Conventional to Nanoscale-Based Carrier Systems in the Management of Ovarian Cancer

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Abstract

Ovarian cancer (OC) is one of the most common and dreadful cancer types which has affected the female population worldwide with an increased number of cases. Broadly, OC has been categorized into two types based on its mutational changes. These are Type 1 OC which is found to show less aggressive tumors without any mutation of the tumor protein p53 gene and Type 2 OC which exhibits tumors resulting from significant mutation of the P53 gene. The major molecular pathways and cellular targets responsible for the progression of OC include VEGF, PDGF, FGF, (PI3K)/AKT pathway, PARP, and others. The conventional therapies for the management of OC include surgery, chemotherapy, hormonal therapy, radiotherapy, monoclonal antibodies, and others. However, conventional

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therapies are restricted due to a few limitations such as unintended toxicities, relapse of the conditions, high dose, less bioavailability, and prolonged therapeutic regimen. Thus, to overcome these limitations nanotherapeutic approaches can be used for the effective delivery of drugs with superior targetability and negligible or no toxicity. In this chapter, we have discussed the major molecular pathways and cellular targets causing ovarian cancer. Also, the significant role of nanotherapeutic approaches and targeting mechanisms of encapsulated bioactive/drugs against ovarian cancer cells is summarized.

Keywords

Ovarian cancer · Cellular responses · Molecular pathways · Nanotherapy · Targeted delivery systems · Bioavailability

5.1   Introduction

The need for advancements in therapeutics is often triggered by the severity of disease and the statistics that revolve around it. Ovarian cancer (OC) is one such dreadful disease that finds itself in the list of common cancers around the globe. As per the American Institute of Cancer Research, OC is the 18th most common cancer, while being the eighth most common for women (Ferlay et al. 2019). In 2021, an estimated 21,410 cases received the diagnosis and around 13,770 lives were expected to be claimed by OC in the USA. All of these data accompanied with a delayed and limited and complicated diagnosis calls for effective treatment of the disease, which shall not only lessen hospital stay, but also prevent the recurrence of the disease. Even though patients respond to treatments initially, about 50–75% of the cases see a relapse (Das and Bast Jr. 2008; Jacobs and Menon 2004; Sarojini et al. 2012). OC can be of two types; Type 1 and Type 2. Type 1 OC houses less aggressive tumors without any mutation of the Tumor Protein p53 gene; whereas Type 2 houses tumors resulting from significant mutation of the P53 gene (Kurman and IeM 2010). OC of Serous type associated with BRCA1, BRCA2, MMR, BARDI, etc. mutations is responsible for more than half the cases. Their area of metastasis is similar(Ducie et al. 2017).

As per FIGO Committee on Gynaecologic Oncology, OC can be classified under 4 stages based on the extent of metastasis. In stage 1, the tumor growth is confined to the ovaries. In stage 2, the tumor has spread to the pelvic region. When metastasis has occurred to the organs of the peritoneal cavity such as the liver and intestine, and lymph nodes, the cancer is in stage 3. If further metastasis occurs, then it can be classified as stage 4 (Prat 2014). Epithelial carcinoma constitutes 85–90% of the cases. Such type of OC includes endometrioid, mucinous, and a few other cell growths such as Brenner; but mostly constitutes epithelial cell growths. Epithelial cell growths have two subtypes; namely high-grade serous carcinoma (HGSC), which is quite common, and the uncommon low-grade serous carcinoma (LGSC) (Chen et al. 2014).

A rare type of OC includes Ovarian Malignant Germ Cell Tumors (OMGCTS), a condition arising from the malignancy of the primitive germ cells of the embryonic gonads. Their various types include the less malignant but more common, dysgerminoma, and the more malignant teratomas, yolk sac tumors, embryonal carcinomas, and polyembryomas. The tumor markers include alpha-fetoprotein, beta-human chorionic gonadotropin, and lactic dehydrogenase, all of which may or may not be present for a tumor type (Shaaban et al. 2014).

5.1.1 Conventional Therapies Used to Combat Ovarian Cancer

5.1.1.1 Surgery

In the early stages of OC, especially in stages 1 and 2, medical practitioners turn to surgeries such as Bilateral Salpingo-Oophorectomy (BSO), which has not only reduced the chance of recurrence, but also minimized the dependence on chemotherapy. BSO is a cytoreduction surgery done to remove small tumors (less than 1 cm diameter). To increase the efficacy of the treatment, the patient may be put through a cycle of cisplatin or paclitaxel administered intravenously every 21 days for 6 cycles. Carboplatin and/or cisplatin may also be used, albeit with some side effects like neuropathy (Wang and Fang 2021; McGuire et al. 1996; Elit et al. 2007).

5.1.1.2 Chemotherapy

Cytoreductive surgeries are usually followed by a few cycles of chemotherapy as mentioned above. However, the relapse of the disease in most cases remains a major challenge. Initially, the disease is seen to progress during platinum-based medication regime; possibly due to platinum resistance or sensitivity. In later stages of the regime, usually after 6–12 months, the condition is again seen to relapse due to resistance to platinum-based therapeutics. Anticancer agents, being low molecular weight compounds, are limited by their inability to attack specific targets; i.e., the site of cancer. Moreover, such agents are required in high doses during the treatment regime; thus, chemotoxicity also becomes a major hurdle. Their low bioavailability needs to be tackled as well (Bharadwaj et al. 2021; Pignata et al. 2011; Das et al. 2020d).

5.1.1.3 Intraperitoneal Chemotherapy

OC has been observed to not metastasize beyond the abdominal cavity. This is a type of treatment where the drug is administered into the abdomen region intraperitoneally (IP). A study conducted by Gynecologic Oncology Group (GOG), a randomized controlled trial with 876 patients, showed that the mean survival for intraperitoneal therapy was 61.8 months, while the same being only 51.4 months for conventional IV therapy. Thus, IP therapy was judged to be more effective when compared to IV therapy(Tewari et al. 2015; Becker et al. 2019; Barlin et al. 2012).

5.1.1.4 Hormone Therapy

Luteinizing Hormone Releasing Hormone (LHRH) receptor agonists like goserelin and leuprolide are administered to lower the gonadotropin secretion leading to lower estradiol level, which is highly increased in cases of OC. Vaginal bleeding, osteoporosis, and vaginal dryness are common side effects of the treatment (Katchman et al. 2017). Tamoxifen, a nonspecific estrogen receptor antagonist, is often used in the treatment of stromal OC. Its anticancer activity is due to the ability to competitively inhibit the binding of estrogen to its receptor leading to a reduction in freely circulating estradiol. Tamoxifen reduces tumor growth factor α. Hot flushes and vaginal dryness are some of the major limitations of this treatment (Katchman et al. 2017). Apart from this, various aromatase inhibitors such as anastrozole, exemestane, letrozole, etc. exhibit potential effects in inhibiting the binding of Oestrogen to the growth hormone receptors of tumors. It acts by competitive inhibition of aromatase enzyme, which is responsible for conversion of androgens into estrogen, primarily in women after menopause. This treatment also has its fair share of side effects like osteoporosis and hot flushes among others (Katchman et al. 2017; Kok et al. 2019).

5.1.1.5 Radiation Therapy

This therapy involves the use of powerful electromagnetic waves like X-rays to treat malignancy. The radiation can be administered either externally; i.e., outside the body; or internally, also known as brachytherapy. In external beam radiation therapy, a linear accelerator machine emits x-ray or photon beams in a controlled manner to attack the malignant areas, while leaving the healthy cells unharmed. External beam radiation therapy can be of various types like Intensity-modulated radiation therapy (IMRT), Proton beam therapy, Image-guided radiation therapy (IGRT), and Stereotactic Radiation Therapy (SRT). Internal radiation therapy or brachytherapy, on the other hand, employs a radioactive material to target the tumor. This material is delivered using capsules, catheters, needles, or other special kinds of applicators. The therapy is permanent if the capsule or any other such delivery system containing the radioactive therapeutic agent is implanted in the affected tissues. The therapy is temporary if the fluidized form of the radioactive therapeutic agent is delivered using needles or catheters. Apart from this, some other specific types of radiation therapy are also used to mitigate OC.

Intraoperative Radiation Therapy

When vital organs are close to the tumors, surgeons make use of this therapy to deliver the radiation. This therapeutic procedure is carried out during surgical operation, where any effect due to the radiation on healthy tissues can be subsided by making way for the radiation to directly reach the affected area.

Systemic Radiation Therapy

For this therapy, the patient has to swallow a pill containing a radioactive therapeutic agent that is supposed to target the tumor tissues. The radioactive material gets excreted from the body through feces, urine, and sweat. (Rai et al. 2014).

Radioimmunotherapy

This type of therapy employs monoclonal antibodies that identify specific markers surrounding tumor tissues. IgG1 antibody, Ibritumomab, is one such therapeutic agent that has found itself useful in cases of lymphomas. It is administered in a combination with a tiuxetan, a chelator that carries a radioactive isotope like yttrium or indium. This system binds to a CD20 antigen present on malignant and normal B cells at tumor sites. The therapeutic activity occurs through two mechanisms; one, through irradiation of the tumor tissue by the beta waves emitted by the radioactive isotopes; and second, through the attachment of the antibody to the antigen to bring about antibody-dependent cell-mediated cytotoxicity. (Song and Sgouros 2011).

5.1.1.6 Monoclonal Antibodies

Following various targets present on tumor tissues and those exhibited during the physiological process of tumor progression, many monoclonal antibodies have paved the way for the effective treatment of OC. A trifunctional antibody molecule currently in Phase 2 of clinical trials, called Catumaxomab, works by targeting Epithelial Cell Adhesion Molecule (EpCAM) on cancer sites and CD3 on T cells. In doing so, it allows macrophages, dendritic cells, natural killer cells, and T cells to make their way to the cancer site that would result in tumor cell death (Das et al. 2020a). This treatment is aimed to be effective in patients who face a recurrence of cancer or in cases where their condition has become resistant to conventional platinum-based chemotherapy. This can be attributed to EpCAM-positive OC cells, which remain viable even after conventional chemotherapy (Tayama et al. 2017). CD25 is another lucrative which targets cancer for immunosuppressant monoclonal antibody in treating serous ovarian; a candidate for which is Daclizumab that suppresses T cell population; although the binding seems to be nonspecific (Santoiemma and Powell Jr. 2015).

5.2 Molecular Targets and Cellular Pathways Associated with Ovarian Cancer

Various molecular targets and pathways have been associated directly or indirectly with ovarian tumors leading to cancer. Some of the major targets have been discussed below.

5.2.1 Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF)

Several factors contribute to the progression of the tumor. Some of the prominent factors include VEGF, PDGF, and FGF. Anti-VEGF agents result in inhibition of angiogenesis at tumor sites by either blocking the receptor-mediated pathways of neutralization of VEGF. Bevacizumab is a monoclonal antibody formulation that inhibits angiogenesis by binding to VEGF and prevents it from binding to the

Table 5.1 Clinical status of a few targeted therapeutic products in ovarian cancer therapy

Drug	Molecular target	Mechanism of action	Phase of development
Aflibercept	VEGF A&B, PIGF	Binds to VEGF A&B and placental growth factor (PGF) and inhibits angiogenesis	Approved Drugs@FDA: FDA-Approved Drugs (n.d.)
Ramucirumab	VEGF receptor tyrosine kinase inhibitor	Blocks the interaction of VEGFR-2 with its ligands, VEGF-A, VEGF-C, and VEGF-D and inhibits angiogenesis	Approved FDA approves ramucirumab plus erlotinib for first-line metastatic NSCLC (n.d.)
Sunitinib	Multiple receptor tyrosine kinase (RTK)	Inhibition of multiple RTKs including PDGF-R and VEGF-R leading to inhibition of angiogenesis	Phase 2 Chan et al. (2018)
Sorafenib with bevacizumab	Multiple receptor tyrosine kinase (RTK)	Interact with multiple intracellular (CRAF, BRAF, and mutant BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß), thus inhibiting tumor cell proliferation	Phase 2 Drugs@FDA: FDA-Approved Drugs US-FDA (n.d.), Drugs@FDA: FDA-Approved Drugs US-FDA (n.d.)
Pazopanib	VEGFR-1, −2 and − 3, PDGFR-α and -β, and c-kit	Inhibition of intracellular tyrosine kinase of VEGF and PDGF receptor leading to antiangiogenesis action	Phase 3 Kasper and Hohenberger (2011); Vergote et al. (2019); Novartis Pharmaceuticals (2013)
Sirolimus, Everolimus	mTOR	Inhibits cytokine by blocking PI3K/AKT signaling pathway	Approved
Olaparib, Rucaparib	PARP	Binds to PARP enzyme and inactivates DNA repair mechanisms	Approved

receptor. Although some side effects like cardiotoxicity, hypertension, and dermatological conditions have been associated with the treatment, Bevacizumab has become a preferred addition to the conventional therapeutic regimen (Burger 2011; Amini et al. 2012). A few targeted therapeutic products that are either under clinical trial or approved are mentioned in Table 5.1.

5.2.2 (PI3K)/AKT Pathway

A signaling pathway that has a major contribution towards cancerous cell growth is the phosphatidylinositol-3-kinase (PI3K)/AKT pathway. A protein kinase in this pathway is the mTOR protein that is encoded by the mTOR gene.

Immunosuppressant cytokine inhibitor drugs like Sirolimus and Everolimus target mTOR protein and inhibit cell proliferation (Das et al. 2020b).

5.2.3   Poly (ADP-Ribose) Polymerase (PARP)

Another lucrative target for beating OC is the enzyme Poly (ADP-ribose) Polymerase (PARP). This enzyme is responsible for DNA repair; in both normal and cancerous cells. PARP detects single-strand breakage on DNA and binds to it and initiates repair by synthesizing poly-ADP ribose. This acts as a trigger for other DNA repairing enzymes like DNA Ligases. Programmed cell death is also regulated by this enzyme. PARP enzyme (PARP 1, PARP 2, etc.) inhibitors like Olaparib, Rucaparib, and Niraparib have been approved for the treatment of OC (AstraZeneca 2021; Barkat et al. 2021).

5.3   Novel Drug Delivery Systems for Treatment of Ovarian Cancer

Conventional cancer therapies come with several limitations; especially unintended toxicities, relapse of the conditions, high dose, less bioavailability, and prolonged therapeutic regimen. This not only makes the treatment inaccessible to the common public, but also increases the chance of propagation of the disease to the next generation. Thus, there is a need for innovation that makes the treatment not only economic, but also effective. Various drug delivery systems based on passive and active mechanisms, aimed to improve the Spatio-temporal response of the therapeutic system, are being continuously developed.

5.3.1   Passive Drug Delivery Systems

Sound knowledge of the physiology of the cancerous tissues helps in designing a drug delivery system that can take advantage of the existing conditions to make the therapeutic agent reach the desired location of action in appropriate amounts. The regions of cancer are characterized by irregular and uncontrolled growth of fenestrated blood vessels that result in the proliferation of the cancerous tissues by a supply of nutrients; while also resulting in hypoxia at that region (Danhier et al. 2010). There are also few angiogenic regulators present at the site that cause the endothelium to become "leaky". Matrix metalloproteinases are one such regulator whose inhibition (e.g., MMP inhibitor like Doxycycline) can form a treatment method. Moreover, the poor drainage of the lymphatic system makes the drug delivery systems like nanocarriers carrying the therapeutic moiety leak out of the fenestrated vasculatures and reach the target cancer tissue; while also staying in circulation for a longer time. This mechanism is termed enhanced permeation and retention effect and is widely employed for targeted therapy (Torchilin 2006).

The process by which passive targeting occurs is diffusion while escaping the reticuloendothelial system (RES). For diffusion to occur effectively, the nanocarriers need to have certain characteristics to remain circulating. Few of the desired characteristics include a particle size between 10 and 100 nm, a mostly hydrophilic composition, and a neutrally charged surface. Few materials that are widely used to develop nanoparticles (NPs) are poly-(vinyl alcohol) and poly-(ethylene glycol). Being immunologically inactive, PEG has been employed widely in varying molecular weights by altering PEG chain length (Tirelli et al. 2002).

Some passive drug delivery systems have exploited the potential of decorating the surface of nanocarriers with a copolymer block made using both hydrophilic and hydrophobic polymers. Hydrophilic polymers like PEG conjugated with hydrophobic polymers like Polyoxypropylene (PPO) form a PEG/PPO block copolymer. The PPO chains are bound to the nanocarrier by hydrophobic interaction and the PEG chains face the surrounding hydrophilic medium providing steric stability. The stability of the therapeutic system is an important consideration for sufficient circulation time in the body for an optimum therapeutic effect (Illum et al. 1987). A Phase 2 trial of combination therapy of carboplatin and pegylated liposomal doxorubicin yielded satisfactory results and the treatment was deemed feasible for gynaecologic sarcomas (Harter et al. 2016).

5.3.2   Active Drug Delivery System

The guiding principle behind designing site-specific targeting drug delivery systems is being able to recognize the receptors on the cancerous cells' membranes. To target these receptors, various ligands, including new generation monoclonal antibodies, can be attached to the nanocarrier. The nanocarriers after getting attached to the cells utilize uptake mechanisms like phagocytosis and endocytosis (Das et al. 2020c; Barkat et al. 2020). Nanoparticulate systems to which PEG is to be attached can be done so by attaching the PEG to polymers like poly-α-hydroxy acids (PLAs) or polylactic-co-glycolic acid (PLGA) copolymers (Milane et al. 2011). A lipidic nanocarrier like that made of distearylphosphatidylethanolamine (DSPE) can be also decorated with PEG, non-covalently; as with the case of adamantane inserted into a cyclodextrin system (Bartlett and Davis 2007; Chenjie et al. 2009). To stabilize a liposomal system, formulators often use PEG of molecular weight 2000 dalton or more. This affords a thermodynamically stable system (Garbuzenko et al. 2005).

PEG chains attached to liposomes have to be attached to a functional group like carbonyl, amide, or sulfhydryl; which can serve as active points (thus forming a bridge) where a therapeutic agent can be attached (van Vlerken et al. 2007). The attachment can take place in the presence of a linking or coupling agent like N, N'-dicyclohexylcarbodiimide or cyanuric chloride, which acts as a catalyst (Cirstoiu-Hapca et al. 2010). One of the major disadvantages of the above technique is the remains of unreacted end groups of PEG chains, those that have not been associated with any functional groups. This can lead to unsuitable interactions of the liposome

with the surrounding system; while also providing hindrances to conjugation of the therapeutic moiety or other ligands to the system (Zalipsky et al. 1997). A strategy to overcome this barrier has been to form a conjugated system consisting of Lipid-PEG-Ligand and make them attach to a preformulated nontargeting liposome. This not only positions the conjugated system outside the liposomal bilayer unlike the previous strategy where the conjugate would be trapped inside the liposome, but also allows a great deal of flexibility in designing an effective drug delivery system that has highly specific actions. Commonly used linkages include peptides, transferrin, and folate moieties (Uster et al. 1996).

These actively targeting drug delivery systems mainly target various receptors, biomarkers, and some biochemicals like proteins that are expressed during tumor proliferation for delivery of the therapeutic moiety. The Follicle Stimulating Hormone or FSH is known to activate FSH Receptor (FSHR) on the ovarian epithelium. This receptor is overexpressed in OC cells which can be targeted by the drug delivery systems (Zhang et al. 2009a). Paclitaxel-loaded NPs conjugated with a peptide derived from FSH have been developed (Zhang et al. 2009b). A tumor in its course of proliferation releases various proteins or antigens that get reflected during the evaluation of the serum of the patient. One such antigen is CA-125. This gets expressed in more than 80% of the cases of OC; which makes it an ideal target for designing therapeutic agents (Bast Jr et al. 1981; Moore and Maclaughlan 2010).

HER-2 is another receptor that is overexpressed in OC that leads to tumor proliferation and various pathways attached to it. A monoclonal antibody approved by FDA and EMA that is currently being used is Trastuzumab in the treatment of HER2-positive breast cancer, but has not proven itself effective in the treatment of epithelial OC (Wilken et al. 2010). Another biomarker expressed during cancer angiogenesis is nucleolin, which is a 31-amino acid F3 peptide. This F3 peptide is synthesized from the protein High Mobility Group (HMG) 2. F3 can bind to nucleolin protein expressed at tumor sites. Thus, it was considered as a targeting moiety; the same has been demonstrated in a study conducted by designing PEG-ylated liposomes functionalized with nucleolin targeting F3 peptide and loaded with Doxorubicin and C6-Ceramide synergistic combination and results show to be effective in generating cytotoxicity towards cancerous ovarian cells (Cruz et al. 2021).

Angiogenesis is also known to be regulated by integrins. Thus, a certain combination of amino acids sequence results in a peptide such as RGD (Arginine-Glycine-Aspartic acid) that can bind to integrin molecules (Janssen et al. 2002). The Transferrin Receptor (Tfr) is overexpressed in OC and is known to be stimulated by certain antibodies and transferrin. Thus, a drug delivery system associated with transferrin and loaded with a monoclonal antibody like R17217 and OX26 (Ulbrich et al. 2009; Béduneau et al. 2007) or Docetaxel-loaded liposomal drug delivery system modified with transferrin can target the OC sites (Yuan et al. 2014).

5.3.3 Materials for Fabrication of Nanoparticulate Drug Delivery Systems

While fabricating a nano delivery system, the materials used are particularly important for compatibility with the therapeutic agent, toxicity and biodegradability, and any adverse effects. Factors governing the feasibility of scaling up the product to the industrial level are also taken into consideration. The ultimate goal shall be to design an effective drug delivery system that possesses enhanced permeation and retention effect (EPR), an optimal dissolution profile, and a good Spatio-temporal response that delivers the drug at the particular cancerous site without causing any harm to the surrounding healthy cells.

5.3.3.1 Biodegradable Polymers Used in the Fabrication of Nanoparticles

Biodegradable polymers are preferred materials for the fabrication of NPs. They are made up of naturally occurring polymers containing amide, ester, and ether functional groups which can be broken down by the biological mechanisms in the body without the generation of toxic residues (Sivasankarapillai et al. 2021). A few examples are mentioned in Table 5.2.

5.3.4 Nanocarriers for Targeted Drug Delivery in Ovarian Cancer Therapy

Various types of nanocarriers, including metallic NPs, polymeric NPs, liposomes, solid-lipid NPs, micelles, and others, have been reported for effective management of OC. These nanocarriers due to their versatile size, shape, and surface charge assist the targeted delivery of loaded drugs/bioactive to the targeted diseases to the site rather than affecting the healthy cells or tissues, thus reducing the chances of systemic toxicity.

5.3.4.1 Nanoparticles

Various metallic elements like gold, silver, and metallic oxides, especially Iron oxide NPs, have been explored to fabricate NPs (Horák et al. 2017). Iron oxide NPs have been shown to exhibit significant cytotoxic effects. The in vitro study performed on OC cell lines found an increased level of ROS, resulting in damaging the mitochondrial membrane of cancer cells. This resulted in the caspase-mediated apoptosis in the OC PA-1 cells (Ramalingam et al. 2020). The success of such systems is attributed to the superparamagnetic characteristic of iron oxide that renders enhanced Spatio-temporal control over drug delivery (Zhi et al. 2020).

Chitosan is another biopolymer that due to its low toxicity and biocompatibility characteristics has found its way to the fabrication of NPs. Several amine and hydroxyl groups in their structure mean that they can be effective sites of associations with therapeutic moieties (Muddineti et al. 2017). NPs fabricated using chitosan and conjugated with proteins, drugs, and nucleic acids have exhibited

Table 5.2 List of some major biodegradable polymers used in the fabrication of novel drug delivery systems used in the management of ovarian cancer

Natural biodegradable polymers			
Polymers	Structure	Examples	Reference
Chitosan	Units of D-glucosamide and N-acetyl-D-glucosamide	Nanogel composed of poly (ethylene glycol)-b-poly(L-glutamic acid)-b-poly(L-phenylalanine) copolymer block incorporating cisplatin and paclitaxel; surface decorated with a folic acid ligand using PEG as a spacer.	Desale et al. (2015)
Proteins	Chains of amino acids of 20–30 residues	Albumin, collagen, gelatine Albumin NPs incorporating Albendazole	Zhang (2008) Noorani et al. (2015)
Polysaccharides	Polymeric carbohydrate molecule composed of monosaccharides	Cellulose, starch, glycogen	Varki et al. (2015)
Synthetic biodegradable polymers			
Poly (lactic-co-glycolic) acid (PLGA)	A dimer of lactic acid and glycolic acid in varying ratios results in different drug release profiles.	Lupron depot developed for prostate cancer	Astete and Sabliov (2006)
Polylactic acid (PLA)	A polyester structure obtained from the condensation of lactic acid monomers	Chitosan-coated Polylactic acid nanoparticle	Babu et al. (2014)
Polycaprolactone (PCL)	A polyester formed by polymerization of ε-caprolactone	Tumor-targeting polycaprolactone NPs with codelivery of paclitaxel and IR780 for combinational therapy of drug-resistant OC	Pan et al. (2020)
Polyhydroxyalkanoates (PHA)	A class of biopolyester consisting of various side chains and fatty acids	Poly(3-hydroxybutyrate-co-3-hydroxy valerate) or PHBV NPs loaded with paclitaxel show anti-OC activity	Vilos et al. (2013)

enhanced localization at cancerous sites and taken up by cells through endocytosis among other internalization phenomena. In a bid to explore the possibility of employing biodegradable photoresponsive NPs in the treatment of OC, chitosan and PLGA-based NPs were designed and loaded with carboplatin (CP) and the near-infrared (NIR) photosensitizer indocyanine green (ICG). The study found effective cytotoxic effects against OC cell lines when the target cells were irradiated with 800 nm laser (Sánchez-Ramírez et al. 2020).

Another nanoparticulate drug delivery system fabricated from PLGA and loaded with Cannabidiol (CBD) has been shown to significantly induce apoptosis by inducing the expression PARP. The drug-loaded nanoparticle was found to have a high encapsulation efficiency of 95% and a drug release lasting about 96 h. The internalization of the NPs into the OC cell line was found to be between 2 and 4 h. Although CBD-NPs showed a tumor growth inhibition similar to CBD in solution, the IC50 value of CBD-NPs was found to be significantly lower than that of CBD solution (Fraguas-Sánchez et al. 2020).

5.3.4.2 Liposomes

Liposomes are nanoparticulate drug delivery systems in the size range of 2 to 400 nm. They are composed of lipid materials that are easily biodegradable and generally nontoxic to the patient's body. Liposomes show high encapsulation efficiency for both hydrophilic and lipophilic pharmaceuticals while also showing Spatio-temporal control. The circulation time of liposomes is of prime importance when it comes to their efficacy. PEG-ylation is a well-explored technique to do the same. A study with PEG-ylated liposomal loaded with paclitaxel observed that the liposomal drug delivery system was able to contain the growth of OC cells both in vitro and in vivo by inducing their apoptosis by TNF-mediated ERK/AKT signaling (Alizadeh et al. 2020).

In a study involving cisplatin-resistant OC cells, Cisplatin-loaded liposomal particles functionalized to target transferrin receptors were designed. Their cell uptake in both resistant and nonresistant cells was found to be similar, but significantly better than that of free cisplatin. Cytotoxicity was related to the accumulation of platinum in both resistant and nonresistant cancer cells when treated with targeting liposomes. However, Tfr targeting was not found to have any significant advantage over nontargeting liposomes (İnce et al. 2020).

Often the idea of co-encapsulating two or more drugs in the liposome gains research attractions for their ability to synergistically act on the cancerous cells. Such a system was designed by encapsulating a topoisomerase inhibitor, Irinotecan, and a DNA transcription inhibitor through various mechanisms, Doxorubicin (in the ratio 1:1 in circulation), by the process of coordination complexation and pH gradient. The encapsulation efficiency was found to be more than 80%. This liposomal formulation was delivered in a xenograft model intraperitoneally growing a human ovarian tumor and found to have effective therapeutic potentiality (Qi et al. 2018).

5.3.4.3 Nanomicelles

Micelles are formed as self-aggregating amphiphilic structures in an aqueous medium above a certain concentration called the critical micellar concentration. Like liposomes, Nanomicelles can also be loaded with hydrophilic and hydrophobic pharmaceuticals. Nanomicelles have been shown to exhibit higher drug loading capacity than other drug delivery systems (Krieger et al. 2010; Shaikh et al. 2013). Small size and effective penetrability and endocytosis at OC sites, accompanied by their unique characteristics like in vivo stability, biocompatibility, long plasma

circulation time, and site-specific action, have made them a quite sought-after candidate for OC therapeutics (Yu et al. 2018; Fathi et al. 2018).

In a study, Paclitaxel-loaded redox-sensitive nanomicelles were designed to target OC cells. Cytotoxicity studies revealed the therapeutic potential of the system (Pantshwa et al. 2020).

Similar effective cytotoxic effects were observed for a nanomicellar system loaded with Docetaxel and functionalized to target folate receptors on OC sites (Feng et al. 2014). A nanomicellar drug delivery system designed to incorporate two synergistically acting drugs has shown promising results. The study fabricated the nanomicelles from an amphiphilic copolymer, phenylboronic acid-coated methoxy poly (ethylene glycol)- *block*-poly-((N-2-hydroxyethyl)-aspartamide). The stability of the system was attributed to an electron donor-acceptor mechanism between the polymer particles and the encapsulated drugs doxorubicin and irinotecan. The nanomicelles were found to be biocompatible, while also affording significant cytotoxicity by the production of ROS. Apart from this, various functionalized nanocarriers have been listed in Table 5.3.

5.4   Conclusion and Future Perspectives

In western countries, OC has been reported as the second most common and the most fatal gynaecologic malice. Till now, there is a deficiency of approaches suggested for screening and early diagnosis of the disease, and if left untreated then at the final-stage OC is incurable in most of the clinical cases. In respect of treatment approaches, several conventional therapies, surgical technologies, and modern therapeutic regimes, entering the preclinical/clinical stages, have led to hope for the effective treatment of OC. In recent times, researchers have been able to develop potential nanocarriers for the establishment of targeted drug delivery systems to transport therapeutic regimens into ovarian carcinogenic cells with more precision. In this review, we have highlighted the outcomes and major findings of the recent articles and clinical trials associated with OC therapy and also have highlighted the significant impact of NPs-based drug delivery systems in OC therapeutics.

Studies have shown that as compared to other routes of administration, the intraperitoneal might be more beneficial for effectively targeting the folate-receptor in OC in vivo. Moreover, the amalgamation of intraperitoneal administration and targeting of the functionalized (peptides, antibodies, and aptamers)-NPs to the tumor-specific proteins might lead to decreased systemic toxicities and also increase the drug payload within the tumors. Apart from this, certain nanomaterial-mediated biosensors, due to superior sensitivity and selectivity, have exhibited a potential role in OC diagnosis. In the future, it is very important to explore the diverse aspects of NPs-based technologies and study their effects in improved tumor targeting, drug efficiency, and toxicity profiles.

Table 5.3 Various functionalized nanocarriers for targeting chemotherapeutic agents in ovarian cancer therapy

Functionalized Nanocarriers	Examples	Major outcomes/ mechanism	Reference
Nanoparticles (metallic/ polymeric functionalized with biodegradable polymers)	Chitosan-silicon dioxide nanoparticle (SiO$_2$-CS) loaded with epigallocatechin gallate (EGCG)	Aptamer conjugation resulted in effective internalization into OC cell lines through nucleolin recognition	Mutlu-Agardan et al. (2020)
	NPs functionalized with radio-iodinated folic acid	Showed improved targeting of SCOV3 cancer cell lines when compared to free thymoquinone	Zhou et al. (2021)
Dendrimers (regularly branched spherical system able to load drugs either attached to the branches or internalized)	Cisplatin-dendrimer conjugate	33% reduction in ovarian tumor size; relative to the control group which was administered free cisplatin; at the highest tolerable dose of 6 mg/kg.	Kirkpatrick et al. (2011)
	Cisplatin-paclitaxel co-encapsulated telodendrimer micelles	Co-encapsulation was done through the introduction of carboxylic acid and cholic acid functional groups in the layers of the dendrimer. The highest in vitro antitumor activity was observed at 1:2 PTX/CDDP loading ratio. Corresponding results were observed in xenograft mouse model studies including demonstration of efficient targeted drug delivery and lesser side effects.	Cai et al. (2015)
	Folate targeted polyurea dendrimer for delivery of L-buthionine sulfoxamine (L-BSO)	Effective inhibition of glutathione (GSH) (usually responsible for chemoresistance) by the designed dendrimer while also reducing the systemic toxicity of L-BSO by targeted delivery.	Cruz et al. (2020)

(continued)

Table 5.3 (continued)

Functionalized Nanocarriers	Examples	Major outcomes/ mechanism	Reference
	Polyelectrolyte nanocapsules loaded with Lapatinib and paclitaxel	In vitro studies on multidrug-resistant OC cell lines yielded promising results for inhibition of cell growth.	Vergara et al. (2012)
Nanocapsules (a vesicular membrane-covered system having a core to load drugs while the targeting ligands or antibodies can be attached to the outer membrane)	Paclitaxel-loaded SLNs composed of trimyristin (TM) as a solid lipid core and egg phosphatidylcholine and pegylated phospholipid as stabilizers.	OVCAR-3 human OC cell line and the MCF-7 breast cancer cell line with paclitaxel-loaded SLNs yielded cytotoxicity comparable to those of a commercially available Cremophor EL-based paclitaxel formulation	Lee et al. (2007)
Solid lipid nanoparticles (SLNs) (polymeric colloidal nanoparticles composed of lipids and surfactants)	Verteporfin, a photosensitizer encapsulated nanostructured lipid carrier (NLC) for targeted photodynamic therapy	In vitro and in vivo studies demonstrated effective targeting of cancer cells while also affording a long circulation time for NLC, thus being more effective than conventionally administered free verteporfin. Laser light exposure of tumors after intravenous administration of NLC-verteporfin (8 mg·kg^{-1}) significantly inhibited tumor growth without visible toxicity; unlike free verteporfin which exhibited severe phototoxic adverse reactions	Michy et al. (2019)
	Paclitaxel-loaded solid lipid microparticles	While affording a sustained release profile in peritoneum as observed through pharmacokinetic studies on Wistar rats, the in vitro studies on SKOV-3 OC cells demonstrated strong cytotoxic activity when compared to Taxol®.	Han et al. (2019)

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