway and continue to grow uncontrollably. The cell death of a normal one get initiated when the basic structural and functional element i.e. DNA gets damaged. However, for cancerous cells bearing this faulty DNA does not die and continue to grow producing multiple cells/ replica cells bearing the same faulty DNA at the site. Further, these cells gain the capacity to invade other parts of the body leading to their metastasis and spread. The DNA damage may be during the replication process, due to mutation or environmental challenge. The mutation may be acquired or inherited type. Whatever, the reason maybe it is to be noted that all the tumors produced due to uncontrolled division may not be cancerous. Based on the capacity to metastasize, tumors may be classified as benign or malignant. Further, for malignant tumors, are named according to their site of origin rather than their site of metastasizing.

For the tumors originating in the cells of the ovary are called as ovarian cancer (OC). Based on the type of cells the ovaries are made up of the tumors can either be of epithelial cell, germ cell or stromal cell tumors. Of the three types, epithelial cell tumors are the most common with incidence of 90% of cases[1]. It can also be noted that the development process for ovarian carcinomas follows peculiar and unique dissemination process[2]. Two types of OC: Type I and II based on the extent of growth which may be either slow or rapid respectively Figure 1. A chart for various histologic subtypes of ovarian carcinoma is presented in the Figure 2. Advanced stage of disease with widely dissemination of tumor nodes throughout the peritoneal cavity are observed in about 70% of patients that are diagnosed. Presence of ascitic fluids may facilitate dissemination of cancer cell in peritoneal cavity[3-5].

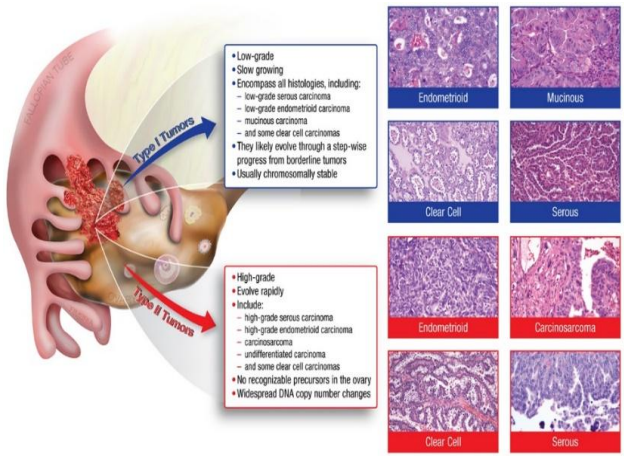

Figure 1: Subtypes of Ovarian cancer tumors

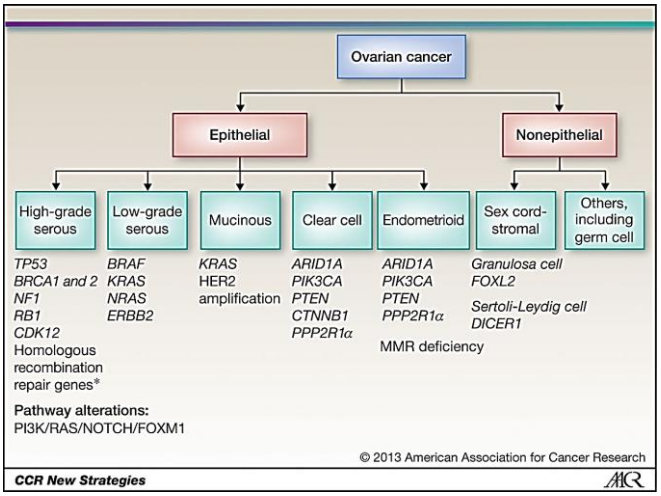

Figure Error! No text of specified style in document.**:** Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations

Ovarian cancer is often referred to as "a cancer that whispers", as the disease progression is not comprehended easily by symptoms and the symptoms are detected at a later stage after tumor has metastasized. Further, despite the progress made in chemotherapy, only 15% of cases are detected at early stage where the tumor is still in localized state and at this stage the 5-year survival rate is 92%. However, in majority of the cases the disease is diagnosed only after metastasis. Further, in most of the cases patients show relapses after treatment with the first line drug along with development of resistance to the chemotherapeutic and this associated with lack of effective second line drug to treat the relapses can be regarded as the main cause of poor survival rate in OC patients. The 5-year survival rate in OC patients with metastatic form is only 20-30%[6].

Key statistics and facts about Ovarian Cancer:

United States: OC ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 75[7]. The American Cancer Society estimates about 22,280 women will receive a new diagnosis of ovarian cancer and about 14,240 women will die from ovarian cancer in 2016. Overall, the 5-year relative survival rates for ovarian cancer patients are 46%. Generally, only 15% of cases are diagnosed at a local stage, for which 5-year survival is 92%[4,7,8].

United Kingdom: Each year in the UK there are approximately 7,000 cases of OC and 4,300 cases of deaths from OC[9].

Australia: Estimated number of new cases of OC diagnosed in 2016 in Australia are 1,480 and estimated number of deaths from ovarian cancer in 2016 is 1,040 with 43% chance of surviving at least 5 years[10].

India: The OC survival rates have declined in India from 23% in 1995-99 to 14% in 2005-09[11]. In most of the population-based cancer registries in India, OC is the third leading cancer among women, trailing behind cervix and breast cancer and has the worst prognosis among all gynecological malignancies[12-14].

Symptoms:

The initiation and progression of OC occurs with no specific symptoms until the disease gets metastasized. However, infrequently some common symptoms those observed are abdominal distention, bloating, pain and urinary urgency.

Diagnosis:

Detection of disease at an early stage is very difficult and no screening test are available for detection of OC in general population. Procedure available for diagnosis can be either imagining technique i.e. transvaginal ultrasound, CT scan, MRI or Positron Emission Tomography (PET). Only two markers that are approved by FDA for monitoring the disease progression are CA125 (Mucin 16) and HE4 (Human Epididymis protein 4). Other tumor markers that have been tested are SMRP, CA72-4,activin, inhibin, osteopontin, epidermal growth factor (EGFR), ERBB2 (Her2), CA15-3 and macrophage colony stimulating factor (M-CSF)[15,16]. Herein, combination of one or more marker increases the sensitivity and specificity of detection. A list of tumor markers associated with OC is summarized inTable 1

Table 1: Tumor marker associated with OC.

Marker associated with OC	Example
Mucin related glycoprotein	CA-125 (Mucin 16); OVX1; HE4; Mesothelin (MES)
Hepatic and acute phase protein	Haptaglobin α; Bikunin; C-reactive protein; Apolipoprotein A1, Transthyretin Inter-α-trypsin inhibitors
Cytokines and growth factors	Vascular endothelial growth factors (VEGF); Macrophage colony stimulating factor (M-CSF); Osteopontin (OPN)
Serum proteases	Human Kallikreins; Prostasin.

Over and above those stated, antibodies have also been screened and though in its infancy have emerged as reliable markers for OC diagnosis. Termed as Radio immune conjugates, these have capability to detect premalignant lesions also. Some examples of antibodies or their antibody fragment used include: B72.3 mAb; HMFG2 mAb; H317; mAb 170; OC-125 F(ab'); MOv18 mAb; Anti CEA Ab; IgovomabF(ab')2mAb(Indimacis 125); CYT-103 mAb; C0C183B2; Nanobody(2Rs15d).

Treatment and Management:

For effective management of OC the following treatment alternatives are available: often, 2 or more different types of treatments are used. This includes Chemotherapy; Surgery; Hormone therapy; Targeted therapy and/or Radiation therapy.

Chemotherapy is the use of drugs to treat cancer. Most often, chemo is a systemic treatment − the drugs are given in a way that allows them to enter the bloodstream and reach all areas of the body. Systemic chemo can be useful for cancers that have metastasized (spread). Most of the time, systemic chemo uses drugs that are injected into a vein (IV) or given by mouth. For some cases of ovarian cancer, chemotherapy may also be injected through a catheter directly into the abdominal cavity. This is called intraperitoneal (IP) chemotherapy. Drugs given this way are also absorbed into the bloodstream, so IP chemotherapy is also a type of systemic chemo. This is discussed in more detail later in this section.

The standard approach is the combination of a platinum compound, such as cisplatin or carboplatin, and a taxane, such as paclitaxel (Taxol®) or docetaxel (Taxotere®). For IV chemotherapy, most doctors favor carboplatin over cisplatin because it has fewer side effects and is just as effective. The typical course of chemo for epithelial ovarian cancer involves 3 to 6 cycles. A cycle is a schedule of regular doses of a drug, followed by a rest period. Different drugs have varying cycles; your doctor will let you know what kind of schedule is planned for your chemotherapy.

Chemotherapy and Cytoreductive surgery are the currently employed therapeutic approach for OC. First line chemotherapeutic agents employed are either plant derivatives i.e. Taxol – Paclitaxel and Docetaxel; or platinum containing agents Carboplatin and Cisplatin[17-18]. For Epithelial tumors, either single or combination of vinblastine, bleomycin and cisplatin may be employed. The preferred treatment strategy for epithelial tumors is by surgery which may be used in combination with radiation therapy to obtain higher cure rates. Subsequently, the surgery has to be accompanied by chemotherapy to prevent relapse[19].

Surgery:

This is the main method that is used for treatment. Goals of the surgery are: staging and debulking. Staging of OC is done based on the spread of cancer to ovaries or fallopian tubes or omentum or farther parts like pelvis or abdomen for which biopsy of target organ is done. The other goal of the surgery is debulking that is removal of tumor as much as possible. Thus, surgery can be helpful in removing solid tumors such an OC.

Ovarian Cancer treatment: Research and clinical status:

Scientists around the globe continue to research on the risk factors, causes, prevention, early detection and treatment of OC. Some of the promising recent research strategies are described below;

Early detection*:* Detection of cancer associated antibodies and radiolabeled antibody conjugates are forming the basis for early diagnosis of ovarian cancer. Only one diagnostic RIC, 111In satumomab pendetide (OncoScint CR/OV®), targeting TAG-72 was developed however, the commercialization of the RIC was discontinued[5,20].

Chemotherapy*:* New chemotherapy (chemo) drugs and drug combinations are being tested. The drugs trabectedin (Yondelis®) and belotecan have shown promise in some studies. Although carboplatin is preferred over cisplatin in treating ovarian cancer if the drug is to be given IV, cisplatin is used in intraperitoneal (IP) chemotherapy. Studies are looking at giving carboplatin for IP chemo. Drugs known as PARP inhibitors are in clinical trials for treatment of patients with platinum-sensitive recurrent OC.

Immunotherapy: Antibodies when given alone act as an anti-angiogenic agent or utilize the protective role of immune system against OC. In addition, when given in combination with chemotherapy, antibodies have turned out to sensitize chemo-resistant tumors. Bevacizumab is the only FDA approved antibody for OC therapy which has shown a marked safety and efficacy profile in clinical trials[5,21].

Hormone therapy: For treatment of recurrent or later-stage ovarian cancer, tamoxifen (Nolvadex, Soltamax), aromatase inhibitors, and enzalutamide (Xtandi), a blocker of the androgen receptor, are being used.

Gene therapy: A new area of research is discovering how damaged genes in ovarian cancer cells can be corrected or replaced. Researchers are studying the use of specially designed viruses that carry normal genes into the core of cancer cells and then replace the defective genes with the functional ones.

Tumor Targeted nanocarrier*:* The concept of site specific drug delivery for treatment of localized disease in the body to improve therapeutic index of the drug is considered as perennial challenge to the formulator in modern formulation design. Antibodies are playing cardinal role in design of highly potent class of targeted therapies, such as antibody-drug conjugates and clinically viable tumor targeted drug nanocarriers.

2.2 Liposomes as a drug delivery carrier

Since their discovery by Bangham et al. about 50 years ago[22], liposomes have drawn a lot of interest as pharmaceutical carriers for drugs and genes. Liposomes are composed of a bilayer structure of either natural or synthetic phospholipids. Phospholipids are a key structural component of the cell membrane. They are amphiphilic in nature, possessing both hydrophilic and hydrophobic regions. Amphiphilic phospholipids self-assemble into bilayers[23-25] by arranging their hydrophilic groups outward to interact with aqueous environments and arranging their lipophilic groups toward the center of the bilayer.

Liposomes can be unilamellar or multilamellar depending on the number of lipid bilayers formed[26].

Liposome surface properties can be easily manipulated for drug delivery. Surface charge can be modified by adjusting the lipid composition to add either neutral character or cationic charge using cationic lipids, which directly influences liposome interactions with the negatively charged cell membrane. Neutral liposomes have no significant cell membrane interaction, and the neutral charge results in liposome aggregation[23]. Aggregation is a key issue for drug delivery because particle aggregates are rapidly cleared by the phagocytosis, which greatly reduces drug delivery efficiency. Anionic liposomes are internalized through clathrin-mediated endocytosis[27,28] while cationic liposomes deliver their contents by membrane fusion and/or by endocytosis.

Liposomes can be used to carry water- or lipid-soluble drugs and its surface can be modified according to the requirement. Unilamellar liposomes have an aqueous core that is used to carry water-soluble drugs[29], while multilamellar liposomes have lipophilic layers between hydrophobic tail groups that are used to carry lipid-soluble drugs. One of the major drawbacks of classical liposomes was their rapid clearance from circulation, due to adsorption of plasma proteins (opsonins) to the naked phospholipid membrane, triggering recognition and uptake of liposomes by the receptors present in themononuclear phagocytic system. A breakthrough in the field of liposomes camewith the development of sterically stabilized (stealth) liposomes, which utilize a surface coating of hydrophilic carbohydrates or polymers, usually a lipid derivative of polyethylene glycol (PEG), to help evade mononuclear phagocytic system recognition. PEG attracts a water layer to the liposome surface, thus providing hydrophilic repulsion to opsonin adsorption. Stealth liposomes are capable of passive accumulations in various pathological sites, such as solid tumors and infarcted areas, via the so-called enhanced permeability and retention effect[30,31]. This effect is based on the fact that the pathological vasculature, unlike vasculature of normal healthy tissues, is 'leaky', that is, penetrable for large molecules and even for small particles, which allows for their extravasation and accumulation in an interstitial tumor space. In addition, solid tumors have elevated interstitial pressure and impaired lymphatics that hinder the diffusion of colloidal particles such as liposomes from the tumor. Once inside the tumor interstitium, cytotoxic drugs are released fromthe liposomes in a sustainedmanner, killing the neighbouring cells.

Some of the marketed products of liposomes incorporating cancer drugs available are, Doxil, DaunoXome, LipoDox, and Myocet, and many others are in clinical trials[32]. Amphiphilic drugs that are weak bases or weak acids can also be loaded into the liposome interior using remote loading methods like the ammonium sulphate method for doxorubicin or the pH gradient method for vincristine. Doxil and its second-generation drug, LipoDox, both contain doxorubicin encapsulated within a liposome with a PEG-modified surface. Doxil has been proven effective in treating drug resistant tumors in clinical trials[33,34] . Both Doxil and LipoDox have been used successfully to treat many cancers including Kaposi's sarcoma, ovarian cancer, and metastatic breast cancer[35]. Myocet is an unpegylated liposomal doxorubicin approved for use in Canada and Europe to treat metastatic breast cancer[36]. DaunoXome, which is a pegylated liposomal daunorubicin, has been approved to treat blood tumors[32].

CONCLUSION:

Being leading cause of death and a silent killer, ovarian cancer is the leading cancer among women of developing as well as developed nations. Diagnostic test methods are available however they are sometime not reliable and misleading and resulting in ovarian cancer diagnosis at very later metastatic stage after which it is difficult to survive. The current treatment methods lacks specificity and effectiveness leading to life threatening adverse effects along with poor survival rate. Thus there is an unmet need to come up with a novel strategies to develop drug delivery carriers which can deliver right drug in a right concentration to the targeted site to improve efficacy and reduce adverse effects. Liposomes are lipidic bilayer vesicular systems which can incorporate both hydrophilic and lipophilic drugs to deliver to the cancer site. Tremendous research has been done in the area of liposomal research and their potential application in effective cancer therapy however, in vitro and in vivo correlations are yet to be proved for novel strategies to commercialise for use.

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