INTRODUCTION TO OVARIAN CANCER

Although ovarian cancer is highly responsive to therapy, it is still the most lethal gynecological malignancy, having a higher mortality rate than uterine corpus, cervix or vulvar carcinoma. In 2016, approximately 22,280 new cases were diagnosed, while an estimated 14,240 deaths resulted in part from chemoresistance and metastatic spread [1]. Even though the incidence and mortality have steadily decreased since the 1980s, the overall 5-year survival rate is less than 40%, which suggests that more research into early detection and treatment is essential [1]. Chemoresistance development and the persistence of quiescent cancer cells are characteristics of ovarian cancer that present major clinical and therapeutic challenges impeding cure.
Disease Etiology and Risk Factors

Even though the ovaries are influential organs that actively secrete hormones in pre-menopausal females, the majority of women diagnosed with malignancy are post-menopausal, suggesting the involvement of other factors in disease etiology [2]. For the majority, ovarian cancer presents itself as an idiopathic, heterogeneous disease. The most common subtype is epithelial ovarian carcinoma which accounts for approximately 90% of all diagnosed ovarian cancers [3]. Other subtypes of epithelial ovarian carcinoma include serous (42% incidence), mucinous (12% incidence), endometrioid (15% incidence), clear cell carcinoma (6% incidence), and undifferentiated carcinoma (17% incidence) [3,4]. Serous adenocarcinoma is further divided into high-grade and low-grade serous carcinoma, which harbors differences among molecular characteristics and therapeutic responses [2]. All subtypes of ovarian cancer are usually classifiable by their molecular signatures detected after histological staining of tumor sections [2].

As previously indicated, most epithelial ovarian cancer occurs in post-menopausal women in the 5th and 6th decade of life, although, germline ovarian cancers and those triggered by inherited BRCA mutations can occur earlier, sometimes as early as the 2nd decade of life [6]. Symptoms are largely non-specific, such as abdominal pain and swelling, bloating, earlier than normal satiety, and changes in urination [1]. Due to the similarity of symptoms with irritable bowel disease, they are often not considered as being indicative of a serious condition, especially given the rarity of ovarian cancer occurring among the general population. This, coupled with a dearth of early detection methods employed during routine gynecological exams, helps explain why malignancy is not typically detected during early stages.

Although there are no definitive causative agents for ovarian cancer, risk factors include obesity, tobacco use, exposure to asbestos, genital use of talc-based body powder, null parity, late-onset menopause, early menarche, familial history, BRCA1/BRCA2 defects and various mutations in apoptosis or cell cycle regulator genes [3]. Mutations confer certain molecular characteristics to ovarian cancer cells and are crucial aspects to consider during therapy, especially during the use of targeted inhibitors. Interestingly, the BRCA1 and BRCA2 genes, both discovered in the early 1990s, play a significant role, not only as risk factors for breast and ovarian cancer, but also as markers for therapeutic outcomes [7,8]. For example, BRCA-mutated patients show better prognostic outcomes on PARP inhibitors, and to date, this is the only known prognostic marker for ovarian cancer [9].

Clinical Challenges

The variety of subtypes that exist under the umbrella of ovarian cancer present a unique challenge to develop precise and efficacious therapeutics to achieve cure. Treatment options are starting to evolve sophistication based on their molecular subtype. For example, mucinous ovarian cancer is treated using therapeutics for gastrointestinal tumors. However, for the
majority of subtypes, this approach is in its infancy compared to other cancers like breast cancer, melanoma and various types of leukemia, that rely on personalized medicine to yield superior disease management and even cure.

Another significant treatment challenge is late clinical presentation, since most patients are discovered at stage III or later with an extremely heterogeneous cancer cell population [10]. Unlike other cancers, ovarian cancer harbors its own staging system known as FIGO staging (Table 1). Upon confirmation of staging and histological analysis for subtype, a patient may then undergo cytoreductive surgery to remove as much of the tumor as possible, followed by chemotherapy and/or targeted therapy [11]. If the tumor is detected in an early stage, surgery and observance are generally sufficient, while chemotherapy is usually reserved for treating and palliation of late-stage, metastatic disease [12]. As such, chemotherapy is often able to achieve a brief period of remission in most patients, but unfortunately the disease frequently returns.

**Table 1**: Summary of ovarian cancer staging as diagnosed in the clinic. Most patients present at stage III with some level of metastatic disease [3,5].

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Physiological Characteristics</th>
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<tbody>
<tr>
<td>I</td>
<td>Localized to ovaries</td>
</tr>
<tr>
<td>Ia</td>
<td>One ovary affected</td>
</tr>
<tr>
<td>Ib</td>
<td>Both ovaries affected</td>
</tr>
<tr>
<td>Ic</td>
<td>One or both ovaries affected with presence of ascites fluid in abdomen</td>
</tr>
<tr>
<td>II</td>
<td>Ovaries and some pelvic disease spread</td>
</tr>
<tr>
<td>IIa</td>
<td>Fallopian tubes and uterus affected</td>
</tr>
<tr>
<td>IIb</td>
<td>Pelvic organs such pelvic wall and broad ligament affected</td>
</tr>
<tr>
<td>IIc</td>
<td>Ascites fluid with malignant cells in abdomen, promoting IIa and IIb stages</td>
</tr>
<tr>
<td>III</td>
<td>Peritoneal metastasis beyond pelvis</td>
</tr>
<tr>
<td>IIIa</td>
<td>Liver and peritoneal metastasis (microscopic)</td>
</tr>
<tr>
<td>IIIb</td>
<td>Liver and peritoneal metastasis (macroscopic; lesions&lt;2cm)</td>
</tr>
<tr>
<td>IIIc</td>
<td>Metastasis beyond pelvic region into distant abdomin, lymph nodes, lungs, and hallmark omental cake (lesions&gt;2cm)</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis</td>
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Ovarian cancer presents atypical challenges due to its characteristics within the abdomen. For example, the disease is initially slow growing, but as it progresses, the heterogeneity of the cancer cell population increases immensely and is a challenge to clinically overcome [13]. More importantly, ovarian cancer presents as numerous solid tumor masses scattered throughout the abdomen and it also harbors free-floating cells in the ascites fluid, leading to bloating and abdominal distention. While ascites fluid can generally be drained from the abdomen, it is a recurring phenomenon that is the largest contributor of metastatic cancer spread to other organs, particularly the omental cake [3,14]. Cancer deposition and growth on the omental cake initiates crosstalk between the adipocytes, their derived growth factors and cancer cells from the omentum, further promoting proliferative tumor spread [14]. Ovarian cancer is, therefore, not only heterogeneous at the cellular level, but also in terms of its existence in a solid and liquid state.
There is currently an urgent need for early detection strategies to discover the disease in early, curable stages. Detecting disease in stages I or II, before significant metastatic spread occurs, would significantly improve outcomes. Alternatively, preventing the development of chemoresistance or even reverting the cancer back to chemosensitivity would be a significant achievement. For individuals at high risk for ovarian cancer, such as those with BRCA1/2 mutations, regular and detailed pelvic examinations as well as transvaginal ultrasounds may be effective, but have yet to be proven as fully reliable [1].

**Overview of Disease Management**

Since outcomes vary per case, patients sometimes undergo multiple rounds of treatment to achieve remission, especially if the cancer is detected at later stages. Generally, surgery to remove the ovaries, fallopian tube, uterus, or all three organs is the first step of treatment, depending on disease staging at diagnosis [9]. Subsequently, the omental cake, or fatty tissue surrounding the organs in the peritoneum, may also be partially resected to decrease the probability of cancer cells adhering to the fatty tissue to further metastasis [6].

After surgical debulking, chemotherapy is administered either intravenously or intraperitoneally, and the patient is regularly observed for further tumor spread. If the cancer continues to grow, second-line therapy may be administered, whereas if the patient goes into remission, they may be observed over time or given maintenance chemotherapy to reduce the possibility of relapse. First-line agents for chemotherapy include the platinum-based agents cisplatin and carboplatin, combined with taxanes such as paclitaxel and docetaxel; these agents target DNA and microtubules, respectively [15]. Anti-angiogenic agents such as bevacizumab may also be given in conjunction with first line-therapy [11]. This antibody therapy targets VEGF, which has been shown to have higher expression in ovarian cancer cells in comparison to benign ovarian lesions and non-cancerous ovarian tissue samples [16]. Other therapies like liposomal doxorubicin, cyclophosphamide or various salvage agents, like topotecan or gemcitabine, might also be appropriate in some cases, especially for patients with chemo-refractory or -resistant disease [11]. Under special circumstances, if a patient is unable to withstand surgery or has a large mass with stage IV disease, they may be administered chemotherapy before surgical debulking to reduce tumor load and increase the target area and cytotoxic effects of subsequent chemotherapy [6]. Second-line therapy involves the same classes of drugs as first-line therapy with varied drug regimens, dosing changes, and palliation for those with rapidly progressing or chemoresistant, late-stage disease [17].

American Cancer Society’s 10-year survival rate for ovarian cancer is approximately 35%. Only 15% of patients have disease that is detected at early stages, and have a 92% chance of survival to 5 years, while late-stage disease occurrence has a 40% 5-year survival rate, emphasizing the importance of early detection. Routine utilization of such methods across the general population could double the 5-year survival rate of this disease, thus completely changing disease lethality. In addition, women under the age of 65 are two times more likely to survive five years post-
diagnosis [1]. This is likely owing to a more robust immune system and ability to withstand side effects of chemotherapy and surgery.

**SPECIFICS ON DRUG TREATMENTS**

As previously stated, the main classes of chemotherapeutic agents used against malignancy include platinum-based agents, taxanes and Poly (ADP-Ribose) Polymerase (PARP) inhibitors. Bevacizumab was approved by the FDA in 2014 as an addition to combination regimens for ovarian cancer, based on a minor improvement in disease-free survival for patients with platinum-resistant disease [18]. Although chemotherapy is used with curative intent, the more realistic uses include an improvement in prognosis, palliation, or as maintenance therapy. Dosing amounts and schedules are crucial for patient remission as first- and second-line therapy utilizes many of the same drugs or drug classes. Since platinum-based agents, taxanes, and PARP inhibitors work in three different ways, the following section will serve to briefly summarize their discovery and development, mechanism of action, highlight their efficacy, and address clinical challenges experienced with use.

**Platinum-based Agents**

Platinum-based chemotherapy agents have been utilized against ovarian cancer since the late 1970s and initially yielded an improvement in overall survival up to three years [19]. This remarkable advance with treatment has not yet been recapitulated by another drug used against ovarian malignancies, a tribute to platinum-based agents. Unfortunately, their use also facilitates the primary pathway to chemoresistance. Upon diagnosis, most patients are administered combination therapy containing dose-dense taxanes, usually paclitaxel, and a platinum agent, usually carboplatin, as the side effects are less toxic compared with cisplatin as the platinum agent [20]. For example, the dose-limiting toxicity of cisplatin is nephrotoxicity and using this drug can also result in untreatable and irreversible neurotoxicity and ototoxicity, whereas carboplatin does not have these adverse effects, except neurotoxicity if it is administered in patients previously treated with cisplatin. Although both drugs have chemotherapy-induced nausea and vomiting which requires pre-treatment with anti-emetic drugs, carboplatin is significantly less emetogenic compared with cisplatin and thus is more desirable for patients. In addition, carboplatin’s dose-limiting toxicity is myelosuppression, which is significant, but also observed among various types of chemotherapy, and therefore management is more straightforward. For these reasons, carboplatin is the primary platinum-based drug used in patients. Although it is reasonably effective as monotherapy, it is combined with taxanes, especially paclitaxel, to yield higher therapeutic efficiency [21]. This combination is often associated with high neurotoxicity as observed in the SCOTROC-1 phase III clinical trial, however, other combinations have yet to replace this carboplatin-paclitaxel as the standard of care [22]. Docetaxel and cisplatin in varied dosage and schedule can replace paclitaxel and carboplatin as a viable first- or second-line option if the above combinations fail or specific side effects are a major concern [23,24].
Platinum-based drugs have a relatively nonspecific mechanism of action through the formation of DNA adducts to subsequently induce apoptosis. Upon passive diffusion into the cell, platinum drugs undergo what is known as an aquation reaction through the help of chloride ions, which in turn assists in the cytotoxic effects of this class of drugs [25]. In this process, one chloride ion is removed from the platinum drug and replaced with a water moiety due to low concentrations of chloride ions inside the cell [25]. Platinum agents can then enter the nucleus and form covalent bonds with the N7 positions of purine bases, particularly guanine [26]. This creates intrastrand crosslinks in DNA, halting replication and initiating DNA repair pathways in an effort to remedy the damage [26]. However, cells are often unable to recover from extensive DNA crosslinks and adduct formation and eventually undergo apoptosis (Figure 1).
**Figure 1:** Drug classes mechanism of action and various pathways to chemoresistance. Platinum therapy results in DNA adducts, halting replication, but can be efﬂuxed out of the cell through drug transporters such as P-glycoprotein to be rendered ineffective [26]. Carboplatin is utilized more often than cisplatin. Taxanes are also efﬂuxed out of cancer cells but function through blocking mitotic spindle formation and arresting cell replication [32]. Note that both paclitaxel and docetaxel are represented here, however, FDA approval exists only for the former. The PARP inhibitor olaparib can cause double stranded breaks to halt replication, but cancer cells may have mechanisms to downregulate PARP-1 to make this drug ineffective [51]. Anti-angiogenic agents such as bevacizumab are unique in their antibody formulation and while they can be effectively added to regimens, target speciﬁcity and stability in circulation may make them ineffective as well [54]. Finally, gemcitabine is the most prominent salvage therapy in ovarian cancer, and works through inserting nucleoside analogs into DNA strands during replication, thereby halting the cell cycle. However, cancer cells are notoriously known to downregulate the receptors transporting gemcitabine into cancer cells, or increase efﬂux transporters to cause chemoresistance [58].

<table>
<thead>
<tr>
<th>Drug/Classiﬁcation</th>
<th>Mechanism of Action</th>
<th>Chemoresistance Mechanism Example</th>
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<tr>
<td><strong>Platinum Agents</strong></td>
<td></td>
<td><img src="image" alt="Platinum Agents Diagram" /></td>
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<tr>
<td>Chlorozinc</td>
<td>Carboplatin</td>
<td><img src="image" alt="DNA Adducts" /></td>
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<tr>
<td><strong>Taxanes</strong></td>
<td><img src="image" alt="Taxanes Diagram" /></td>
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<tr>
<td>Paclitaxel</td>
<td>Docetaxel</td>
<td><img src="image" alt="Mitotic Spindle Formation" /></td>
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<tr>
<td><strong>PARP Inhibitors</strong></td>
<td><img src="image" alt="PARP Inhibitors Diagram" /></td>
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<tr>
<td>Olaparib</td>
<td><img src="image" alt="Double Stranded Breaks" /></td>
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<tr>
<td><strong>Anti-angiogenic agents</strong></td>
<td><img src="image" alt="Anti-angiogenic agents Diagram" /></td>
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<tr>
<td>Bevacizumab</td>
<td><img src="image" alt="Antibody Formulation" /></td>
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<tr>
<td><strong>Salvage Therapy</strong></td>
<td><img src="image" alt="Salvage Therapy Diagram" /></td>
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<tr>
<td>Gemcitabine</td>
<td><img src="image" alt="Nucleoside Analog Insertion" /></td>
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During or after the first round of chemotherapy, patients can be classified as platinum-sensitive, -resistant, or -refractory [27]. Specifically, platinum-sensitive disease responds well to platinum therapy, without relapse for at least 12 months, while patients with platinum-resistant disease will relapse within six months of beginning treatment [28]. Platinum-refractory disease is the most drastic and challenging to treat, as patients relapse within weeks of beginning chemotherapy [28]. Unfortunately, almost all patients relapse within 18 months after beginning first-line therapy [11].

Chemoresistance to platinum drugs has multiple mechanisms, the simplest being their efflux from the cytoplasm following the aquation reaction through glutathione-S-transferase mediated efflux [29]. This way, they are unable to even reach their target in the nucleus to induce damage, let alone cause apoptosis. Incidentally, decreased uptake due to upregulation of the P-glycoprotein drug transporter plays a more significant role in platinum resistance than drug efflux following aquation [30]. Therefore, various mechanisms of chemoresistance against platinum-based therapy represent a major clinical challenge. This frustrating dilemma demonstrates why ovarian cancer is considered a highly responsive, yet seldom curable malignancy.

**Taxanes**

Taxanes are a large class of anti-cancer drugs that target microtubules to block formation of the mitotic spindle, therefore resulting in lack of cell division and eventually, apoptosis [31,32]. Paclitaxel, the most prominent of the taxane drugs, is naturally derived from the Pacific Yew Tree, and was discovered in 1962 [33]. Interestingly, over 13 pounds of bark from the Pacific Yew Tree is required to yield 0.5 grams of paclitaxel, which likely led to the passing of a protection act for the tree in 1992 [34]. This occurred well after the rapid evolution of synthetic organic chemistry required to manufacture sufficient quantities of the compound and prevent ongoing drug shortages that initially resulted following FDA approval of paclitaxel. A semi-synthetic version of paclitaxel, docetaxel, evolved as a result. However, docetaxel is not FDA approved for this indication, but may be used off-label. It is approved for the treatment of other malignancies.

Although targeting microtubules is the major mechanism of action for paclitaxel, it is also responsible for activation of apoptotic pathways, and some indirect anti-angiogenic activity [35]. Most importantly, paclitaxel’s effects against tumor cells are highly dose dependent; higher doses and lower doses yield drastically different effects, which may negatively influence clinical prognosis. For example, high doses of paclitaxel induce Raf expression in cancer cells, a kinase that controls apoptotic pathways to increase proliferation, while low doses show little to no involvement of Raf, eventually contributing to apoptosis [35,36]. Therefore, paclitaxel is often administered in moderate doses at greater frequency, a concept known as dose dense therapy [37].

Taxanes, especially paclitaxel, are also prone to chemoresistance like the platinum-based drugs. While taxanes can somewhat counter platinum-based chemoresistance, patients developing resistance to both therapies show poor prognosis [38]. As expected, drug efflux is a major
contributor to taxane resistance, involving the P-glycoprotein transporter [39]. Additionally, hypoxic regions of tumors, due to the rapid and unorganized nature of tumor growth, exhibit a lack of adequate blood circulation, which makes them inaccessible to drugs, especially those delivered intravenously [40]. Intraperitoneal injection partially solves this problem while reducing systemic side effects. However, the magnitude of cancer spread in the abdomen may also render some lesions difficult to target, and patients treated using intraperitoneal injection report decreased quality of life [41].

Emerging studies demonstrate that newer forms of paclitaxel can combat chemoresistance induced by dose-dense and platinum-based combination therapy through various strategies. One such example is Abraxane, an albumin-bound paclitaxel nanoparticle, which has increased solubility and eliminates the use of Cremophore as a vehicle, decreasing hypersensitivity during administration [42]. Cremophores are often used to solubilize hydrophobic drugs such as paclitaxel to ensure stable delivery to the target site within the body. Abraxane in nanoparticle form can specifically bind an albumin receptor and cross the endothelial membrane into the tumor site from circulation. Altered pharmacodynamics also allow for Abraxane to be administered at higher doses than paclitaxel without high-grade side effects [43]. While Abraxane is yet to be approved as first-line therapy for ovarian cancer, it has shown great potential at solving key pharmacokinetic issues commonly observed with paclitaxel use.

**PARP Inhibitors**

PARP inhibitors were initially tested in vitro against BRCA-mutated breast cancers and in 2011 discovered to have efficacy against wild-type BRCA cancers as well [44,45]. However, the mechanism of action of PARP inhibitors is enhanced by previously damaged DNA, as is observed in BRCA-mutated cancers [46]. BRCA deficient cancers are unable to repair double stranded breaks that occur during DNA replication and are therefore predisposed to DNA damage leading to cancer [47]. PARP enzymes, especially PARP-1, are involved in repairing single-stranded breaks in DNA [48]. The combination of BRCA mutations and PARP inhibition causes synthetic lethality, a concept where two mechanisms of damage cause cell death where either mechanism alone does not, increasing apoptosis in BRCA-mutated cancer cells [49].

Olaparib is the first PARP inhibitor used against ovarian cancer and was approved by the FDA in 2014 for use as a single agent against both platinum-resistant and -sensitive disease [50]. It was indicated for use as maintenance therapy after patients with BRCA mutations have failed at least three rounds of chemotherapy involving platinum agents and taxanes. Currently, olaparib is still the only PARP inhibitor used in therapy, and is also in clinical trials in combination with cediranib (anti-angiogenesis agent) for recurrent platinum-resistant or -refractory ovarian cancer. Since PARP inhibitors represent the newest drug class used against ovarian cancer, these inhibitors are involved in a large number of clinical trials examining their efficacy as maintenance therapy, in combination with chemotherapy, and anti-angiogenic agents. Considering olaparib's success, veliparib and niraparib are currently in phase III clinical trials to test efficacy against ovarian cancer in combination with cisplatin and bevacizumab, respectively.
Interestingly, BRCA-mutated ovarian cancers are more sensitive to platinum-based chemotherapy and less sensitive to taxanes compared to wild-type BRCA ovarian cancers [51]. Therefore, if BRCA-mutated patients relapse after multiple lines of chemotherapy, PARP inhibitors are able to utilize their inherent BRCA-deficient phenotype to increase apoptosis in cancer cells. Unfortunately, even PARP inhibitors are prone to chemoresistance, especially BRCA wild type tumors that are not susceptible to synthetic lethality. One mechanism of PARP inhibitor resistance is the lack of PARP-1 expression in the cancer cells, thus leaving no target and yielding no therapeutic efficacy [52]. Another common resistance strategy in cancer cells is to efflux PARP inhibitors from the cancer cells through drug resistance transporters. Specifically, the P-glycoprotein transporter can effectively efflux PARP inhibitors from cells, leading to resistance [39].

**CHEMORESISTANCE**

Chemoresistance is an unfortunate hallmark of ovarian cancer treatment. Most patients experience some level of relapse that eventually becomes insurmountable. Ovarian cancer patients usually have one of two chemoresistant types: primary / de novo resistance, which is present in the cancer cells before any therapy is administered, commonly appearing in late stage disease, and acquired resistance, which evolves as the result of chemotherapy treatment [53]. Cancer stem cells likely play a major role in primary resistance as they are quiescent and divide at slower rates than cancer cells, evading chemotherapy and subsequently resulting in disease progression [53]. In other words, these cells do not proliferate rapidly, thus naturally avoiding the mechanisms required for chemotherapy to be effective. In contrast, cells with acquired resistance develop mechanistic changes that will avoid the apoptotic effects of chemotherapy, mainly through genetic variations or successful mutations, which results with increased survival and subsequent expansion of the resistant population [53].

Although all cells may have, at one point, been derived from one small population of cancer cells, due to the high heterogeneity of ovarian cancer, the genetic makeup emerging in the tumors present in progressive disease is extremely varied. These differences result in molecular variations in oncogene activation, tumor suppressor inactivation and an array of random genetic mutations that confer a survival advantage [39]. Therefore, targeting cancer cells in a monotherapeutic manner is insufficient and ineffective over the long term because cells exposed to single agents will more readily overcome a drug’s mechanism of action and then repopulate the tumor microenvironment.

Patients receiving chemotherapy are closely monitored for disease progression throughout treatment. As the course of chemotherapy is administered, patients can be classified and reclassified as chemosensitive, chemoresistant or as having refractory disease [54]. While the median time to disease recurrence is approximately 16-18 months, over 75% of patients experience relapses during treatment [6]. Unfortunately, if ovarian cancer relapses after second-
line treatment is administered, it is rarely curable and patients are either directed to pursue clinical trials or given palliative care [54]. Cancer subtypes like non-small cell lung and colon carcinoma have options for third-line chemotherapy, but ovarian cancer lacks additional therapeutic options. A well-known molecular event that is responsible for some of the import and export of chemotherapy across the cell wall involves drug transporters. For example, drug transport into the cell that is necessary for efficacy is also one of the first mechanisms thwarted by cancer cells, using a variety of techniques. The most notorious mechanism is that of the P-glycoprotein multidrug transporter, which is an efflux pump highly expressed on ovarian cancer cell membranes. These transporters are involved in the binding and subsequent exportation of chemotherapy into the extracellular environment, rendering it ineffective [55,56].

Cancer Stem Cells (CSCs) were recently discovered to be extremely significant players in promoting chemoresistance. Ovarian cancer is unique in that it is comprised of both solid tumors throughout the abdominal cavity and a somewhat liquid tumor component in the ascites fluid at later stages [3]. The presence of CSCs in the ascites allows for fast dissemination and spread. Alternatively, quiescent CSCs do not quickly replicate and are therefore highly resistant to chemotherapy, even when it is delivered intraperitoneally. Therapeutics that lack specificity against CSCs, such as platinum agents and taxanes commonly used against ovarian cancer, are unable to eliminate CSCs, although they would be initially effective against rapidly-dividing tumors [57]. However, CSCs in ovarian cancer can be identified through their expression of CD44+, a cell surface glycoprotein marker that mediates cell-cell adhesion and interaction [10]. It is crucial that CSCs become a major focus of future research in the ovarian cancer field, as targeting them will have a significant influence on disease progression and chemoresistance.

Stromal cells in the tumor microenvironment are another crucial subset of cells involved in promoting chemoresistance and metastasis in ovarian cancer [59]. Mesenchymal stem cells, in particular, are able to differentiate in the tumor microenvironment into several cells types like fibroblasts, adipocytes, and osteoblasts [14]. In ovarian cancer, mesenchymal stem cells are located in the ascites fluid and release both paracrine and endocrine growth factor signals to promote tumor progression [60]. As they are undifferentiated and therefore do not rapidly replicate, they evade chemotherapy and remain quiescent, similar to CSCs [61]. More importantly, they can also promote chemoresistance in cancer cells by releasing specific growth factors that confer protection against chemotherapy in response to platinum drug delivery [61]. Acquired resistance is, therefore, largely promoted by mesenchymal stem cells in ovarian cancer.

**CONCLUSION**

Treatment of ovarian cancer patients is challenging. Platinum-based agents are, widely used chemotherapeutics against ovarian cancer, usually administered alongside taxanes. PARP inhibitors, on the other hand, are the newest class of drugs and administered to platinum-resistant, BRCA-mutated cancer patients that have relapsed following at least three rounds of
chemotherapy. In addition, the anti-angiogenic agent bevacizumab can be administered alongside platinum agents and taxanes in patients that are not platinum-sensitive [54].

As chemoresistance is a major challenge of clinical treatment, research must focus on new avenues to target cancer stem cells, and evolve strategies to enhance precision medicine tailored to specific cancer subtypes. There are two broad strategies to overcome chemoresistance in ovarian cancer: early detection and effective targeted inhibitors. Patients often present to the clinic in late-stage disease, and there is an urgent need for reliable, early-disease biomarkers to combat chemoresistance and increased heterogeneity as the disease progresses. Specific drug targets are needed to counter chemoresistance through targeted killing of cancer cells to achieve holistic, long-term remission. However, this process requires a thorough molecular analysis of each patient and their tumors to deliver the precise therapy. Conclusively, as there is no absolute cure for ovarian cancer, multifactorial therapeutic strategies and early detection must be the future focus of research in the field to improve overall survival rates.

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