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Novel Therapeutic Trends in Prevention and Management of Ovarian Cancer

Surendra Katikala *, Ch. Varshitha, Shaik Anisa, M. Amarjothi

Swathi College of Pharmacy, Next to Nellore Toll Plaza, Venkatachalam Mandal, Nellore, A.P-524320

A B S T R A C T

The ovaries are a pair of organs in the female reproductive system. They are in the pelvis, one on each side of the uterus (the hollow, pear-shaped organ where a fetus grows). Each ovary is about the size and shape of an almond. The ovaries make eggs and female hormones (chemicals that control the way certain cells or organs work in the body). The fallopian tubes are a pair of long, slender tubes, one on each side of the uterus. Eggs pass from the ovaries, through the fallopian tubes, to the uterus. Cancer sometimes begins at the end of the fallopian tube near the ovary and spreads to the ovary. The peritoneum is the tissue that lines the abdominal wall and covers organs in the abdomen. Primary peritoneal cancer is cancer that forms in the peritoneum and has not spread there from another part of the body. Cancer sometimes begins in the peritoneum and spreads to the ovary. Ovarian cancer is most common in postmenopausal women. From 2010 to 2019, the number of new cases of ovarian cancer decreased slightly each year. There was also a slight decrease in the number of deaths from ovarian cancer each year from 2011 to 2020. Women who have a family history of ovarian cancer and/or certain inherited gene changes, such as BRCA1 or BRCA2 gene changes, have a higher risk than women who do not have a family history or who have not inherited these gene changes. For women with inherited risk, genetic counseling and genetic testing can be used to find out more about how likely they are to develop ovarian cancer. It is hard to find ovarian cancer early. Early ovarian cancer may not cause any symptoms. When symptoms do appear, ovarian cancer is often advanced. Improving the prevention and early detection of ovarian carcinomas will be a critical component of reducing morbidity and mortality from ovarian cancer. The through understanding of risk factors has limited utility in accurately predicting risk at the individual level; thus, there is a clear need for improved and validated risk prediction models that can be used to screen the general population of women which would lower the ovarian cancer risk at the community.

Keywords: Ovaries, Ovarian cancer, fallopian tubes, gene changes, ovarian carcinomas ovarian cancer risk.

A R T I C L E I N F O

***Corresponding Author**
Dr. Surendra Katikala
Professor, Department of Pharmaceutical Analysis,
Swathi College of Pharmacy,
Venkatachalam Mandal, Nellore, A.P-524320

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1. Introduction

Ovarian cancer (OC) is the presence of abnormal cells that initially grow in the ovary and then reproduce out of control, which can form a tumor malignancy when they spread into the surrounding tissues. Ovaries are made up of three types of cells, and each cell can develop into diverse types of tumors. Approximately 90% of ovarian cancers have been found to be of epithelial origin, including high-grade and low-grade serous carcinoma and clear cell,

endometrioid, and mucinous carcinoma, while 7% of OCs have been shown to be stromal types, and OCs from germ cell tumors are found only rarely. It has been found that there are frequently warning symptoms and signs for OC; however, the earliest symptoms are unclear and hard to detect due to shared gastrointestinal, genitourinary, and gynecological conditions. A number of barriers to the treatment of the disease exist. Despite the early high rates of response to initial chemotherapy and radical surgery for about 70% of patients with relapses and intermediate progression-free 12- to 18-month survival, long-term survival remains poorly understood, with a high risk of reappearance. Additionally, chemotherapeutic treatments for OC have an undesirable impact on quality of life because of their severe side effects, including fatigue, arthralgia, and neurotoxicity. Therefore, understanding the biology of heterogeneous OCs is vital for exploring the disease's mechanisms more accurately Potential therapeutic targets for the management of OC are being explored, such as intrinsic signaling pathways, angiogenesis, hormone receptors, and immunologic factors[1-5].

Targeting Numerous Signaling Pathways of Ovarian Cancer

Surgery and chemoradiotherapy are the most frequently used treatment options for ovarian cancer. However, severe side effects have been associated with chemo- and radiotherapy (RT), while the only minor therapeutic benefit from RT eventually leads to succumbing to the disease and poor survival outcomes. Hence, targeting specific signaling pathways would be a promising molecular approach to ovarian cancer therapy in terms of inhibiting tumor growth, cell invasion or migration, and metastasis. It was found that seven major signaling pathways are commonly upregulated in ovarian cancers (>50%): the PI3K/AKT/mTOR, Jak/STAT, Src, lysophosphatidic acid (LPA), NF-κB, PKCι, and Mullerian inhibitory substance receptor signaling pathways have shown high levels of mutation and/or hyperactivation strongly associated with aggressive phenotypes and advanced disease stages, leading to poor prognosis for the disease. In this section, we briefly describe some signaling pathways related to tumorigenesis and metastasis that may be potentially targetable and provide information regarding novel inhibitors currently in clinical trials.

PI3K/AKT/mTOR Pathway

Phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling is one of the most important pathways controlling cell growth, proliferation, differentiation, and survival. The pathway is regulated by multiple ligands, such as growth factors (IGF, EGF, TGF, and others), receptor tyrosine kinases (IGF-1R, FGFR, HER2, EGFR, and PDGFR), and various membrane receptors. Indeed, mutations in several components of the pathway are very common in most human cancers, including subtypes of OC. It has been shown that the aberrant expression and activation of AKT (pAKT) is strongly correlated with poor progression-free and overall survival in epithelial OC. Whole-genome sequencing analysis revealed that gene breakage frequently inactivates the tumor-suppressive ability of RB1, PTEN, NF1, and RAD51B in high-grade serous ovarian cancer, resulting in acquired chemoresistance. In particular, OC stemness (CSC), the key regulatory factor of aggressive cancer, is directly modulated by PI3K/PTEN/AKT signaling, causing CSC enrichment, CSC phenotyping maintenance, and multidrug resistance (MDR), which leads to abnormal cell proliferation and cancer metastasis through epithelial–mesenchymal transition. The well-studied mTOR inhibitors for OC include temsirolimus, ridaforolimus, and everolimus, for which phase II clinical trials have been completed.

JAK/STAT Signaling Pathway

The JAK/STAT pathway is a crucial signaling pathway that is abnormally activated in OC, and its constitutive activation is strongly related to tumor progression and poor prognosis for the disease. Hyperstimulation of this pathway has also been found in other cancers, including breast, gastric, lung, prostate, and hematopoietic malignancies. JAK/STAT pathway-mediated tumor progression is mainly due to the expression of a variety of proteins and cytokines involved in cellular proliferation, stemness and self-renewal, survival, and evasion of antitumor immunity. Studies have found that more than 50 cytokines and growth factors are responsible for this pathway initiating hematopoiesis, inflammation, and immune suppression in the tumor microenvironment. STAT is a key driver of immunosuppression through triggering the production of immune checkpoint genes (e.g., PD1, PD-L1, PD-L2, and CTLA-4), promoting radio- and/or chemoresistance and the failure of targeted immunotherapies

Wnt/β-Catenin Pathway

The interest in Wnt signaling began in 1982 and has steadily increased due to the extreme renewal, proliferation, and differentiation properties of CSCs, thus showing an important role for them in tumorigenesis and therapy resistance in many malignancies. Wnt signaling exemplifies several pathways, such as Notch–Delta, Sonic–Hedgehog, Hippo, and transforming growth factor β (TGF-β)/bone morphogenetic protein (BMP), which are directly implicated in developmental and evolutionary processes, thereby facilitating its widespread activity. Wnt signaling seems to regulate tumorigenesis in ways that are both β-catenin-dependent (canonical, primarily for cell proliferation) and β-catenin-independent (noncanonical, controlling cell polarity and movement)[6-15].

Mutations in the components of the Wnt pathway are causal factors for multiple growth-associated pathologies in cancer. A number of possible mechanisms are involved in Wnt pathway hyperactivation, including the upregulation of ligands and receptors, the downregulation of the Wnt/beta-catenin pathway inhibitors, and altered protein function, which in turn control the interaction between beta-catenin and E-cadherin or beta-catenin and TCF. These abnormalities have been noted in EOC, especially in the high-grade serous subtype. Furthermore, the involvement of several noncoding RNAs (IncRNAs, miRNAs, and circRNAs) in regulating beta-catenin signaling in EOC has recently been demonstrated. Wnt signals regulate the cell

cycle at several points. In endometrial and mucinous subtypes of EOC, mutations have been observed in, for example, the CTNNB1, AXIN, and APC genes. The crucial role of the Wnt pathway in OC development, progression, angiogenesis, metastasis, and chemoresistance is supported by its strong CSC (cancer stem cell) self-renewal, EMT (epithelial–mesenchymal transition), and invasion capabilities and tumor immunity suppression. Apart from tumorigenesis, there is a direct impact of the Wnt signaling pathway on immune responses. Recently, several cancer-specific inhibitors of this signaling pathway have been identified, including WNT974, which increases antitumor immunity in ovarian cancer. Thus, β-catenin may be a promising therapeutic target in chemoresistance subtypes of EOC with CSCs.

Apoptotic Signaling Pathway'

Apoptosis is a characteristic and orderly energy-mediated biochemical cellular suicide process that maintains homeostatic equilibrium between the proportion of cell death and cell formation in multicellular creatures. It is well evidenced that apoptosis induction acts as a hallmark barricade to cancer development. The B-cell lymphoma-2 (BCL-2) family and inhibitors of apoptotic proteins (IAPs) are the predominant components of intrinsic apoptotic pathway induction through caspase activation, which regulates mitochondrial membrane permeabilization through apoptotic switching. Alternatively, the extrinsic apoptotic pathway triggers tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) to the cell surface receptor signaling cascade. Several studies imply that both signaling cascades may be activated simultaneously to induce apoptosis in human ovarian cancer. In particular, it has been proposed that apoptosis induction is broadly mediated by caspase-3 pathway activation, which has been established by increased sensitivity to paclitaxel using adenoviral type 5 E1A in human HER-2/neu-overexpressing ovarian cancer SKOV3.ip1 cells[16-22].

Enzastaurin (LY317615.HCl), a radiosensitizing, ATP-competitive, discriminating protein kinase C beta (PKC-beta) inhibitor, is an alternative drug that inhibits tumor cell growth through the upregulation of caspase-3 and caspase-9′s proapoptotic activity. Among different analyses, a combination treatment with enzastaurin and pemetrexed was shown to cause apoptosis induction in chemotherapy-resistant ovarian cancer HEY cells, controlling phosphorylated GSK3β and inhibiting mitogen-activated protein kinase ERK-1/2 (extracellular signal-regulated kinase)-mediated cell growth. In addition, a current study reveals that metformin induces an apoptotic pathway in OVCAR-3 and OVCAR-4 cell lines in an AMP-activated protein kinase (AMPK)-independent manner, resulting in S- and G2/M-phase cell cycle arrest. Metformin may also induce apoptosis by downregulating Bcl-2 and Bcl-xL protein expression and caspase 3/7 activation, and augmenting Bax and Bad expression in human OVCAR-3 and OVCAR-4 cell lines. Furthermore, metformin-induced apoptosis is augmented by the addition of cisplatin without modulating the appearance of Bcl-2 proteins in the OVCAR-3 cell line, although BcL-2 was expressed in the OVCAR-4 cell line.

Resveratrol, a small polyphenol compound, increases apoptosis induction by activating it in an AMPK-dependent manner, and activates caspase 3, which leads to the inhibited expression and activation of mTOR, a downstream signaling target of AMPK, in ovarian cancer cells. Moreover, TRAIL has been reported as an alternative therapeutic target for ovarian cancer management, although the targeted restriction of tyrosine kinase family proteins (PYK2 and FAK) and BCL-XL works synergistically and increases apoptosis in human ovarian carcinoma cell lines. The study revealed that the mitochondrial division inhibitor-1 (mdivi-1) increases the sensitivity of ovarian cancer cells to cell surface ligands such as FAS, TRAIL, and TNF-alpha. A recent study demonstrated that berberine (BBR), a potent anticancer drug, combined with cisplatin (DDP) enhanced apoptosis by inhibiting PCNA and Ki67 expression and upregulating caspase-3, caspase-8, RIPK3, and MLKL expression and activation in the OVCAR-3 and POCCL ovarian cancer cell lines.

Autophagy Modulation in Ovarian Cancer Management

Autophagy is a self-digestion process that assists in maintaining cellular homeostasis by recycling unwanted or damaged toxic cellular organelles in cells. The modulation of autophagy has been implicated in regulating several cancers. It has been suggested that autophagy is an important function in ovarian cancer via the expression of autophagy-related proteins, which comprise the microtubule-associated proteins light chain (LC-3), beclin-1, and p53. Beclin-1 is a tumor-suppressor protein that has an essential checkpoint role in apoptosis and autophagy in tumor cells. Beclin-1 expression has been found to be downregulated in ovarian cancers compared to benign lesions, suggesting the predictive potential of the beclin-1 protein in OC. Furthermore, the cytoplasmic localization of p53 mutants has been shown to prevent autophagy.

Aplasia Ras homolog member I (ARH1), another protein, has been found to be upregulated in autophagy via the mTOR-dependent pathway, which activates autophagy-mediated dormancy. In approximately 70% of cases of ovarian cancer, PI3K/AKT/mTOR pathways have been shown to be constitutively triggered by autophagy, which has been considered to be a therapeutic target of ovarian cancer. It was reported that a specific PI3K inhibitor, LY294002, given as treatment for ovarian cancer in an established mouse model, prevented ovarian cancer cell proliferation. Additionally, the cellular cytotoxic effects of novel chemotherapeutic agents were shown to be efficiently improved through cotreatment with a noncompetitive AKT inhibitor, TAS-117, in in vivo models of ovarian cancer.

Novel Treatment Strategies for Epithelial Ovarian Cancer (EOC): The identification of novel therapeutic targets has been linked to better prognosis in ovarian cancer (OC). Advancements in the understanding of ovarian cancer

biology have resulted in the development of numerous molecular targets, including growth factor receptors, cell cycle regulators, signal transduction pathways, and angiogenic mechanisms. The molecularly targeted agents possess higher selectivity and lower toxicity than conventional chemotherapy.

Therapeutic Approaches and Targets in Ovarian Cancer

Given the enormous number of potential epithelial ovarian cancer treatments, it is useful to review the pathobiology of the disease to find relevant targets. The drug targets telomerase, HER2, AKT EGF-R, VEGF-R, and p53 are currently being studied in clinical trials.

Angiogenesis and VEGF Signaling Pathway

Angiogenesis is the process of forming new blood vessels, which enables nutrients and oxygen to enter the surrounding tissues, thus promoting tumor cell proliferation, invasion, and metastasis. The growth of blood vessels or new capillaries starts with vasodilation, increased vascular permeability, stromal disintegration, and endothelial cell proliferation and migration. Researchers have discovered that receptor tyrosine kinases (RTKs), VEGF and its receptor (VEGFR), and Flk-1/KDR RTK play key roles in pathological angiogenesis, particularly tumor neovascularization. An immediate impact on tumor growth is observed (slowdown or stoppage) when the VEGF signaling pathway is blocked or inhibited.

Bevacizumab is an anti-VEGF antibody and the most studied VEGF-targeting therapy for ovarian cancer. The best response of the drug has been found in recurrent ovarian cancer, and it can be administered alone or with chemotherapy. Current ovarian cancer clinical trials with bevacizumab show promising results (PFS) in two major first-line studies, ICON7 and GOG 218. Along with carboplatin/paclitaxel, the GOG study uses bevacizumab as part of a triplet to treat patients with minimal cytoreduction of ovarian cancer. Other potential VEGF-targeting medicines, including soluble decoy VEGF receptors such as aflibercept and VEGF kinase inhibitors such sunitinib (SU11248, Sutent, Pfizer), have shown significant treatment benefit in EOC patients.

ErbB Family Kinases

The EGF family of RTKs, also known as ErbB or HER receptors, has been widely investigated in pharmacological research targeting human cancer. Numerous hypotheses have been suggested for HER2-mediated cell transformation through multiple mechanisms, such as EGFR and ErbB-3 interaction, which exhibit tyrosine phosphorylation and the activation of a cytoplasmic signaling pathway, while ErbB1 and ErbB2 homodimers transform fibroblasts using differential signaling. Trastuzumab (Herceptin), a targeted monoclonal antibody for ErbB2, is approved for treating ErbB2 1 breast cancer. According to the GOC study, trastuzumab had limited action in ovarian cancer. A partial but long-lasting response was observed when combination therapy with trastuzumab–pertuzumab was used in a young woman with high-grade serous ovarian cancer (FIGO stage IV). Furthermore, a number of EGF-R targeting agents are currently in clinical trials while some agents have shown exciting antitumor performance in CRC-based xenograft models and cell lines, such as cabozantinib, and are awaiting clinical trials.

Ansamycins and HSP90 Degradation[23-29]

Benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin (17-AAG) is an early described tyrosine kinase inhibitor that interacts with HSP90, leading to the proteasomal degradation of Hsp90-targeted proteins

Many biological functions of 17-AAG are common with those of its parent compound geldanamycin (GA), including the ability to inhibit the growth of tumor cells. It has been shown that Hsp90 originating from tumor cells has a 100-fold higher affinity to bind with 17-AAG than Hsp90 from normal cells, and also a strong affinity for oncogenic signaling proteins such as HER-2/ErbB2, Akt, Raf-1, mutated p53, and Bcr-Abl, emphasizing it as an attractive candidate for new treatment options in OC. For example, ErbB2 appears to be a potential target, because high ErbB2-expressing cells are more susceptible to ansamycin-induced growth inhibition at minimal doses. Surprisingly, this effect seems to be linked to ErbB3- and PI3K/AKT-dependent pathways. Ansamycins are known to have a strong affinity for the AKT protein. For AKT to remain stable, HSP90 needs to be linked to it, and the addition of HSP90 inhibitors results in a gradual decrease in AKT function. Thus, the PI3K–AKT signaling pathway is highly active in the progression of OC, and combination therapy of 17-AAG with cisplatin or taxol may enhance cell apoptosis via the inhibition of PI3K/Akt signaling. In addition, the combination of olaparib and 17-AAG may increase drug sensitivity in HR-proficient EOC and reverse multidrug resistance, suggesting the rational use of 17-AAG in ovarian cancer.

26S Proteosome Inhibition with PS341 (Bortezomib)

The activity of the proteasome directly represents a promising therapeutic strategy for cancer. PS341 (bortezomib), a dipeptide boronic acid derivative, prevents protein degradation by the reversible inhibition of the 20S proteasome. Cyclins (CDKs) and IkB proteins, which are corepressors of nuclear factor-kappa B (NF-κB) activation, seem to be the prospective targets. The inhibition of IkB degradation reduces NF-κB transcription factor activity.

Tubulin-Targeting Molecules

Anticancer drugs, including taxanes and vinca alkaloids, which are directed against microtubules, have long been used as first-line drugs for breast cancer and a wide range of other cancers, including ovarian, prostate, head and neck, and lung cancers. Polyglutamated paclitaxel (CT2103), a cytotoxic agent, was found to have fewer side effects and better treatment responses than paclitaxel in phase III clinical trials. Compared to the original paclitaxel, this new formulation has a decreased risk of hypersensitive side effects and can be administered more quickly.

Ovarian Cancer-Specific Targets: MUC16/CA125

For more than two decades since its discovery, CA125 antigen has been permitted for clinical use for the OC screening of high-risk women in the US. Later, it was suggested as a predictive marker in preinvasive OC. Although it has limited sensitivity and specificity, the CA125 antigen is strongly related to epithelial OC.

Drug-Delivery System for Ovarian Cancer Treatment

Treating OC using traditional chemotherapy has serious limitations, including the rapid clearance of drugs, undesirable biodistribution, and adverse side effects. To minimize these limitations, researchers have focused on a variety of drug delivery systems (DDSs) with which to encapsulate anticancer agents so they can directly reach tumor cells. Many types of DDSs have been developed, such as liposomes, drug conjugates, microspheres, micelles, nanoparticles, implants, and injection depots.

In 1996, researchers published the first report on biodegradable and biocompatible nanoparticle compositions using poly(lactic-co-glycolic) acid. Various improvements and adjustments have been made to the material, and nanoparticle synthesis processes have been continually updated. Recently, there has been growing interest in employing naturally existing protein cages, such as viral particles, as drug carriers, while the majority of research has focused on designing nanoparticles for delivering chemotherapeutic agents such as cisplatin, doxorubicin, and paclitaxel as an advanced therapeutic option for OC. The polymers most widely used in drug delivery systems include polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), poly(γ-glutamylglutamine), polyethylene oxide, modified poly -ε-caprolactone (PCL), and polypropylenimine (PPI).

Single-Agent Delivery Systems

To enhance the efficacy of cancer treatment, a minimum of one chemotherapeutic agent is encapsulated or embedded into nanoparticles. The drug cisplatin is widely used as first-line therapy for ovarian cancer, but it has a dose restriction due to its nephrotoxicity. Therefore, researchers have made efforts to improve the distribution of cisplatin and reduce kidney damage by using surface modification and nanoparticle engineering techniques. Polyisobutylene-maleic acid (PIMA) linked to glucosamine (GA) was used to generate cisplatin nanoparticles by forming platinum (Pt) complexes toward each monomeric unit at various polymer-to-Pt ratios.

The chemotherapeutic agent paclitaxel is widely used in combination with a therapeutic drug carrier, but the small molecule is hydrophobic in nature (DrugBank, DB01229). To overcome the obstacle of its low aqueous solubility, the clinical dosage is used with absolute ethanol, making a combination called Cremophor EL, which is physiologically and pharmacologically potent; however, it has been shown to cause severe acute hypersensitivity. ABI-007 (Abraxane®), an alternative to Cremophor EL, was later developed to improve the solubility of paclitaxel, and an albumin-bound paclitaxel nanomaterial was approved by the FDA for treating different types of cancers.

Co-Delivery Nanoparticles

To achieve superior efficacy, particularly in chemotherapy, and minimize the toxicity of single-drug therapy, nanodrug co-delivery systems (NDCDSs) have been developed, using combinations of at least two anticancer drugs with different physicochemical and pharmacological properties. It is possible to incorporate drugs, antibodies, and siRNA into the nanoparticles, facilitating the administration of numerous drugs in a single dose. For example, paclitaxel and ceramide were co-delivered utilizing PEO-PCL nanoparticles. Ceramide buildup within cancer cells induces apoptosis and enhances the effectiveness of chemotherapy. However, ceramide cannot be administered to the systemic circulation due to its hydrophobicity, limited cell permeability, and metabolic inactivity. Therefore, biocompatible and biodegradable nanoparticles with paclitaxel and ceramide co-delivery were developed for effective ovarian cancer treatment[30-38].

2. Ovarian Cancer Treatments

Current first-line treatment regimen for OC patients comprises complete debulking surgery. The reductive tumor procedure includes hysterectomy, omentectomy, and other affected tissues possible to remove. The goal of surgery is to reduce tumor burden and minimize residual disease, which is inversely proportional to survival. Indeed, residual lesions smaller than 2 cm have been associated with better survival than bigger ones. At the same time, debulking surgery allows to precisely establish the histologic subtype of the disease and, therefore, it is very important for diagnosis. Even though surgery is the basis for OC treatment, it is rarely curative alone for patients with advanced disease and it needs to be combined with chemotherapy.

In late 1990s, two phase III clinical trials combined cisplatin (CDDP) with paclitaxel (PTX) as adjuvant treatment for advanced stage OC. Ever since, the combination of taxane and platinum derivatives, like CDDP and carboplatin (CBT), has been used as a standard therapeutic approach for OC patients, leading to response rate, and complete clinical remission of 60–80%. Nevertheless, the majority of these patients will ultimately relapse with a median progression-free survival of 18 months. Usually, response rates to second-line chemotherapy are proportional to treatment-free interval. Different combinations of chemotherapeutics have been tested to overcome chemoresistance following first-line paclitaxel-platinum treatment, but clinical responses are short-lived and led to only minor survival improvements for patients with chemoresistant tumors. So far, radiation therapy (RT) has played a minor role in ovarian cancer. Abdominopelvic RT was associated with serious side effects and poor therapeutic efficacy for most of the patients. Acute toxicity was most commonly due to cramps, diarrhea, nausea, vomiting and more severe myelosuppression, whereas long-term toxicity was associated with bowel obstruction.

The better understanding of tumor biology and chemoresistance over the past years supported the development of molecular targeted therapies, improving survival and increasing the quality of life in OC patients. Many different inhibitors, such as tyrosine kinase inhibitors (30) and monoclonal antibodies (mAbs) targeting multiple crucial cancer pathways, including angiogenesis, cell

survival, cell growth, metastasis formation and DNA repair, are currently tested in clinical trials. The most promising investigational agents include vascular endothelial growth factor (VEGF)-specific inhibitors and poly (ADP-ribose) polymerase inhibitors (PARPi). Bevacizumab (Avastin®, Genentech, Inc.), a recombinant humanized mAb against VEGF, blocks angiogenesis, enhancing the efficacy of standard therapy. In 2004, Bevacizumab has been clinically approved in the U.S. as the first angiogenesis inhibitor for colon cancer. In 2018, based on phase III GOG-0218 clinical study (NCT00262847), the FDA approved its use in combination with CBT and PTX, followed by single-agent bevacizumab for the treatment of patients with advanced (stage III or IV) ovarian epithelial, primary peritoneal or fallopian tube cancer after initial surgery. PARP enzymes are involved in different cellular functions, including DNA single-strand break (SSB) repair through base-excision repair by PARP1. The first PARPi approved in the clinic was Olaparib (AZD2281, Ku-0059436 trade name Lynparza), an orally administered drug. In 2014, based on phase III SOLO-2 (NCT01874353) and phase II Study 19 (NCT00753545) clinical trials, Olaparib obtained an accelerated FDA approval as maintenance treatment for patients with a recurrent ovarian epithelial, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. In the same year, based on phase II Study 19 and phase II Study 42 (NCT01078662), the EMA authorized Olaparib as maintenance treatment for patients with platinum-sensitive, relapsed BRCA-mutated (germline or somatic) HGSC, who responded to the last platinum-based chemotherapy. Other types of tumorigenic pathway inhibitors targeting PI3K/AKT, mTOR, Src, and FRα are still in the early phase of development.

Early Detection

As discussed in Chapter 1, one of the chief causes of the significant morbidity and mortality from ovarian cancer is the late stage at which most women are diagnosed, which is partly due to the lack of clear and unique ovarian cancer–specific symptoms. Because of this absence of specific symptoms, researchers have investigated other strategies for early ovarian cancer detection, such as assaying for one or more biomarkers, often in combination with imaging technologies. While the use of these strategies in large screening trials has resulted in more women being diagnosed with ovarian cancer at earlier stages, to date these strategies have not reduced overall mortality. Furthermore, because some ovarian carcinoma subtypes originate away from the ovaries, it is difficult to know where to look to detect the earliest lesions associated with ovarian cancer. Because this is an issue specific to ovarian cancer, it is difficult to draw on early detection methods from other heterogeneous cancers[39-44]. Thus developing effective and reliable early detection strategies for ovarian cancer will require ongoing research aimed at better understanding the early molecular and genetic events associated with the carcinogenesis of each subtype of ovarian cancer, along with better assessment of disease-specific symptoms.

Biomarkers

A biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Although the most commonly used biomarkers in clinical care are proteins, the definition includes a broad spectrum of biochemical substances, including nucleic acids (e.g., DNA and various types of RNA), lipids, small metabolites, and even whole cells. Biomarkers are used throughout the cancer care continuum. Predictive biomarkers are used in risk assessment and to measure the biological response to an intervention, and prognostic biomarkers are used to describe outcomes such as progression-free or overall survival. In research on ovarian cancer, the most extensively studied and frequently used biomarkers are two proteins, cancer antigen 125 (CA-125) and human epididymis protein 4 (HE-4). The following sections discuss how these and other biomarkers have affected our understanding of ovarian cancer risk and describe these biomarkers' utility in screening and early detection.

CA-125

CA-125 gained prominence following a study that identified an antibody against CA-125 that reacted predominantly with malignant ovarian tissue (Bast et al., 1981). Nearly 80 percent of women with an advanced (Stage III or IV) ovarian carcinoma have elevated CA-125 serum levels at diagnosis.

The biology behind CA-125's apparent association with ovarian cancer risk and prognosis is currently unclear. Laboratory research suggests that CA-125 may play roles in metastasis to the peritoneal cavity and in promoting chemoresistance to several drugs that are used in standard ovarian cancer chemotherapy protocols, but these findings have not been replicated clinically. For early detection, CA-125 is a predictive tool that becomes increasingly powerful with proximity to diagnosis and may signal the presence of precursor lesions.

(Jacobs et al., 1999). Using trends in CA-125 levels to select women for imaging may improve its screening performance (Karlan et al., 2014). This strategy is currently being tested in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Several algorithms developed over the past decade can help predict the presence of ovarian cancer in women with a pelvic mass so that they may be triaged to appropriate specialists (i.e., gynecologic oncologists). The majority of these algorithms have incorporated CA-125 along with other biomarkers or diagnostic indicators.

HE-4

A 1999 study looking for genes that are significantly over expressed in ovarian tumors when compared with normal ovarian tissue singled out WFDC2, which encodes the HE-4 protein, as a potential diagnostic marker for ovarian cancer

Other Ovarian Cancer Biomarkers

As described in Chapter 2, microRNAs (miR) appear to play a role in several biological processes related to ovarian

cancer. A number of microRNAs are expressed at either a higher or lower level in ovarian cancer tissue than in normal ovarian surface epithelium, and they also differ in their levels of expression among the various ovarian cancer subtypes.

Advances in protein and nucleic acid analysis technologies such as microfluidic chips, nuclear magnetic resonance, and other high-throughput platforms make possible the analysis of small amounts of patient-derived samples for numerous potential biomarkers. The ovarian cancer sample sources that are currently investigated include tumor cells in ascites (i.e., fluid that accumulates in the peritoneal cavity after metastasis), circulating tumor cells in the blood, and exosomes (i.e., small membrane-bound vesicles secreted by cancer cells into bodily fluids).

Biomarker Tests

FDA-approved protein tumor markers include ROMA (HE-4 and CA-125), OVA-1 (measures levels of apolipoprotein A1, beta 2 microglobulin, CA-125, prealbumin, and transferrin), HE-4, and CA-125 (Fung, 2010; Moore et al., 2010; Moss et al., 2005; Muller, 2010; Wu et al., 2012). Although a great deal of research is being carried out on identifying and developing new biomarkers for ovarian cancer, scientists often find it difficult to navigate the analytical, diagnostic, and regulatory requirements for a clinical assay (Fuzery et al., 2013). Currently, none of the FDA-approved protein tumor markers are approved as screening tests for ovarian cancer.

Imaging Technologies for Early Detection

Imaging technologies help measure the size of tumors and the extent to which they have spread after the masses have been detected during a clinical examination, and these same technologies may have a role to play in earlier detection of ovarian cancer. Most of these technologies are noninvasive or minimally invasive and may be performed in the outpatient setting using no anesthesia or only local anesthesia. The most common imaging technologies used for ovarian cancer are ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Modifications to these technologies that incorporate radiologic markers or sound waves have improved image quality and resolution, and some newer techniques may enable up-close visualization of tumor growth in the fallopian tubes and on the ovary surfaces[45-55].

Transvaginal Ultrasound

TVU (also known as transvaginal sonography) is the most widely used imaging technique for the examination of pelvic organs (Manegold-Brauer et al., 2014). TVU is used primarily to evaluate gynecologic symptoms and pathologies, including pain or pressure in the pelvic region, irregular bleeding, fibroids, and adnexal masses (e.g., ovarian cysts, ectopic pregnancies, and tumors near the uterus). While TVU can identify most adnexal masses, the majority of these masses are benign, and TVU is limited in its ability to differentiate between malignant tumors and benign tumors. Overall, TVU has not yet shown value as a primary screening tool for ovarian cancer, but it may be useful with specific populations (e.g., women at high risk) or in conjunction with biomarkers for ovarian cancer screening.

Doppler and contrast-enhanced ultrasound techniques have been added to routine TVU to provide information on tissue vascularity and angiogenesis in an effort to improve the ability to differentiate between benign and malignant masses. However, studies using Doppler imaging with TVU for ovarian cancer screening have revealed a wide range of specificities and a lower sensitivity than TVU alone (Kinkel et al., 2000). The use of non-targeted and targeted micro bubbles to distinguish benign from malignant ovarian lesions is still in the investigational stage.

Magnetic Resonance Imaging

MRI is commonly used for a number of diseases and disorders, and it may be useful for the diagnosis and staging of adnexal masses (Manegold-Brauer et al., 2014). One meta-analysis found a 91.9 percent sensitivity and 88.4 percent specificity for classifying adnexal masses as malignant. These values are similar to the sensitivity (96.0 percent) and specificity (90.0 percent) of TVU for classifying adnexal masses as malignant.

3. Computed Tomography

While CT scanning is commonly used in the management of ovarian cancer, it is primarily used as a staging tool. However, the early stages of ovarian cancer development may be readily missed by CT alone as its ability to distinguish benign from malignant masses is lower that that of MRI.

^{18}F-fluoro-deoxyglucose Positron Emission Tomography (^{18}F-FDG-PET)

An improved understanding of the role of glucose metabolism in tumor development has led to the use of glucose-based positron emission tomography (18F-FDG-PET) for tumor imaging. While basic functional imaging techniques such as PET can detect actively growing masses, distinguishing between benign and malignant lesions is better done with 18F-FDG-PET combined with CT scanning (18F-FDG-PET/CT) (Manegold-Brauer et al., 2014; Yamamoto et al., 2008). Only a few studies have examined the usefulness of this technique for ovarian cancer screening, and early results indicate there is a high likelihood of missing borderline and low-grade tumors when using ^{18}F-FDG-PET/CT.

Challenges to early detection of ovarian cancer

Because of the marked heterogeneity of ovarian carcinomas, it is likely that no single tumor biomarker will be sufficient to aid in the early detection of all the histologic subtypes. Research shows, for instance, that the distinct carcinoma subtypes express different sets of post-translationally modified proteins and microRNAs . There are also questions concerning the timing and type of patient samples that will need to be collected in clinical studies, although one screening trial suggests that serial biomarker measurements have better predictive power than single-time-point sampling (see detailed discussion in next

section). It is becoming clearer that a more individualized approach to measuring CA-125 may be needed rather than having a single threshold for all women. This individualized approach could include longitudinal biomarker, genetics, and epidemiologic results in order to more accurately assess the risk for ovarian cancer. Another outstanding challenge is determining which marker or combination of markers meets the sensitivity and specificity requirements for early detection of a rare and heterogeneous disease. The difficulties of performing such validation studies are exacerbated by the low incidence of ovarian cancer, especially when separating out the different subtypes.

Prevention Strategies

Most medical strategies designed to prevent the occurrence of ovarian cancer are structured around modulating female hormone cycles and the surgical removal or modification of gynecological tract components, including the fallopian tubes (salpingectomy), ovaries (oophorectomy), and uterus (hysterectomy).

Bilateral Salpingo-Oophorectomy (BSO)

BSO, also known as risk-reducing salpingo-oophorectomy (RRSO), is the surgical removal of the fallopian tubes and ovaries, which dramatically reduces the risk of ovarian cancer in women at average risk and high risk due to inherited genetic susceptibility. The USPSTF and SGO advocate RRSO for women at high genetic risk, but it may also be effective for women at average or unknown genetic risk[56].

The GOG-0199 study, also known as the National Ovarian Cancer Prevention and Early Detection Study, a number of factors linked to a higher risk of ovarian cancer were found during RRSO, including being postmenopausal or having mutated BRCA1 or BRCA2 genes, abnormal CA-125 test results, and abnormal transvaginal ultrasound (TVU) results. However, the risk reduction achieved with RRSO is not 100 percent, and the procedure is not without inherent risks and side effects, including early menopause, osteoporosis, cardiovascular disease, and increased overall mortality. As such, no formal body has recommended RRSO for the primary prevention of ovarian cancer for the general population.

Bilateral Salpingectomy with Ovarian Retention (BSOR): To avoid the long-term complications associated with removing the ovaries, BSOR, a surgical procedure that removes the fallopian tubes but leaves the ovaries intact, may prove to be a valuable option for women at risk for developing ovarian cancer. There is a growing evidence base suggesting that the various ovarian carcinoma subtypes have different sites of origins. However, the proportion of ovarian cancers that originate from sites outside the ovaries is unknown, and therefore the effectiveness of BSOR in preventing ovarian cancer is uncertain and may differ by subtype. For example, BSOR may be most effective in preventing the ovarian carcinoma subtypes postulated to arise in the fallopian tubes. Furthermore, BSOR can prevent retrograde menstruation of endometrial tissue, which is thought to be the origin and cause of endometriosis.

BSOR might allow high-risk women to delay removal of ovaries until the procedure is desired or warranted. For average-risk women, BSOR at the time of a planned hysterectomy may be a prevention opportunity. Until recently, salpingectomy was typically not performed as part of a standard hysterectomy unless the ovaries were also being removed. Data suggest that a salpingectomy at the time of hysterectomy is feasible, safe, and does not affect short-term ovarian function.

Tubal Ligation

Tubal ligation, a surgical procedure in which the fallopian tubes are tied or blocked in such a way that eggs released from the ovary cannot reach the uterus, reduces the risk for ovarian cancer in both high-genetic-risk and average-genetic-risk populations (Rice et al., 2012). One meta-analysis found that the risk for ovarian cancer for women who underwent tubal ligation dropped by 33 percent compared with women who did not undergo surgery.

Hysterectomy

A hysterectomy may prevent ovarian cancer by limiting the ability of endometriotic tissue to access the fallopian tubes and the ovaries through retrograde menstruation, thereby stopping the associated inflammation and protumorigenic environment. Thus, a hysterectomy may prevent the development of certain types of ovarian cancer, but no formal body has recommended hysterectomy as a prevention strategy[57-59].

Prescription Medications

One of the primary alternatives to surgical intervention for the prevention of ovarian cancer is use of hormone-modulating prescription drugs such as OCs.

4. Conclusion

Ovarian cancer is a deadly gynecological illness that affects women worldwide. Due to a lack of precise diagnostic biomarkers, the majority of women with ovarian cancer are diagnosed at an advanced stage, which reduces their chances of survival. Chemotherapy resistance in late-stage ovarian cancer is a significant clinical challenge, because various signaling pathways are involved in the pathophysiology of chemotherapy resistance. In order to address this, the focus is on developing biomarkers and diagnostic tools that can help with the early detection and prediction of the disease. It is hard to determine the molecular changes occurring in ovarian cancer, which is very important for choosing the right therapeutic drugs, the success of which can improve clinical outcomes. Thus, it is critical to understand the biology of this heterogeneous disease in order to conduct more precise investigations into its mechanisms. Advancements in our understanding of ovarian cancer biology has resulted in the identification of a variety of molecular targets, including signal transduction pathways, growth factor receptors, angiogenic processes, and cell cycle regulators, as well as drug delivery systems. In addition, advances in therapeutic technology have allowed significant insight into the molecular complexity, creating opportunities for diagnosis and prognosis to inform new therapeutic efforts which have the potential to

significantly improve the overall survival rate and quality of life of patients with ovarian cancer.

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