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Ovarian Cancer Metastasis to the Central Nervous System: A Literature Review

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Abstract

Ovarian cancer is one of the leading causes of cancer-related deaths among women in the United States. Metastasis to the central nervous system has become more frequent in the previous decades, however, treatment options remain limited. In this review, we discuss the pathophysiology of ovarian cancer and how metastasis to the central nervous system typically occurs. We then discuss cases of metastasis presented in the literature to evaluate current treatment regimens and protocols. Finally, we highlight emerging treatment options that are being utilized in clinics to provide personalized treatment therapy for a patient's unique diagnosis. This review aims to further the understanding of pathophysiology, stimulate further innovative treatments, and present accessible resources through tables and figures.

Keywords

Ovarian cancer; Metastasis; Brain; Central nervous system; Emerging treatments

Introduction

Ovarian cancer is one of the leading causes of cancer-related deaths among women in the United States [1]. Ovarian cancer largely develops from 3 tissue types: epithelial cells, stromal cells, and germ cells, and generally spreads to the neighboring ovary and uterus, however, distant metastases may occur in the liver, lungs, adrenal glands, brain, and spine [1]. Currently, brain and central nervous system metastases have an extremely poor prognosis for most patients. A majority of the metastases occurring in the central

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nervous system originate from epithelial cell-derived ovarian cancer which has an incidence of less than 2% in all cases [2]. Importantly, reported incidences of ovarian metastasis to the brain may appear much lower than the true incidences rates, as brain scans are not part of the standard clinical care for patients with ovarian cancer [2]. While there has been a slight decline in the incidence of ovarian cancer, the rate of ovarian metastasis to the central nervous system has increased over the previous two decades [3]. This may be due to an increased advancement of therapy and an increased survival time following diagnosis, consequently creating new, more distant patterns for metastasis [4,5].

Pathophysiology of ovarian cancer metastases to the brain and spine

Most ovarian cancers arise from the epithelial layer that surrounds the ovary [6]. One of the second most common and highly aggressive epithelial layer cancers is epithelial ovarian cancer (EOC) [7]. Patients who present with this type of cancer, at the time of diagnosis, show metastasis beyond the ovaries to other parts of the body [7]. Typically, these tumor cells don't present in the brain at the time of diagnosis, only in rare circumstances. However, it has been speculated that the route of access to the brain and spinal cord could be due to the tumor cell's ability to penetrate the vascular barrier, invade the parenchyma, or spread along the perineurium from cranial or spinal nerves [8]. Once the tumor cells invade the CSF, they can then begin to manifest themselves in the cerebral hemispheres, particularly the frontal lobe, as well as the spinal cord [2,7,8]. Metastasis to the spinal cord has been hypothesized to originate from ovarian cancer tumor cells detaching themselves from the primary tumor and traveling, either in cell clusters or in singles, within the peritoneal fluid into the peritoneum and omentum [9].

While there is no sole cause triggering ovarian cancer to spread, there are several predictable pathways that cancer cells may use to metastasize to the brain and spine through a multi-step process. Ovarian metastasis generally starts when the ovarian carcinoma cells detach from the primary tumor due to an epithelial-mesenchymal transition (EMT) [10] (Figure 1). This transition promotes the detachment of epithelial cells to the basement membrane which then loosens the adhesions between cancer cells. In fact, up to 90% of ovarian cancers are due to neoplastic transitions of surface epithelial cells [11]. Most notably, the loss of epithelial adhesion transmembrane protein E-cadherin has been demonstrated to promote metastasis and invasiveness [12,13] by loosening the connections of α - and β -catenin to the actin microfilaments within the cytoplasm [10]. Furthermore, the EMT phenotype has been shown to allow epithelial cells to take on a more mesenchymal form that enhances cellular migration [14]. A phenomenon known as cadherin switching may also promote poor adhesion by shifting the expression of E-cadherins to N-cadherins which are expressed by the more motile and less polarized mesenchymal cells [15]. Therefore, cells affected by cadherin switching adhere more readily to collagen which is part of the extracellular matrix rather than the basal membrane. While cadherins and other adhesion proteins such as integrins may be attractive targets for targeted cancer therapy, it should be noted that their complicated roles cause issues when isolating pathways; some metastases contain high levels of E-cadherin despite its role in epithelial adhesion [16,17]. The mechanisms by which E-cadherins minimize ovarian cancer metastasis are still not well understood and

future work on its activity at the cell surface may be a promising approach to controlling metastasis.

Another known pathway wherein ovarian cancer cells detach from the primary tumor and migrate throughout the body is through cancer's dependency on the body's hemodynamic systems. Compared to typical mature blood vessels, angiogenic agents enhance the density of immature, highly permeable blood vessels that have a thin basement membrane and few intercellular junctional complexes [18]. However, some organs with metastatic cells receive almost equal amounts of blood yet have different pathways through which cells migrate [19]. Scientists have been looking more into a hypothesis that remedies this conflict, denoted as the "seed and soil" hypothesis which proposes that the "seed" and "soil" of tumor metastasis are the beneficial interactions between metastatic tumor cells and the organ microenvironment, respectively. Specifically, targeted therapy in this area involves targeting the tumor microenvironment and the angiogenic agents that support tumor growth. The pro-angiogenic factor VEGF is known to increase vascular permeability and is expressed on numerous non-endothelial cells including tumor cells [20], and anti-VEGF antibodies are currently in clinical use to inhibit neovascularization.

Ovarian carcinoma is unique when compared to other known metastasis from other cancers such as breast and colon. A case series demonstrated that patients who had peritoneovenous shunts implanted to help relieve ascites, consequently, transferred metastatic cancer cells into the venous system as a side effect [10,21]. Interestingly, after 2 years, none of the 29 patients developed metastases, further supporting the seed and soil hypothesis. This suggests that ovarian cancers metastasize efficiently within the peritoneal cavity, but spreads poorly into organs from the outside. Overall, special features of ovarian carcinoma such as the tumor invading the mesothelial cell layers but rarely deeper [1] have not been well investigated.

Loss of E-cadherin has been consistently observed at sites of EMT during cancer development. Specifically, SLUG (SNAI2) genes, part of the SNAIL superfamily of zinc-finger transcription factors, was shown to be strongly correlated with repressing endogenous E-cadherin expression as well as loss of E-cadherin transcripts via E-box elements in E-cadherin promoter [22]. Another factor affecting the decreased expression of E-cadherin is a RING finger-containing E3 enzyme known as MDM2. Overexpression of MDM2 is found in many metastases [23,24] as it is involved in protein degradation via the ubiquitin-proteasome system (UPS) [25]. E-cadherin serves as a substrate for MDM2, which binds to it and ubiquitinates it, leading to degradation [26]. Thus, both SLUG/SNAIL transcription factors as well as the MDM2 enzyme are very likely in inducing EMT as well as promoting invasion, making these factors areas for further understanding and preventing cancer metastasis.

One of the most studied factors that increase the invasiveness of these tumor cells is the loss of the E-cadherin protein. E-cadherin is a membrane glycoprotein located at adherens junctions that plays a role in cell adhesion, chemical signaling inside the cell, cell maturation and movement, and gene regulation [6]. A decreased expression of this protein leads to ovarian cancer cells' invasive phenotype by activating signaling cascades

involved in tumor metastasis, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) [6,27]. Sawada et al. conducted a study to determine what cell-matrix adhesion receptors were affected when downregulating E-cadherin. The group discovered that upregulation of $\alpha 5$ -integrin protein expression was seen when E-cadherin was downregulated, resulting in an increase in tumor cell adhesion and invasion. $\alpha 5$ -integrin is a transmembrane protein that has been linked to the progression of cancer via cell proliferation, angiogenesis, and metastasis [28].

Although E-cadherin and other EMT-related markers have been found to be a strong prognostic factor in ovarian cancer and cancer cells in general, there is still little and conflicting knowledge regarding how levels of expression of these factors can relate to tumor growth, spread, and aggressiveness. Therefore, analysis of the specific pathways in E-cadherin adhesion function may prove beneficial in understanding the mechanisms behind cancer progression.

Pre-clinical literature

Recent studies report that ovarian carcinoma often proliferates through the peritoneal cavity via peritoneal fluid, but in some cases, ovarian cancer travels hematogenously and through bone metastasis to the spine and brain [10]. Lesions that form due to the metastasis of ovarian cancer may have several different textures. These growths can be a variety of solid, cystic, and mixed tumors. The histology of these various lesions in decreasing order of frequency are epithelial, endometrioid, adenocarcinoma, mucinous, undifferentiated, and clear cells [2]. 57.3% of cases evaluated in a systematic review reported brain metastasis from ovarian cancer [29]. The distribution of metastasis location from ovarian cancer to the brain varies in several studies with the cerebellum and cerebrum being the most frequent locations. It has been suggested that the cerebellum experiences higher rates of metastasis due to its blood supply [29]. However, one study suggests that the cerebrum's frontal lobe experiences the highest level of metastasis, followed by the parietal lobe, temporal lobe, and cerebellum [2]. Simultaneously, the falx cerebri and the spinal cord were areas less susceptible to metastasis [3].

A case report of a 62-year-old female presented by Liu et al. reported the detection of brain metastasis in an ovarian cancer patient 12 years after her diagnosis and a left oophorectomy in 2004 [30]. Clinically, the patient presented with headaches. The authors found increased levels of tumor markers CA125, CA242, and CA19-9. An MRI taken one month after the detection of brain metastasis revealed a tumor mass in the right cerebellar hemisphere [30].

Unlike lung and breast cancer, spinal metastasis from ovarian cancer is extremely rare, with only ten known cases of intramedullary spinal metastasis and one case of extramedullary spinal metastasis from ovarian cancer (Table 1).

As a result, general treatment protocols for these patients do not yet exist. Within the existing literature, expected survival for patients with spinal cord metastasis from ovarian cancer ranges from 5 months to 3 years. Common treatments following surgical resection of the tumor include steroids, chemotherapy, and radiotherapy. In a case report by Ravindra

et al., the authors describe a rare BRCA2 mutation in ovarian cancer [36], where surgical removal of the tumor was followed by external beam radiation to the thoracic spine and the use of oral steroids. Additional research would be necessary to determine if BRCA2 mutation is related to ovarian cancer metastasis to the central nervous system or improved prognosis for these patients [30].

Further understanding of the mechanisms of brain and spinal metastasis of ovarian cancer, as well as routine MRI examination in patients with late-stage ovarian cancer, may aid in early diagnosis, successful treatment, and improved prognosis of the disease.

Emerging treatments

Current treatments like radiosurgery, neurosurgery, chemotherapy, and corticosteroids have developed into effective therapies that can give the patient a better chance of survival. Emerging therapies include a more unique and targeted approach that considers the individual patient's tumor genetics and microenvironment. Brain metastases specifically arising from epithelial ovarian cancer have specifically seen novel treatment regimens (Table 2).

Genetic targeting

Taking advantage of genetic sequencing may highlight mutations of genes that are known to be related to ovarian cancers. Identifying biomarkers of sequence alterations and their correlation to clinical characteristics will pave the way for creating novel therapeutics that can specifically target malignancies based on the tumor type. The Cancer Genome Atlas identified several potential biomarkers of high-grade serous ovarian adenocarcinomas (HG-SOC), including RB transcriptional corepressor 1 (RB1) and phosphatidylinositol 3-kinase/RAS type GTPase family (PI3K/RAS) (42). Since then, new genes have been identified to play an important role in cancer progression including tumor protein p53 (TP53), neurofibromin 1 (NF1), and BRCA1/2 among others [43].

An issue with using genetic sequencing of tumors to scan for biomarkers of genetic mutations is that not all mutation sources are known. Currently, the research on the genomics of ovarian cancer is mostly focused on epithelial ovarian cancers, more specifically, HG-SOC type cancer. This is beneficial as the majority of patients have this variation of cancer, but simultaneously also means that rarer cancers are still understudied on a genetic level [43]. Novel biomarker candidates are being discovered for rarer cancer types, such as hepatocyte nuclear factor 1 β (HNF1 β), which is expressed in nearly all cases of ovarian clear cell carcinomas (OCCC) [44]. As sequencing costs continue to decrease, whole genome sequencing (WGS) analysis will become further utilized in clinical settings. WGS provides vast amounts of information that help identify new genomic aberrations that promote tumor growth, and these drivers of mutations can be inhibited using an ever-growing collection of molecular targeted therapies. Additionally, genetic sequencing of a patient's tumor has the potential to be used to track the genomic evolution of cancer over time.

Targeting DNA repair pathways

Poly (ADP-ribose) polymerase (PARP) inhibitors in combination with chemotherapy and surgery have emerged as primary maintenance treatment options for ovarian cancer [45]. PARP is a protein responsible for the repair and replication of damaged cells. PARP inhibitors are able to disrupt DNA repair mechanisms by damaging the replication forks of cancerous tumor cells, which in turn prevent the cancer cells from proliferating [46] (Figure 2). One study has looked at the efficacy of Niraparib, an orally administered PARP inhibitor, as a monotherapy in patients with brain metastasis from ovarian cancer. Niraparib is unique in its ability to cross over the blood-brain barrier compared to other PARP inhibitors [45]. A case study that evaluated the administration of niraparib over a 29-month period showed a steady average of CA levels in the patient's serum. Additionally, the patient's KPS score rose to 100, with head MRI and chest CT scans showing no signs of disease advancement [45]. While these results are promising for the maintenance of this disease, future clinical studies must be conducted to determine the feasibility of this course of treatment.

Immunotherapy

Recent studies have looked at the use of immune checkpoint inhibitors (ICI) as a treatment option for the disease. The most researched of these checkpoints include cell death protein 1 (PD-1), its ligand PD-L1, and the CTLA-4/CD80/CD86 pathways [47]. The use of monoclonal antibodies to inhibit T-cell checkpoint molecules have been beneficial in treating numerous types of advanced cancers [48]. Pembrolizumab, an inhibitor of PD-L1, in combination with bevacizumab and oral cyclophosphamide has shown promising results in phase 2 non-randomized clinical trials for the treatment of recurrent ovarian cancer (n=40). The treatment was well tolerated by all the enrolled participants, with an average response rate of 47.5% and a median progression-free survival of 10 months [49]. Due to these results, several other studies have looked at the use of pembrolizumab as an immunotherapy for the treatment of brain metastases. However, initial data from these studies are not as promising, with median response rates of only 10–15% [47]. These complications may stem from the lack of knowledge about reliable biomarkers in patients with brain metastases that will respond to ICIs [47]. Other studies have speculated that immunotherapy in combination with radiotherapy could prove to be beneficial in the management of ovarian cancer [50]. Future clinical studies are underway to determine the effects of these two therapies together in a multimodal approach. DNA repair aberrations can lead to further accumulation of genetic changes within cells and can result in improved risk for developing cancer. Determining these carries of genetic changes can have a two-fold effect: identification of patient population susceptible to specific types of cancer, and further subclassification of cancer.

Chemotherapy

Although chemotherapy is a standard treatment option for recurrent ovarian cancer, data supporting its efficacy for the treatment of brain metastases as monotherapy is limited. In one case study, a woman with brain metastases from ovarian cancer had initially been treated successfully through a combination of cis-platin, adriamycin, and cyclophosphamide

(CAP) [51]. She experienced remission after 3 months and was given another cis-platin regimen in combination with vinblastine and peplomycin. She died from organ failure 5 months after therapy, suggesting that chemotherapy alone was not sufficient to treat brain metastases. Another study however acknowledged the effectiveness of cisplatin in combination with etoposide for the treatment of brain metastases from ovarian cancer [52]. A 54-year-old woman suffering from cerebellar metastasis had undergone multiple rounds of CAP therapy to treat the tumor. Following treatment, she received a combination of cisplatin and etoposide. Combination chemotherapy was able to lower her serum CA-125 levels back to normal whereas normal CAP therapy could not. Resulting rounds of chemotherapy showed no more signs of recurrence of cancer. Therefore, while chemotherapy as an individual therapy may not be sufficient for the treatment of brain metastases, evidence suggests that combinational chemotherapy may prove to be an effective treatment strategy. In order to fully understand the benefits and risks of this approach, future clinical trials must be investigated.

Therapeutics for chemotherapeutic-resistant tumors

Relapsed or recurring malignancies commonly mutate to be resistant to previously used treatments, including radiation and chemotherapy. This requires new therapeutic strategies to be developed as second-line treatment options for better efficacy in treating ovarian cancers that have metastasized to the CNS. A promising target for platinum-resistant epithelial ovarian cancer includes the inhibition of histone deacetylases (HDACs) [53]. One newly developed therapeutic includes the receptor tyrosine kinase inhibitor, Sorafenib. This drug inhibits protein kinases that are commonly found in tumors, and it may additionally block HDAC expression [53]. Phase II clinical trials have been found to be successful in stabilizing disease in patients with advanced ovarian cancer [53]. Anti-angiogenic drugs are also undergoing study as new treatments to limit or prevent cancer metastasis. Bevacizumab is a novel antiangiogenic that inhibits VEGF and has been found to improve the efficacy of chemotherapy treatment when used in combination with phase III clinical trials [53].

Oncolytic viral therapy

Another potential avenue for therapeutic strategies includes oncolytic virotherapy. Previous studies have failed to develop an effective oncolytic virus, shadowing the potential of this strategy. However, in a study performed by Hammad et al., a novel chimeric poxvirus was developed and shown to have the oncolytic potential for ovarian cancers with minimal cytotoxicity in mouse models [54]. Further testing may prove that this is a worthwhile and unique strategy for chemotherapeutic-resistant tumors.

Conclusion

Metastatic ovarian cancer may be a distressing diagnosis for many patients, especially when existing therapeutic options are ineffective due to gained resistance. Standard treatment protocols for metastases to the brain and spine include radiosurgery, neurosurgery, chemotherapy, and corticosteroids. Many of these therapies have their own shortcomings and are often used in combination with one another. Novel treatments aim to utilize tumor-

specific traits creating a more personalized approach to treating a patient's cancer. Although these new approaches will have their own drawbacks, they are still considered significant progress in the field. They offer an optimistic future for patients with ovarian cancer that has metastasized to the brain and a better prognosis.

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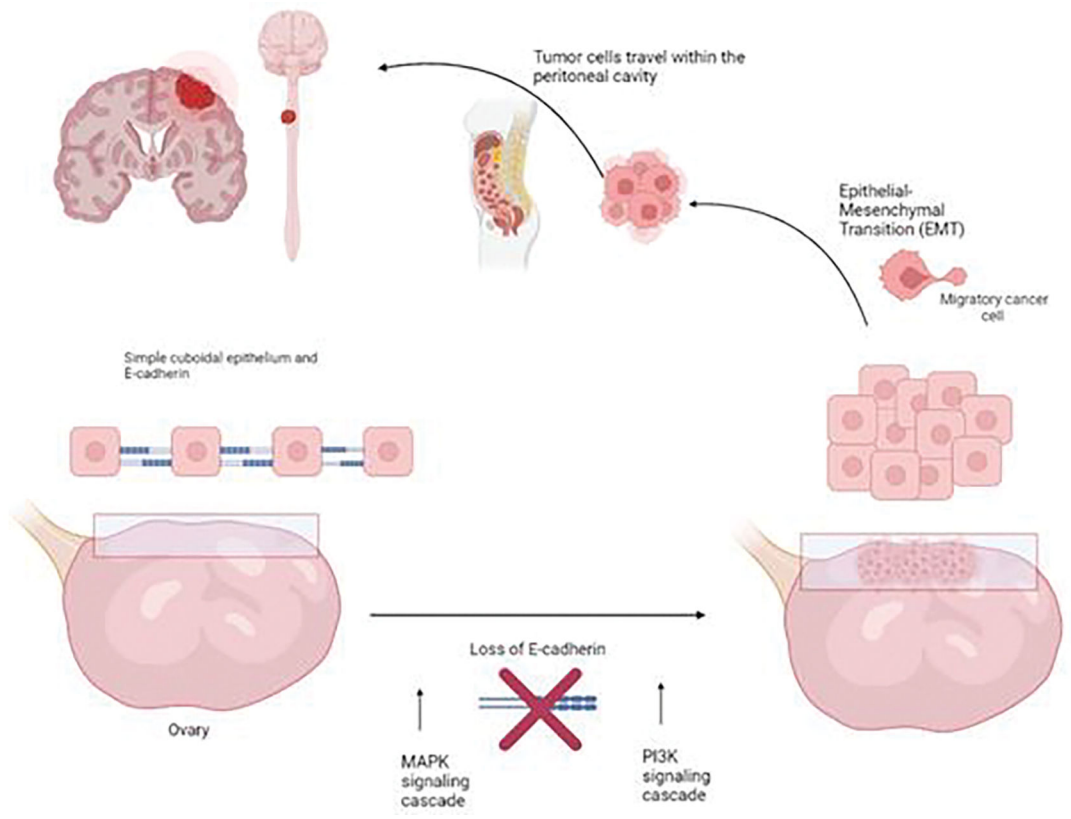


Figure 1: Process of ovarian cancer cells metastasizing to the brain due to an epithelial-mesenchymal transition (EMT) [10].

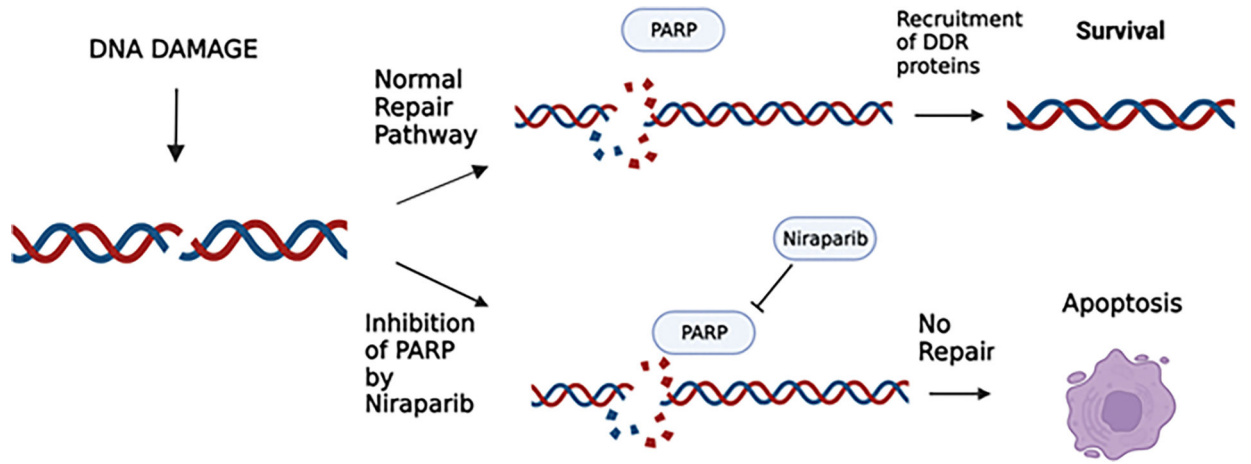


Figure 2: Disruption of DNA repair by niraparib, a Poly (ADP-Ribose) polymerase inhibitor (PARPi).

Current reported cases of intramedullary spinal metastasis from ovarian cancer [5,9,31–38].

Table 1:

Lesion Site	Reported time from primary diagnosis to spinal metastasis*	Surgical Intervention	Adjuvant therapy	Outcome
C6-T1	4.5 years	None	30Gy, steroids	Strength improved; died six months later
C5-C6	1.5 years	None	30Gy, steroids, chemotherapy	Strength improved; died 10 months later
T10	4 years	Subtotal resection	Radiotherapy (dose unspecified)	No neurological improvement; alive two years after surgery
T11	2 years	Gross total resection	30Gy (10 fractions)	Near-complete strength improvement; MRI shows no spinal recurrence 16 months on
Conus medullaris and cauda equina	2 years	None	Steroids, chemotherapy, radiotherapy (dose unspecified)	Symptomatic improvement; three-year complete remission
C2-C5	2 years	Subtotal resection	30Gy, steroids	Strength improved; three weeks postoperative spinal epidural hematoma; died five months later
T10-T11	2 years	Gross total resection	steroids, radiation therapy (dose unspecified)	Died 1 year later
T11-T12	17 months	None	Steroids, chemotherapy	Strength improved, but did not regain full function of lower extremity
C7-T1	2 years	Subtotal resection	Steroids, chemotherapy	Free of disease at 6 months follow up
D6-D7	1.5 years	Gross total resection	Steroids, radiotherapy (dose unspecified)	Free of disease for 2 years before lost to follow-up

Emerging pharmaceutical chemotherapy treatments for various types of ovarian cancers [39–41].

Table 2:

Type of Ovarian Cancer	Targeting Drug Name	Drug Class	Mechanism of Action	Route of Administration
Epithelial Ovarian Cancer	G129R	Antagonist Peptide of Prolactin (PRL)	Blocks the PRL/PRLR signaling axis to prevent protumoral events within murine models of ovarian cancer	Cell Culture
Epithelial Ovarian Cancer	Carboplatin for Intraperitoneal (IP) Chemotherapy	Antineoplastic Agent	Introduces cytotoxic agents into the IP area, directly into the abdominal spread of ovarian cancer	Intraperitoneal (IP) Chemotherapy
Epithelial Ovarian Cancer	Paclitaxel with Carboplatin	Antineoplastic Agent	Introduces cytotoxic agents into the body via weekly paclitaxel and triweekly (every three weeks) carboplatin chemotherapy, unlike the standard three-week regimen	Intravenous (IV) Dose-Dense Chemotherapy