Mechanisms and Treatment Considerations of Chemotherapeutic Resistance within BRCA-Mutated Ovarian Cancer

Priyal Tyagi

Abstract

Ovarian cancer is the cause for the most gynecological cancer deaths and can develop through hereditary syndromes such as Hereditary Breast and Ovarian Cancer syndrome (HBOC). Ovarian cancer developed by this hereditary syndrome occurs when an individual has mutations in tumor suppressor genes BRCA1 and BRCA2, resulting in cancers such as breast or ovarian cancer. While it is often treated with chemotherapies such as cisplatin (platinum-based chemotherapy), many patients develop chemoresistance to first line therapies. Chemoresistance can arise through DNA repair by cancer cells, drug efflux for medication to be pumped out of the cell, and autophagy to recycle damaged organelles for energy. Following chemoresistance, patients must be treated with a second-line therapy such as combination therapy, which uses the effects of two types of chemotherapies simultaneously, or drug holidays, where patients take breaks from treatment, increasing chemosensitivity. However, despite having found viable treatment approaches, medical professionals are researching methods of preventing chemoresistance. Monitoring the growth of cancer through biomarkers can help alert doctors to development of chemoresistance. In addition, combination therapy can be administered as a first-line therapy in order to prevent the onset of chemoresistance. By studying mechanisms of chemoresistance, effective treatment options and prevention methods can be used to benefit patients with ovarian cancer.

Introduction

Ovarian cancer is the second most common malignancy in women over the age of 40, following only breast cancer. It is also the seventh most common cause of all cancer-related deaths[1] and the most common cause for gynecological cancer deaths[2] . Ovarian cancer is often detected when it reaches an advanced stage due to a lack of severe symptoms prevalent in early stages[3]. It can be a result of hereditary (genetic) factors, carcinogens, and/or lifestyle factors[4]. Though hereditary ovarian cancer can occur due to a variety of different family syndromes, a common one is Hereditary Breast and Ovarian Cancer syndrome (HBOC). Genes affected within this syndrome are breast cancer-1 (BRCA1) and breast cancer-2 (BRCA2). The incidence rate for women that have BRCA1/2 mutations within ovarian cancer populations is 12-14%[5]. Women who possess BRCA1 and BRCA2 mutations have a 50% and 30% increased risk of developing ovarian cancer, respectively[6]. Knowledge of HBOC can encourage early testing which can help decrease the risk of late-stage cancer[2].

BRCA genes are tumor suppressor genes that regulate cell division to prevent the onset of cancer. Through DNA double-strand break (DSB) repair, BRCA genes repair damaged DNA caused by errors in cell division[6]. Hereditary mutations in BRCA genes prohibit proper cell regulation, ultimately resulting in an uncontrolled growth and division of cells known as cancer. The BRCA1 gene codes for proteins that are involved in inspecting DNA strands to look for DSBs, while the BRCA2 gene helps attach proteins to required repair sites[7].

As cancer progresses, medical professionals use a variety of treatment methods, the most common of which is chemotherapy, which uses cytotoxic chemicals to kill cancer cells[8].

However, cancer cells may develop chemoresistance over the course of treatment and cancer progression. The cancer cells develop resistance to chemotherapies through varying mechanisms, rendering these therapies ineffectual over time[9]. Chemoresistance is often observed in cases of uncontrollable cancer or patient relapse. 70% of patients in an advanced stage of ovarian cancer recur within 2 years despite chemotherapy treatment[10]. By understanding different mechanisms of resistance, doctors can offer alternative treatment options for patients, such as combination therapy[11]. However, despite efforts to develop alternate treatment procedures, working towards chemoresistance prevention will help increase the effectiveness of primary treatment approaches. This review considers the mechanisms of chemoresistance such as DNA repair by cancer cells, drug efflux, and autophagic processes to review chemotherapeutic treatment intervention within BRCA-mutated ovarian cancer.

Methods

Two main databases were consulted: Google Scholar and PubMed. Literature was sorted by relevance, as opposed to date, and ranged from the years of 1990 to current date. Search results also ranged in type including reviews and primary literature. Key terms such as Hereditary Breast and Ovarian Cancer (“HBOC”), “BRCA-mutated ovarian cancer”, “chemoresistance”, “drug efflux”, “autophagy”, “combination therapy”, “drug holiday”, “biomarkers” were used to find sources.

Results

Mechanisms of Chemotherapeutic Resistance

Type of Chemotherapy	**Chemotherapy Resistance Mechanisms/Treatment**	**Source**
Platinum Chemotherapy	DNA Repair Drug Efflux Combination Therapy Drug Holiday	Gasco et al. 2003, Ali et al. 2013, Oritz et al. 2022, Pfisterer et al. 2005, Bukowska et al. 2015, Niveditha et al. 2019
Olaparib	Autophagy	Santiago et al. 2019, Bellare et al. 2021
PARP Inhibition	DNA Repair Drug Efflux	Toss et al. 2013, Ortiz et al. 2022
Taxane	Drug Efflux Combination Therapy	Madariaga et al. 2019, Pfisterer et al. 2005, Bukowska et al. 2015

Table 1. Different types of chemotherapy as well as their relevant resistance mechanisms and treatment approaches

DNA Repair

Chemoresistance refers to cancer cells' reduced sensitivity to administered chemotherapies, preventing their function of inhibiting cancer cell growth. A possible precursor to chemoresistance is alterations in DNA repair pathways. Normal cells use DNA repair for restoration purposes. However, DNA repair becomes a hindrance within chemotherapy treatment because it repairs the damage in cancer cells induced by chemotherapy. While BRCA-mutated cancer cells are originally developed through a lack of DNA repair for genetic mutations in somatic cells (cells other than gametes), chemoresistance emerges due to the ability of cancer cells to become tolerant to DNA damage through using alternate DNA repair pathways to repair DNA lesions[12].

Platinum-based chemotherapeutic agents, such as cisplatin and carboplatin, work through binding to DNA and deforming its helical structure to prevent DNA replication, inducing DSB[13]. BRCA genes help repair double strand breaks through the homologous recombination repair (HRR) pathway[14]. HRR uses the sister chromatid as a model to reconstruct the DNA in the repair process. However, for BRCA-mutated ovarian cancer cells, they cannot use this pathway to repair DNA strands. As a result, cancer cells depend on nonhomologous end joining (NHEJ) as an alternate pathway to repair double strand breaks[15], making it resistant to platinum agents. However, the use of poly(ADP-ribose) polymerase (PARP) inhibitors results in aberrant activation of NHEJ, so that the unreliability of the pathway results in more mutations that cannot be repaired, causing cell death[16]. PARP inhibitors can also develop a second mutation by using another DNA repair pathway, microhomology-mediated end joining (MMEJ), which results in the overriding of PARP inhibition by cancer cells. MMEJ pathway repair is invoked by the enzyme aldehyde dehydrogenase 1 family member A1 (ALDH1A1). An increase in this enzyme results in the use of MMEJ pathway, causing chemoresistance to PARP inhibition, preventing apoptosis for ovarian cancer cells[17]. The cells use various alternate pathways to bypass ones that are inhibited due to treatment, resulting in chemoresistance. Understanding this pathway fail-safe system is pivotal in devising therapeutic interventions to overcome chemoresistance in BRCA-mutated ovarian cancer cells and patient prognosis.

Drug Efflux

Efflux pumps are used by ovarian cancer cells to moderate the amount of medication in them. As a result, chemotherapies are pumped out of the cancer cell as a defense mechanism. For example, ATPase copper transporting alpha and beta (ATP7A and ATP7B) are genes that produce proteins that work to efflux platinum making the cell incapable of using platinum therapy to get treated due to its cisplatin resistance[17]. ATP7B transports cisplatin through the binding of the drug to the surface of vesicles or by transporting it directly into the vesicle. As ATP7B binds to cisplatin, it uses ATP in order to transport it across the vesicular membrane[18]. Additionally, ATP-binding cassettes (ABC) are membrane proteins that work to transport substrates and toxins outside of cells. ABCB1 is an example of an ABC drug transporter that forms multidrug-resistant protein 1 (MDR1) also called pump molecule phenolic glycoprotein (PgP). It corresponds to efflux of a variety of different drugs such as doxorubicin and paclitaxel. The ABCB1 gene creates a pump molecule phenolic glycoprotein (PgP)[19]. Transport uses the

hydrolysis of ATP and a drug concentration gradient to transport medication outside of the cancer cell[20]. The rate at which PgP is able to pump out the medication exceeds the rate at which the medication enters the cell. Therefore, as multiple proteins work to moderate chemotherapy concentration, the medication is pumped out of the cell, rendering treatment ineffective.

Autophagy

Autophagy recycles remnants of chemotherapy-affected cancer cells to synthesize other cellular structures in other cells. It allows damaged cell organelles to provide energy for the cell through converting the organelles into fatty acids. Autophagosomes fuse with lysosomes to produce autophagolysosomes. The enzymes from lysosomes break down cells into amino acids that can provide energy for the cell and protect it. However, due to the protective nature of the autophagy process for the cell, it has adverse effects on individuals with cancer. The proteins that are in dying cells are recycled into amino acids and fatty acids in adjacent cells. The energy that is generated through the activation of amino acids allows cancer cells to continue to rapidly divide and grow[21].

Though varying treatments can be introduced to patients, autophagy becomes a mechanism of resistance. This was demonstrated in a study where they decreased the presence of ATG5 and ATG7, proteins typically used to help form autophagolysosomes, to suppress autophagy, allowing for the cell to be more sensitive to the cancer treatment, olaparib. The decrease of the proteins meant that there were decreased amounts of autophagy which had resulted in higher levels of apoptosis, suggesting that the cancer cell is dependent on autophagic processes in order to survive[22]. Another study demonstrated that cancer medication, such as olaparib and talazoparib, result in the production of autophagosomes and lysosome fusion, directly resulting in autophagy[23]. The damage induced on cancer cells by chemotherapies is counteracted by the recycling process of autophagy. The anaerobic glycolysis creates oxygen for tumor cells thus encouraging autophagy. While chemotherapy is administered in an effort to induce apoptosis of cancer cells, autophagy is used as a defense mechanism to avoid it instead[24]. Autophagic processes result in the survival of the cell despite the medication being administered making the cell resistant. Therefore, the cells are unable to undergo apoptosis making treatment ineffective. The mechanism of autophagy emphasizes the crucial concept of the ability of cancer cells to use typical cell function as a way to inhibit cancer treatment. Through targeting this concept, the efficacy of cancer therapies can be enhanced.

Treatment for Chemoresistance

Combination Therapy

In order to combat chemoresistance of first-line therapies, many doctors try a cocktail of therapies. By using two drugs in conjunction, patients have a smaller chance of developing resistance. This is also seen in cases of antibiotic resistance where the use of combination therapy has resulted in greater effective treatment[25]. The drugs have a different mechanism of action while having improved efficacy. Furthermore, the reduction in dosage can help alleviate the severity of the side effects of the chemotherapy on the patients. The drugs work within different types of interactions: synergism and additivism. For a synergistic effect, the two drugs work in tandem to produce a stronger effect than if they were to be administered separately. On

the other hand, additive effects are when the individual effects of both drugs are exerted simultaneously.

Olaparib is a type of PARP inhibitor that can be affected by chemoresistance through synthetic lethality. It can be administered along with carboplatin and cisplatin for platinum-sensitive ovarian cancer patients and has resulted in highly effective results with improvements in progression-free survival as well. The efficacy of the olaparib-carboplatin treatment combination also allows for administration of smaller doses of carboplatin, reducing harmful side effects on healthy cells[26].

Following 6 months of therapy, a paclitaxel-platinum treatment is found to be highly successful in comparison to monotherapies[27]. A study was done to compare the efficiency of carboplatin-paclitaxel to the cisplatin-paclitaxel combination and its effects on women with ovarian cancer. It was found that although both treatment combinations were found to be similar in efficacy, the carboplatin-paclitaxel combination results in less severe toxicity to the nervous system and gastrointestinal tract[28]. The use of combination therapy allows for treatment of cancer despite chemoresistance, while also reducing dosage, resulting in a fewer amount of harmful side effects. In cases where combination therapy is not effective in treating specific mechanisms, doctors turn to other general therapies.

Drug Holiday

When chemoresistance is first developed, medical professionals look for different drugs to use because it seems as though cancer cells have stopped reacting in an adverse manner to it. However, new studies have shown that by continuing therapy after taking a break from chemotherapy administration, called “drug holidays”, it is possible for cancer cells to regain sensitivity to the drug[29]. For example, if a patient were to be platinum-resistant, they could take a break from the platinum-based treatment and instead be administered non-platinum chemotherapy. This allows the cells to regain the platinum-sensitivity that they had at the start of treatment[30]. As a result, for some patients, they do not have to switch to a second-line therapy and can continue their initial therapy following a break that is determined by a medical professional. This allows doctors to also test the efficiency of the drugs for the patient as opposed to switching to different medications.

Preventing Chemoresistance

In order to prevent chemoresistance in women with ovarian cancer, it is vital that the prognosis stage is earlier in the development of the disease. When cancer becomes chemoresistant, it often results in a relapse. As a result, if doctors are able to identify continued growth of cancer or its return, they can use this information to assess for altered treatment early on. An emerging method of monitoring clinical response is through the technology of biomarkers, macromolecules that help indicate any changes in biological processes. Biomarkers can help doctors track the resistance in cancer cells and the effects of drugs that are administered[31]. These biomarkers can also help predict responses to specific chemotherapies through gene expression of cancer cells. By using this data, medical professionals are able to determine a course of action for different patients and the efficacy of different types of treatment[32].

Monotherapy is more likely to result in chemoresistance. However, combination therapy can use fewer cycles to result in a more effective treatment, decreasing the likelihood of

developing chemoresistance[33]. Using epigenetic drug therapies such as PARP inhibitors within a combination therapy approach as a first-line therapy can help prevent the formation of cancer progenitor cells. The epigenetic drugs can strengthen the effects of other drugs that it is used in combination with. Therefore, if cancer cells develop chemoresistance to a specific therapy, the simultaneous use of another medication will allow for a continued effect on the cancer cells. Preventing the growth of progenitor cells will reduce effects of chemoresistance such as relapse in patients[34]. Chemoresistance prevention methods are crucial for patients as they minimize the need for second-line therapies that may have debilitating side effects, promoting better patient well-being.

Discussion

Chemoresistance is the cause of more than 90% of treatment failure for metastatic cancer patients[35]. Although cancer treatment and care has drastically improved over the years, chemoresistance continues to be a significant hurdle within treatment for the increasing number of cancer patients[36]. Addressing chemoresistance is crucial for improving efficacy of first-line treatments. This will help to diminish rates of cancer relapse and positively impact patient survival. Learning about different mechanisms of chemoresistance will allow doctors to be able to identify the best treatment on a patient-to-patient basis. Understanding mechanisms such as DNA repair, drug efflux, and autophagy in relation to chemoresistance is crucial in helping doctors determine effective treatments, unique to each patient. By understanding the function of DNA repair pathways and how they are manipulated through cancer cells, we can see how alternative pathways are used in order to avoid inhibited pathways. Chemoresistance helps illustrate the potential negative effects of DNA repair as it restores cancer cells that chemotherapy is killing. Additionally, drug efflux is a mechanism of resistance that pumps chemotherapy out of the cancer cell as a defense mechanism. Similarly, autophagy defends the cell against chemotherapy by reusing damaged cell organelles to produce energy for the cell. While an understanding of these mechanisms can give insight for clinical implications, it also demonstrates that normal functions of a cell that are typically used to ensure survival are harmful in the context of a cancer patient. As a result, most therapies are developed to bypass the regular functions of a cell.

To combat first-line chemoresistance, patients are administered second-line therapies based on responses to varying treatment approaches. However, an exact therapy regimen does not work for all patients. Instead, doctors often try to find second-line therapies that best suit a patient's needs with minimum harmful side effects. Following signs of chemoresistance, many patients try combination therapy instead. Using multiple types of medication allows doctors to target various pathways and mechanisms at once using the different functions of the chemotherapy. While specific combinations may vary between patients, combination therapy has a wider scope for different mechanisms of chemoresistance that it can treat. An additional treatment for chemoresistance uses breaks in treatment to increase chemosensitivity. This gives patients a break from side effects that they may experience on chemotherapy while also treating chemoresistance. Whether doctors change drug administration schedules giving their patients a “drug holiday”, or use cisplatin and carboplatin pairs, therapy depends on the patient and not just the disease.

Though treatment is important to help people who are currently suffering from chemoresistance with their cancer, it is important to evaluate how we can eliminate or reduce

this problem in the future. By using biomarkers, doctors can collect data to predict the effects of a certain chemotherapy on a patient in order to prevent chemoresistance. As a result, treatment will become more effective by allowing doctors to be mindful of specific issues that can arise within the patient's treatment. Similarly, doctors may use combination therapy as a prevention method to cover different pathways and mechanisms before a person reaches chemoresistance. It is crucial to implement forward thinking in the domain of public health in order to create prevention strategies. Through studying chemoresistance and its effects on varying patients, doctors will be able to predict the effects of therapies and even prevent chemoresistance to lower ovarian cancer mortality rates.

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