SCHOLARLY REVIEW

Brain Metastases from Ovarian Cancer: A Comprehensive Review

By Anna Cui

Author Biography

Anna is a rising senior at Mulgrave School in Canada. She is intrigued by neuroscience and biology and its psychological implications. In her free time, she loves to spend time with family and friends and play volleyball. She is also passionate about raising awareness of lesser-known topics, such as neuro-oncology. Her dedication to these topics stems from a hope that translating biological brain facts into comprehensible news on human and environmental development can educate the public and enhance community wellness. She is eager to study neuroscience at university and aspires to pursue neurosurgery.

Abstract

Ovarian Cancer

Ovarian cancer (OC) is the current leading cause of gynecological cancer deaths. Despite its fatal outcome, only 20% of ovarian cancers are detected in the early stage. The reason involves a combination of factors — there is no reliable screening for ovarian cancer, and any symptoms of ovarian cancer tend to be vague and easily ignored. Consequently, OC is given the advantage of metastasizing due to ignorance. However, recently, overall survival from ovarian carcinoma has been reported to increase after improvements in treatment (Siegel et al., 2020).

Brain Metastases from OC

Central nervous system (CNS) metastasis from epithelial ovarian carcinoma (EOC) is uncommon, with an incidence of brain metastases ranging from 1–3% (Zumrut et al., 2020). Moreover, the treatment of brain metastases from ovarian carcinoma is currently ill-defined because of its rarity and the small affected population. The median survival after diagnosis of brain metastases was six months, meaning BMs mainly occurred while the patient was in stages III or VI of OC. Nevertheless, the median interval between diagnosis of ovarian carcinoma and consequent brain metastases is also quite long, approximately 2 years (Piura et al., 2011). However, neuro-cognition and quality of life across therapies are increasingly recognized as essential endpoints for patients as survival continues to increase. This paper is a comprehensive review of brain metastases from ovarian cancer, investigating tumour proliferation, metastatic mechanisms, the role of BRCA 1/2, and several therapy options, such as PARP inhibitors.

Keywords: ovarian cancer, brain metastases, metastasis, central nervous system, proliferation, therapy, BRCA 1/2, tumour, PARP inhibitors.

Introduction

Due to OC's metastatic nature, approximately 58% of patients present with distant metastases at the time of diagnosis. Despite its sensitivity to chemotherapy, most tumours relapse within three years from the end of adjuvant treatment, with 60-80% of patients with advanced OC metastasis often experiencing tumour recurrence after treatment. Ovarian cancer frequently metastasizes to the peritoneum, pleura, liver, lung, and distant lymph nodes (vaan Baal et al., 2018).

Several genes, including BRCA1 and BRCA2, can be mutated in ovarian cancer. Twenty percent of patients with high-grade serous ovarian cancer carry both germline and somatic BRCA1/2 mutations, meaning the mutations occurred during conception and developed later in life (Ratner et al., 2019). The lifetime ovarian cancer risk for women with a BRCA1 mutation is estimated to be between 35% and 70%. For women with BRCA2 mutations, the risk has been estimated to be between 10% and 30% by age 70 (ACS, 2021). Mutations in BRCA1/2 genes inactivate the BRCA proteins, leading to defective DNA repair machinery.

Methodology

The resources for this literature review were selected only from recent open-sourced papers published after 2002. The search used many sources, mostly from the PubMed database (pubmed.gov), using the keywords "ovarian cancer, brain metastases, BRCA, PARP." There was limited research regarding the effectiveness of PARP inhibitors on brain metastases in a large population of patients, but there were many specific to either brain or ovarian cancer. After careful review, the final number of papers used for this review was 25. By utilizing available research, this review aims to gain an all-encompassing understanding of the treatment of OC and its consequential BMs.

Brain Metastases

Brain metastases are the most common type of brain tumour and a common complication of cancer. It is estimated that 10% to 26% of patients who die from their cancer will develop brain metastases. While few cancers that metastasize to the brain can be cured using conventional therapies, long-term survival is possible with minimal adverse effects on patients (Amsbaugh et al., 2023).

Type and Site of Brain Metastasis

Brain metastases most commonly occur in stages III and IV of OC and are histologically grade 3 (poorly differentiated). Metastases throughout the central nervous system are more common in areas of high blood flow. However, different patients tend to have distinct location distributions within the brain (Amsbaugh et al., 2023). The anatomical sites most frequently affected include the cerebellum (30%) and frontal (20%), parietal (18%), and occipital (11%) lobes (Pakneshan et al., 2014). Metastatic cancer passes through the bloodstream and enters the central nervous system through a blood-brain barrier (BBB) breakdown. Cells then divide by mitosis and proliferate, causing invasion, displacement, inflammation, and edema. To reach the brain, parenchyma metastatic cells have to cross the endothelial cell layer of brain capillaries, which forms the morphological basis of the BBB. While the BBB helps form a tight barrier that protects the central nervous system from entering cancer cells, it also actively prevents certain therapies from reaching metastatic cells during extravasation and proliferation from specific treatments targeting the brain (Wilhelm et al., 2013).

Cellular Mechanism of Ovarian Cancer and its Metastatic Mechanisms to the Brain

Does ovarian cancer metastasis occur exclusively via intraperitoneal seeding, or does it follow the "seed-and-soil" hypothesis, which plays a vital role in the confinement of the disease within the abdomen? According to the seed-and-soil hypothesis proposed by the English surgeon Stephen Paget in 1889, the pattern of metastasis is not a random outcome. Instead, certain tumour cells (seeds) have a specific affinity for certain organs (soil) (Yeung et al., 2015). Paget stated that a plant's seeds are carried in all directions but can only live and grow if they fall on congenial soil.

Brain metastases from OC result from hematogenous spread (through the blood). When considering the development of brain metastasis, the role of G-protein coupled receptors (GPCRs) should be considered. GPCRs are part of the largest family of cell-surface molecules and are expressed in most cells in the central and peripheral nervous tissues. In tumours, they have been observed in processes such as vasculogenesis and angiogenesis (creation and branching of blood vessels), as well as the proliferation, invasion, and survival at the secondary tumour site. During this process, GPCRs are notably facilitated by lysophosphatidic acid (LPA), a lipid responsible for signal transduction between cells. LPA levels in plasma are increased even in the early stages of OC and have been considered a potential diagnostic marker in OC, stimulating proliferation, migration, and invasion of OC cells (Lee et al., 2006). LPA signalling influences several processes in the central nervous system, including the proliferation of neural precursor cells, neural and glial development, proper cell migration, and cell survival. GPCRs are functionally linked to olfactory and taste transduction pathways. Recent reports indicate that several olfactory receptors (ORs) display high expression in several cancer cell lines and may contribute to tumorigenesis. The ability of ORs to sense small organic molecules may activate these pathways in cancer cells (Adams et al., 2017). However, ORs are not well studied in cancer genomics because they are assumed to only exclusively affect the olfactory epithelium. Nevertheless, from a treatment perspective, the nose-brain pathway may allow for delivering small therapeutic molecules to the brain, bypassing the BBB (Duchnowska et al., 2022).

Symptoms of Brain Metastases

Common presenting symptoms and signs of brain metastases from ovarian carcinoma included headache (~50% of patients), confusion, dizziness, decreased mental status, consciousness disturbance, general weakness, extremity weakness, gait disturbance, neurological motor deficit, hemiparesis, ataxia, visual disturbance, papilledema, incontinence, nausea, vomiting, speech impairment, paresthesias, syncope, and seizure (Piura et al., 2011).

The Immune System

The immune system plays a significant role in the development of ovarian metastases. Previous studies have shown that disrupting regulatory T-lymphocytes is associated with a metastatic phenotype and poor survival. In contrast, tumour-infiltrating lymphocytes or an immunoreactive gene expression profile are associated with a favourable prognosis (Duchnowska et al., 2022).

Immune checkpoints are a normal part of the immune system. Their role is to prevent an overactive immune response from destroying healthy cells in the body. Immune Checkpoint inhibitors include checkpoint proteins such as PD-L1 on tumour cells and PD-1 on T cells. When proteins on the surface of immune cells called T-cells recognize and bind to tumour cells, they send a signal to the T cells, which prevents the immune system from destroying the cancer. However, when an immune checkpoint inhibitor is used, it blocks the binding of PD-L1 to the PD-1, allowing the T cells to kill tumour cells (Duchnowska et al., 2022).

The immune system's stimulation is also reflected in brain metastasis from ovarian cancer, for example, by activating genes related to toll-like receptors that detect and respond to microbial antigen receptors expressed in neurons, astrocytes, and microglia. These receptors may link inflammation and neurodegenerative diseases via the activation of brain microglia 25. Until now, the immunological profile of the brain has been examined in only 2 cases, and both lesions showed a high mutational burden and increased PD-L1 expression compared with primary tumours 26 (Duchnowska et al., 2022).

BRCA Genes

The BRCA1 and BRCA2 proteins are essential in maintaining genomic stability by promoting efficient and precise repair of double-strand breaks. The primary role of BRCA2 appears to involve regulating the function of RAD51, an ATPase responsible for invading homologous DNA sequences to enable accurate and timely DNA repair (Bonilla et al., 2020). BRCA1 has a broader role upstream of BRCA2, participating in various cellular processes in response to DNA damage. BRCA1 and BRCA2

are two genes that are important in fighting cancer. When they work, they are tumour-suppressing genes that help keep breast, ovarian, and other types of cells from growing and dividing too rapidly or uncontrolled. However, if a gene is mutated, it significantly increases the risk of breast cancer and ovarian cancer in women (Gudmundsdottir et al., 2006).

In previously reported studies, patients with OC and BRCA mutations were diagnosed with BMs on average eight months earlier than the BRCA wild type (median time 27 months versus 35 months). The longer course of the disease in mutated patients may not be a relevant factor for the development of BMs. Another study demonstrated that patients with ovarian cancer and a mutated BRCA had a 4-fold increased risk for brain metastases than patients with BRCA wild type (Borella et al., 2020).

Concerning specific genes, BRCA1 was the most commonly altered gene in BMs from OC. A next-generation sequencing-based genomic analysis of eight OC BMs exhibited BRCA1/2 mutations in 7/8 cases, and all samples showed mutations in at least one gene involved in DNA repair (BRCA1/2, ATM, CHEK2) (Balendran et al., 2017). Furthermore, two authors demonstrated a high prevalence of BRCA1 protein loss in patients with BMs from OC (Borella et al., 2020).

Treatment Targeting both OC and BMs

Platinum-based Chemotherapy

Platinum-based chemotherapy is a cancer treatment involving drugs containing platinum ion compounds. The most common drugs include Cisplatin, Carboplatin, and Oxaliplatin. In short, platinum compounds in chemotherapy drugs form chemical bonds with DNA molecules in cells and cause structural changes and damage to DNA. This process damages cell mitosis and prevents the proliferation of cancer cells. The DNA damage also triggers apoptosis, hence eliminating cancerous tissue. In the last decade, it was discovered that platinum-based chemotherapy drugs, especially oxaliplatin, cause immunogenic cell death (ICD), by which cancer cells are killed in a way that triggers the immune system to recognize and attack them, enhancing the body's ability to eliminate cancer (MNT., 2023).

Trimodal Therapy

Trimodal therapy includes radiotherapy, surgery, and chemotherapy. A study by Pakneshan et al. reported a significant improvement in survival, with a median OS of 20.5 months, OS being the length of time from the start of treatment that the patient is alive (Pakneshan et al., 2014). Similar results were observed by Anupol et al. (median OS 20.5 months), Chiang et al. (median OS 30 months), and Marchetti et al. (median OS 24 months) (Anupol et al., 2002) (Chiang et al., 2011) (Marchetti et al., 2016). Trimodal therapy is now rarely used to treat ovarian cancer because the cancer usually involves too many organs and too much tissue in the area for radiation therapy to work effectively (Radiation Therapy for Ovarian Cancer). However, Trimodal therapy has proven effective in treating BMs from OC (Radiation Therapy for a Metastatic Brain Tumor). Currently, the best survival results for BMs from OC have been obtained with trimodal therapy (Borella et al., 2014).

PARP inhibitors

PARPs are a family of proteins involved in several cellular processes, such as DNA repair, genomic stability, and programmed cell death (Morales et al., 2014). Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have been shown to prolong the overall survival in patients with BMs from platinum-sensitive recurrent OC. There are four main PARP inhibitors: Olaparib (Lynparza), Niraparib (Zejula), Rucaparib (Rubraca), and Talazoparib (Talzenna) (FORCE inhibitors., 2022).

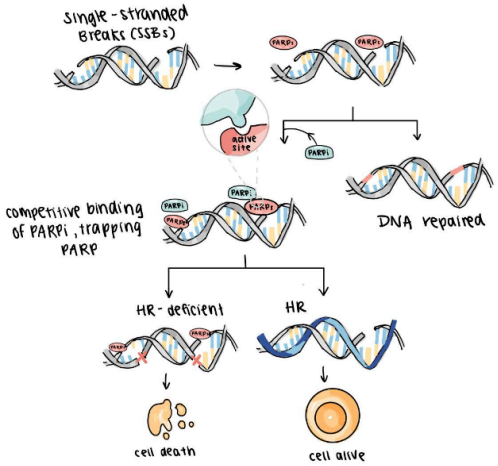

Figure 1. Self-made Diagram of the Mechanism of PARPi.

PARPs are recruited to DNA single-stranded breaks (SSBs) sites and rapidly activate. This initiative maintains DNA damage repair. PARPi contains a nicotinamide moiety that binds to PARPs, which block the synthesis of PAR chains and interfere with the repair of SSBs, preventing cancer proliferation. PARP1 autoPARylation leads to its release from the site of ENA damage. After the competitive binding of PARPi, PARPs are allosteric and enhance the binding strength to damage DNA. Trapped PARPs will eventually cause an accumulation of unrepaired SSBs. This impairs the proper progression of replication forks in DNA strands and ultimately results in the formation of DSBs (double-stranded breaks) that need homologous recombination (HR) repair. If the HR repair is deficient, the DNA breaks may not be repaired, leading to cell death (Fu et al., 2023).

Ethics

With rapidly increasing incidences, high prevalence, and delayed diagnosis leading to poor prognosis in many developing countries, cancer is a major global health challenge. Although the progression of new technology and the growing body of public knowledge contribute to a better prognosis and treatment pathways, these technologies are often beyond geographical and financial reach for low and middle-income countries. Furthermore, in countries where women face oppression, women are more likely to present symptoms to a doctor at a much-advanced stage of the disease, leading to a poor prognosis with much higher mortality. Ultimately, the outcomes of many preventable cancers vary significantly between developing country populations; thus, it should be a focal point for global health initiatives aiming to bridge these disparities.

Limitations

Brain metastasis from ovarian carcinoma is uncommon, with less than 600 cases documented to date in the literature. Because few cases of BMs from OC are reported and the prognosis of BM is poor, most reports online include singular cases or series of patients in which patient accrual occurred over prolonged periods during which treatment approaches and modalities changed. Hence, conclusions based on case studies with limited sample sizes are excluded from this paper to prevent overrepresentation. BMs from OC remain rare, and the current evidence on the treatment of a large population of patients is limited; thus, further studies are needed.

Conclusion

In conclusion, BMs from OC remain rare, with less than 600 cases documented in the literature; BMs most commonly manifest in symptoms such as headache, confusion, dizziness, and seizures. Since BRCA1 and BRCA2 are tumour-suppressing genes that inhibit the rapid and uncontrolled growth of cancer cells, it makes sense that 20% of patients with high-grade serous ovarian cancer have BRCA1 or BRCA2 mutations (Borella et al., 2020). Furthermore, patients with OC and BRCA mutations were diagnosed with BMs on average eight months earlier than the BRCA wild type (Borella et al., 2020). In addition, due to the long median period between the diagnosis of BMs and OC, the prognosis and in-depth research that can be applied to a larger population still need improvement. The median interval between diagnosis of ovarian carcinoma and detection of brain metastasis is about two years, with the primary ovarian carcinoma metastasizing to the brain at an advanced stage (III/IV). Most often, brain metastases affect the cerebrum (30%), followed by the frontal (20%), parietal (18%), and occipital (11%) lobes (Pakneshan et al., 2014). Although not used to treat OC itself, trimodal therapies have shown the highest survival rates for BMs from OC. On an ethical note, when considering survival rates, however, it should be noted that prognosis continues to be poor among low-medium income countries. Nevertheless, as the global community continues to grapple with cancer research, such endeavours should include addressing these disparities, as it is crucial for improving cancer outcomes globally, particularly by enhancing access to early detection and treatment in under-resourced regions.

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