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Considerations for Chemotherapy Treatment in Platinum Resistant High-Grade Serous Ovarian Cancer

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ABSTRACT

Ovarian cancer is considered to be the most fatal type of any gynecological cancer. Prognosis for the disease is poor, with a median survival of only thirty-two months following diagnosis and a five-year survival rate of only 39%. Many of the most lethal ovarian cancer cases are classified as part of the high-grade serous ovarian cancer (HGSOC) subtype, which is the most aggressive form of the disease. The primary concern with regards to treatment is that nearly 30% of patients will develop a resistance to forms of platinum chemotherapy, which is the main method of treatment. This suggests that a one-size fits all approach cannot be taken to treat ovarian cancer, and that further research must be done to understand how to treat the patients who present with platinum resistance. This literature review examines the mutations within two susceptible loci, specifically, the p53 and BRCA1/2 genes, in order to understand how platinum resistance develops and why it is present in some patients. The objectives of this review are to characterize the underlying genetic mechanisms affecting platinum resistance, specify the biomarkers associated with those mechanisms, and describe alternative methods for approaching the treatment of ovarian cancer on an individual scale.

Keywords: Ovarian cancer, platinum resistance, HGSOC

INTRODUCTION

In the broad sense, ovarian cancer refers to a cancer that originates near or within the ovaries, or on the outer layer of the ovary.[1] As is typical of many cancers, the disease can then spread throughout the body. Ovarian carcinomas usually migrate to local regions such as the pelvis and abdomen, but can eventually metastasize to distant areas of the body.[2] Data suggests that in 2017, around 2,800 women in Canada developed ovarian cancer and 1,800 of these women died as a result.[3] Prognosis is poor, with a five-year survival rate of around 39% and a median survival of thirty two months following diagnosis.[4]

Ovarian cancers can be subdivided into type I and type II cancers, as shown in Figure 1, each with a unique presentation.[2] Type I cancers have a large, unilateral growth that is typically low grade.[5] These low grade tumours appear similar to healthy cells at the microscopic level and typically grow at a much slower rate than high grade cancerous cells.[6] Patients with type I tumours usually have a higher survival rate, accounting for only 10% of ovarian cancer deaths. Type II cancers are typically much more lethal. They are high grade, present an abnormal morphology under a microscope, and proliferate at a faster rate.[6] Overall, tumour volume in type II ovarian cancers tends to be lower than in type I tumours, but this disease is much more aggressive and results in 90% of recorded ovarian cancer deaths.[5] Unfortunately, over 75% of ovarian cancer cases are advanced stage type II tumours at the time of diagnosis.[5]

The most common type of ovarian cancers that are diagnosed are type II carcinomas known as serous cancers.[5,7] Although they were believed to arise from the

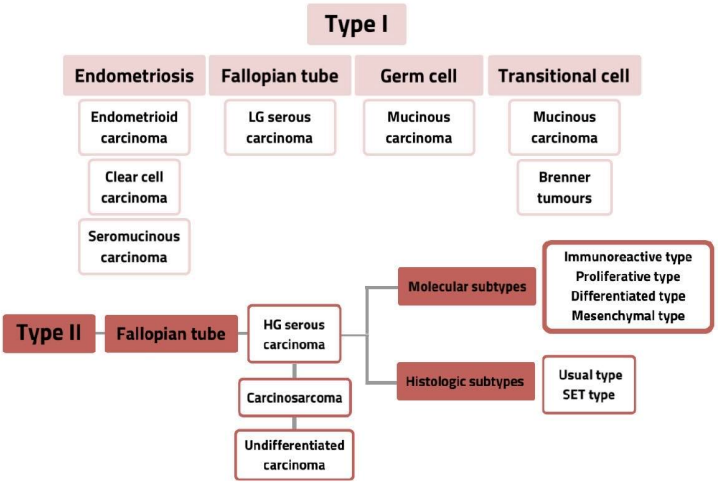

Figure 1. Characterization of type I and type II ovarian cancers.[5]

epithelium of the ovary, researchers now believe that they originate from secretory cells of the fallopian tubes.[7,8] When considering all types of ovarian cancer, the most aggressive type is high-grade serous carcinomas (HGSOCs) and most patients with advanced stage tumours present with this cancer type.[7] For this reason, the diagnosis, treatment, and challenges associated with this type of cancer will be discussed in more detail in an attempt to remodel how the medical community views and treats high-grade serous carcinoma.

HGSOC and other types of ovarian cancers are notable for being difficult to detect. Symptoms often do not present distinctively until later stages of the disease,[9] and one challenge in diagnosis is differentiating between symptoms of the cancer and conventional function in women, such as menstrual cycle-related pain in the uterus[10]. Around 95% of women reported symptoms in advance of their diagnosis, with common concerns including abdominal pain, pelvic and urinary problems, or issues pertaining to the gastrointestinal tract.[10] These are typical symptoms of many other diseases, making early diagnosis of HGSOC rather challenging.

CONVENTIONAL TREATMENT

This cancer has a great level of heterogeneity, thereby requiring different types of treatments depending on the individual.[11] The most common treatment methods are surgery and chemotherapy. Hormonal therapy and radiation therapy are also used infrequently, due to the fact that they require a small target area, whereas ovarian cancer tends to spread to multiple organs.[11]

Chemotherapy treatment commonly consists of a combination of carboplatin and paclitaxel; however, many other chemotherapeutic agents have been used to date.[12]

Carboplatin is a compound comprised of platinum and organic functional groups. Its main mechanism of action to kill cancer cells is through crosslinking DNA, or creating bonds between nucleotides that do not normally exist.[13] In the cell, carboplatin is activated and forms crosslinks through reactive platinum complexes that bind to nucleophilic groups in DNA, forming intrastrand and interstrand DNA crosslinks, as shown in Figure 2. The crosslinks result in apoptosis because that part of DNA is no longer functional.[13]

Carboplatin is more commonly used for treatment than cisplatin, another platinum compound that acts through crosslinking DNA due to cisplatin's propensity to cause nephrotoxicity – toxic activity in the kidneys that can lead to renal failure.[13] However, carboplatin induces myelosuppression in high doses, which causes reduced bone marrow activity and a decrease in both red and white blood cells.[13] Paclitaxel is usually administered with carboplatin to prevent microtubule depolymerization, however, it can cause nerve damage in high doses.[13]

Figure 2. Mechanism of intrastrand and interstrand crosslink formation in platinum-based chemotherapeutics (adapted).[12] Figure created using BioRender.

RESPONSES TO TREATMENT AND PLATINUM RESISTANCE

Initial response rates in patients undergoing chemotherapy treatments of carboplatin and paclitaxel tend to be 60-80%.[12] However, many patients that initially respond well to platinum-based chemotherapy treatments eventually develop some level of platinum resistance and either stop responding to treatment or relapse because the platinum is no longer able to effectively form crosslinks.[14] Platinum resistance in chemotherapy is measured by "platinum-free interval" (PFI), which is defined as the time period between the final treatment and the point at which the patient relapses.[15] If the relapse occurred more than six months after the completion of treatment, it is considered platinum sensitive, but if the patient relapsed sooner than six months, it is characteristic of platinum resistance.[14,15]

To better understand the mechanisms of platinum re-

sistance in serous ovarian cancer and guide future treatments, the Cancer Genome Atlas Project performed a genomic analysis of DNA samples in diseased subjects.[16] Part of the difficulty in treating HGSOC is the great deal of heterogeneity within the tumours and in patient responses; however, genomic data has provided some similarities. It was found that TP53 mutations are present in nearly all ovarian cancers, with a prevalence rate of 96%.[16] While less common, breast cancer gene (BRCA) mutations were found in 20% of DNA samples.[16] Many other genes have an influence on the molecular biology of ovarian cancer, including NF1, CDK12, over 100 copy number aberrations, and 168 genes associated with promoter methylation events. CCNE1, NOTCH, FOXM1, *src*, and E2F3 signaling also affect the molecular biology of the cancer.[16] The role of BRCA will now be highlighted because it could be significant in determining treatment regimes. Mechanisms of platinum resistance in TP53 will also be discussed in this review due to the prevalence of mutations in the gene.

BCRA1 AND BCRA2 MUTATIONS RELATING TO PLATINUM-RESISTANCE

BRCA1 and BRCA2 genes are both implicated in the development of ovarian cancer, but can also influence an individual's treatment regimen for HGSOC. Mutations in these genes increase an individual's likelihood of developing ovarian cancer. For those with mutations in BRCA1, the likelihood of developing ovarian cancer in an individual's lifetime is nearly 40%; the probability lowers to 11-18% for mutations in BRCA2.[17] However, despite an increased propensity for the development of carcinoma with these mutations, the prognosis is often better than those with wild-type BRCA1/2, which is the non-mutated gene form.[18]

BRCA1 is located on the long arm of chromosome 17 at position 21. Specifically, it is located at base pairs 43,044,294 to 43,125,482.[19] BRCA2 is located on the long arm of chromosome 13 at position 12.3, spanning base pairs 32,315,479 to 32,399,671.[19] Both genes are thought to have an "ovarian cancer cluster region" (OCCR) where an increased prevalence of mutations may lead to the development of ovarian cancer.[19] In the body, BRCA1 gene products are involved in tumour suppression and DNA repair.[20] The gene has an N-terminal RING domain that undergoes protein interactions, as shown in Figure 3.[21] The C terminus has BRCA1 C-terminus (BRCT) domains, which researchers have also uncovered in other proteins that are involved in DNA repair. Mutations in BRCA1 likely cause improper folding of the BRCT domain or change the interface where dimerization occurs.[21]

Similarly, BRCA2 gene products also play a role in tumour suppression. They have eight residues known as BRC repeats that assist in the binding of the protein RAD51 and BRCA2, as shown in Figure 4.[21] The binding of BRCA2 to the protein allows for the repair of DNA via homologous recombination.[23]

When these particular genes are mutated, the risk of developing cancer increases significantly. Research has shown that tumours originating from carriers of the mutated gene have undergone a deletion at the BRCA1/2 locus, which results in the disappearance of the wild-type allele leading to BRCA1/2 deficiency.[23] This deficiency makes cells more susceptible to cross-linking agents,[23] which is the typical mode of action of some chemotherapeutics, including cisplatin.[13] This means that patients who have BRCA1/2 deficiency usually have a more promising initial response to platinum agents since their mutated cells are more sensitive to these drugs than patients who possess the healthy genotype.[14]

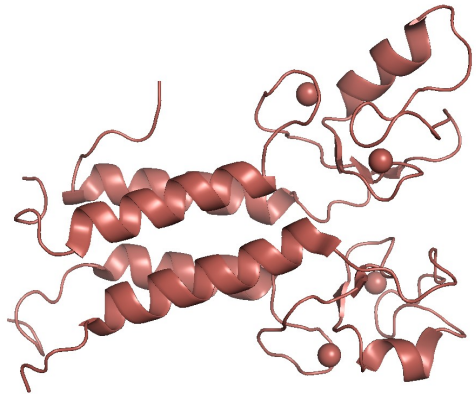

Figure 3. BRCA1 RING domain that forms a heterodimer with BARD1.[22]

A study by Alsop et al. (2012) found that for patients with BRCA mutations who relapse soon after the first round of treatment, platinum therapy has a better prognosis than in those without the mutation. However, while the original treatment for those with mutations in BRCA1/2 typically has a promising response, they may also develop resistance to platinum-based chemotherapeutic agents.[23] It has been suggested in the literature that secondary mutations could be the reason for this resistance.[14,17,23] This likely occurs by altering the proteins involved in DNA repair mechanisms, which increases the amount of DNA repair that occurs. An increased amount of DNA repair can cause an increase in homologous recombination, among other repair mechanisms,[14] which is the method by which BRCA1/2 engages in DNA repair.[20,23] Homologous recombination can lead to secondary mutations that revert the mutated BRCA gene back to the wild-type gene and restore the typical BRCA phenotype.[14,23] In order to revert to typical function in BRCA2, one study identified that the reading frame that was altered by a frameshift mutation of 6174delT must be restored.[23] In this study, all samples that were resistant to cisplatin

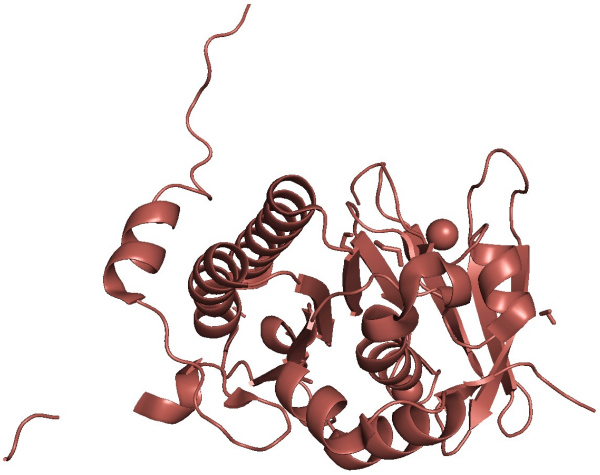

Figure 4. RAD51-BRCA2 BRC repeat complex.[24]

had mutations that corrected errors caused by the original frameshift.[23] Furthermore, it is reported that 28.3% of ovarian tumours that result from relapse have secondary mutations.[17] In addition, while 5.3% of carcinomas that are sensitive to platinum drugs have these mutations, the number is much higher for platinum-resistant tumours.[17] Secondary mutations were found to be present in 46.2% of platinum-resistant ovarian tumours, which builds upon the evidence of secondary mutations being responsible for the acquired resistance.[17]

TP53 AND p53 MUTATIONS RELATING TO PLATINUM RESISTANCE

Along with BRCA1/2, the TP53 gene also has a significant impact on the development and drug resistance of HGSOC. TP53 is located on the short arm of chromosome 17 at position 13.1.[25] It is 19,198 nucleotides long and contains seven exons, with the sequence beginning in exon two.[25] The gene is responsible for encoding p53, a tumour suppressor protein that regulates transcription through binding DNA at various genomic segments.[26] P53 is able to regulate cell cycle growth, control gene expression, and damage repair mechanisms.[26] Most of the mutations in the gene occur in the DNA binding domain, but it is also possible to detect mutations elsewhere within the sequence.[25]

There are a variety of mutations that occur within the gene, including base substitutions, deletions, and insertions.[25] To date, 2,329 different p53 mutations are known to affect human ovarian cancers, most of which are missense mutations, or mutations of a single nucleotide.[26] p53 can undergo a gain of function, loss of function, or dominant-negative mutation[26], however, the type of mutation is dependent upon where the mutation has occurred[25]. It is predicted that the mutated protein, mutp53, affects the body because it loses its ability to bind to necessary elements of DNA, altering its efficacy as a transcription factor.[25] Mutations of p.Arg175His, p.Gly245Ser, p.Arg248Trp, p.Arg248Gln, and p.Arg273His are all linked to promoting tumour growth, while mutations in p.Arg175His and p.Arg273His are connected to the development of platinum resistance in tumours.[25] A study by Brachova et al. (2014) determined that mutations where tumour growth is promoted have increased levels of platinum resistance and significantly worse survival rates compared to other alterations such as loss-of-function mutations.[27] Another study on platinum resistance suggests that activated p53 upregulates proteins that promote apoptosis and downregulates proteins that prevent cell death. This leads to the conclusion that inactive p53 may result in chemotherapeutic resistance.[28]

APPLICATIONS TO TREATMENT IN HIGH GRADE SEROUS OVARIAN CANCER

Evidently, platinum resistance is a significant problem in the treatment of ovarian cancer. Genetic analysis and a better understanding of the underlying molecular mechanisms could give medical professionals new strategies for approaching patient care. A review of the literature leads to some potential recommendations in treating HGSOC. Although platinum resistance is common, original treatment has a success rate of 60-80%.[12] These statistics indicate that administering a round of platinum-based chemotherapy could be the most effective and feasible option. However, it is also recommended that a more individualized approach be taken in order to improve prognosis in patients with HGSOC.

A good first step would be to begin screening for BRCA mutations following diagnosis. The results of this test can determine how well patients will react to platinum -based therapies. Those with BRCA mutations should be monitored for any potential secondary mutations, as this is an indicator that platinum resistance is more likely and other courses of treatment should be considered. Although TP53 mutations are common in ovarian cancer, it may improve treatment if medical professionals can narrow down the type and location of the mutation that affected the gene, as certain mutations are correlated with increased resistance. Knowing whether or not a patient has the propensity to develop platinum resistance can aid physicians in outlining treatment plans. If it is determined that a platinum treatment will prove less effective, it is possible to turn to options such as rational drug design, enrolling patients in clinical trials for novel chemotherapeutics that are currently being developed, or employing strategies such as maintenance chemotherapy in order to delay the inevitable resistance.[28]

In theory, genomic screening can provide information to medical professionals to guide HGSOC treatment. However, the question of feasibility still remains as it

would be necessary to perform molecular analysis on thousands of affected patients in order to take an individualized approach to their care.

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