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Platinum- and Non-Platinum-Based Chemotherapy in Patients with Recurrent Platinum-Resistant Ovarian Cancer: A Review Article

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ABSTRACT

Ovarian cancer is the second most common malignancy in women worldwide, causing many deaths each year. Chemotherapy is one of the most important therapeutic strategies that can increase the survival of these patients; however, one of the problems in chemotherapy is resistance against platinum treatment. Evaluating the effect of platinum- and non-platinum-based chemotherapy in patients with recurrent platinum-resistant ovarian cancer can enhance our view on this issue. The present review article sought to identify the treating efficacy of platinum and non-platinum-based chemotherapy in patients with recurrent platinum-resistant ovarian cancer by searching scientific databases and examining the aspects of platinum resistance in various articles. Oncological results have shown that ovarian cancer is a deadly disease, and most cases are diagnosed when the cancer spreads outside the ovary and often throughout the entire abdomen. On the other hand, in many cases, disease recurrence is associated with drug resistance. The use of a platinum-free interval has played an important role in its treatment efficacy. Understanding the cause of platinum resistance and discovering strategies to reduce drug resistance, especially to new ones, is very important. The present article suggested oncology teams agree on treatment methods and the best treatment approach against platinum resistance in malignant ovarian cancers and offer a better treatment solution by considering innovative strategies.

Keywords: Chemotherapy, Platinum, Recurrence, Ovarian Cancer

Introduction

Ovarian cancer is the second most common known malignancy in women worldwide, causing 150,000 deaths annually (1). The 5-year survival rate for patients suffering from this cancer is approximately 45% (2). The prevalence of ovarian cancer is 9.2 per 100,000 in Iceland, 9.4 per 100,000 in the black population, and 10.3 per 100,000 in Spain (3, 4). Overall, ovarian cancer is the seventh most common cancer among women. In 2018, 4.4% of all cancer deaths among women were attributed to ovarian cancer. Although the prevalence of cancer is higher in countries with high Human development index (HDI), the mortality rate is lower in these countries. Various factors affect the incidence of ovarian cancer, among which the genetic factor is the most important. Pregnancy, breastfeeding, and oral contraceptives all play a role in reducing the risk of this disease. Early diagnosis and early prevention of ovarian cancer is difficult due to its heterogenic nature (5, 6). Most patients with ovarian cancer relapse within the first 3 years following diagnosis (7, 8). At the time of disease recurrence, surgical treatment and chemotherapy are used as the main therapeutic approaches (9). Platinum-based chemotherapy is one of the most commonly used treatment regimens offered for this cancer. Despite its effectiveness, platinum induces drug resistance after prolonged use (10). Although patients are sensitive to platinum in the early stages of relapse, eventually they show resistance to platinum (11). Due to the important issue of resistance to platinum, the present review article was performed to evaluate the treating efficacy of platinum- and non-platinum-based chemotherapy in patients with recurrent platinum-resistant ovarian cancer.

Methods

The present review article investigated the therapeutic status of platinum- and non-platinum based chemotherapy in patients with recurrent platinum-resistant ovarian cancer. For this purpose, papers which investigated ovarian cancer and resistance induced by platinum during chemotherapy in patients with ovarian cancer and published from 1997 to 2020 were selected.

The search for articles was done in May 2020, and databases of Nature, WHO, NCBI, PsycINFO, Pubmed, and Medline were searched to find articles on ovarian cancer. Research on ovarian cancer, treatment, and drug resistance was searched and evaluated. During the search, keywords of ovarian cancer, ovary, carboplatin, platinum, platinum resistance, platinum sensitivity, resistance mechanism, etc. were used. Duplications and articles that were not related to our topics were identified and deleted during the data collection process. Out of a total of 316 articles, 74 ones were finalized for further investigation.

Ovarian carcinoma

Ovarian carcinoma is a type of cancer in women that is often associated with differentiation from epithelial cells **(12)**. The main subtypes of ovarian carcinoma include high-grade serous carcinoma (HGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), low-grade serous carcinoma (LGSC), and mucinous carcinoma (MC) (Table 1) **(7, 13, 14)**. In the following, these types of ovarian carcinoma are elaborated.

High-grade serous carcinoma (HGSC)

HGSC is the most common subtype of ovarian cancer. HGSCs are responsible for 70 to 74% of ovarian carcinomas, and less than 5% of HGSCs are diagnosed at stage I **(15)**. HGSC presents in women later than LGSC, so that the mean age of HGSC onset is 60 years. HGSCs are usually widely disseminated and may involve large masses in the ovaries and other intra-abdominal locations, with or without ascites **(4, 16-18)**.

Endometriosis carcinoma (EC)

Approximately half of the ovarian ECs are diagnosed at stage I, of which about 15% involve two ovaries **(13)**. EC is one of the two main types of ovarian cancer associated with endometriosis. Around 5% of ovarian ECs are concurrent with uterine EC at the time of diagnosis. The origin of carcinoma is important for both treatment and prognosis. In many cases, these two cancers are thought to be from a primary tissue, but the prognosis of an EC that originates from the uterus and then metastasizes to one or both ovaries is considerably worse and more serious **(19-21)**.

Clear cell carcinoma (CCC)

CCCs are the main group of ovarian carcinomas associated with endometriosis. Researchers have observed several growth patterns for CCC, such as solid, papillary, and tubulocystic pattern **(22-25)**.

Low-grade serous carcinoma (LGSC)

LGSCs are uncommon types of ovarian cancer, and only 10 to 20% of them are diagnosed at stage I **(26, 27)**. Although LGSCs are usually less prevalent than HGSCs, they are relatively more resistant to chemotherapy **(28)** and the overall survival rate is low for women diagnosed at an advanced stage of this disease **(29)**. HGSCs are most associated with serous borderline tumors (SBTs) and present in the form of palpable masses in one or both ovaries. LGSCs are less likely to progress to malignancy tumors than HGSCs, and there are two types of ovarian carcinomas with different mutation patterns for most cancer cases **(28, 30-33)**.

Mucinous carcinoma (MC)

Benign ovarian mucinous tumors account for approximately 12% of all ovarian tumors in the Western world **(34)**. Many malignant ovarian tumors are metastases from MC appearing in other subtypes of cancer, such as the gastrointestinal and biliary tracts and pancreas **(35, 36)**. Since most MCs show evidence of intestinal-type differentiation, differentiating between primary and metastatic MC can be challenging. Consequently, in some cases, it is possible to mistakenly classify metastatic ovarian adenocarcinoma as the primary ovarian MCs **(37, 38)**.

Chemotherapy

Types of chemotherapy

A) Curative chemotherapy: It is done with the aim of eliminating all cancer cells from the body and removing the cancer completely.

B) Adjuvant chemotherapy: It is done to destroy hidden cancer cells that may remain in the body after surgery but are not detectable.

C) Neo-adjuvant chemotherapy: Some tumors are very large or are in places such as the liver, below the diaphragm, or attached to large arteries, and completely removing the tumor is not possible through the first surgery. In these cases, neo-adjuvant chemotherapy, known as preoperative chemotherapy, can be done before surgery to shrink the tumor.

D) Palliative chemotherapy: Chemotherapy is called palliative when it is no longer possible to remove all the tumor cells.

Among the treatment's studies, platinum is one of the most important cytotoxics in inhibiting ovarian cancer. In most cases, during the treatment of ovarian cancer, the efficiency of chemotherapy and the treatment process is impaired due to platinum resistance **(40, 41)**.

Platinum-based chemotherapy

Platinum is one of the most common anticancer drugs used in chemotherapy. It interacts/ reacts with /binds to DNA atoms, damaging DNA strands and killing cancer cells. Despite its effectiveness, platinum induces drug resistance after prolonged use in most cases. It is important to note that some tumors are initially resistant to platinum and generally do not respond to platinum treatment **(10, 41, 42)**. Although platinum-based chemotherapy is the first line of treatment for advanced-stage ovarian cancer, platinum resistance usually occurs after 6 months. Many cells

react differently to platinum (Table 2), and platinum exerts different biological effects on cells **(43-45)**.

Table1. A summary of the five major histotypes of ovarian cancer and risk factors (39)

Item	All invasive	High-grade serosa (HGSC)	Low-grade serous (LGSC)	Mucinous (MC)	Endometrioid (EC)	Clear cell (CCC)
Precursor lesion	NA	Serous tubal intraepithelial carcinoma (STIC)	Borderline serous tumor	Cystadenoma, borderline mucinous tumor	Atypical endometriosis	Atypical endometriosis
Somatic mutations	NA	BRCA1/2, TP53	BRAF, KRAS	KRAS	PTEN, CTNNB1, ARID1A, PIK3CA	ARID1A, PIK3CA
Established risk factor						
Age at menarche	Null-weak protection	Null	NE	Null	Null	Weak protection
Age at menopause	Moderate increase	Null	NE	Null	Weak risk	Moderate risk
Parity	Weak-moderate protection	Weak protection	NE	Weak protection	Moderate protection	Moderate-strong protection
Lactation	Weak-moderate protection	Weak protection	NE	Moderate protection	Moderate protection	Null-weak protection
Endometriosis	Moderate-strong risk	Null	Strong risk	Null	Strong risk	Strong risk
Tubal ligation	Moderate protection	Null-weak protection	Null	Null-weak protection	Strong protection	Strong protection
Oral contraceptives	Moderate protection	Moderate protection	NE	Null-weak protection	Moderate protection	Moderate protection
Hormone therapy	Moderate risk	Moderate-strong risk	NE	Null	Moderate-strong risk	Null-weak protection
Body mass index	Weak risk	Null	Weak risk	Weak risk	Weak risk	Weak risk
Smoking	Null	Null	NE	Moderate-strong risk	Null-weak protection	Null-weak protection

Weak: ≤25%, Moderate: 25%–50%, Strong: ≥50%, NA= not available, NE= not estimated.[a] Given that the majority of serous tumors are high-grade, risk associations for overall serous subtype are reported when no data is available by grade.

Table 2. Biological effects of platinum derivatives on normal cells in ovarian cancer (45)

Activity	Mechanism	Cell type	Drug
Catabolic metabolism	Increased consumption of glucose and generation of lactic acid	Fibroblasts	CIS; CAR
	Induction of autophagy	Tubular epithelial cells	CIS
Drug resistance	Increased expression of anti-apoptotic proteins in cancer cells related to increased production of IL-11 by fibroblasts	Skin fibroblasts	CIS
	Accumulation of drugs in normal cells instead of cancer cells	Skin fibroblasts	CIS

Activity	Mechanism	Cell type	Drug
Induction of cellular senescence	Up-regulation of cell cycle inhibitors; deterioration of cell–cell communication; Induction of SA-β-Gal	Skin fibroblasts	CIS; CAR
Induction of pro-inflammatory phenotype	Activation of NF-κB-dependent inflammatory response	Proximal tubule epithelial cells	CIS
	Overproduction of IL-1 and IL-6	Umbilical vein endothelial cells	CIS; CAR
	Overproduction of ICAM-1 and IL-8	Retinal endothelial cells	CAR
	Overproduction of ICAM-1 and ELAM-1	Dermal endothelial cells	CAR
Induction of cell death	Dysfunction of mitochondria; activation of caspases	Renal epithelial cells; endothelial cells	CIS
Induction of oxidative stress	Increased production of ROS; decreased activity of antioxidants; deregulation of mitochondrial metabolism	Renal proximal tubule epithelial cells	CIS
	Increased DNA damage	Hippocampal neurons	CIS
	Increased DNA damage	Fibroblasts; Schwann cells	CAR
Modulation of angiogenesis	Impaired MMP-2-related reactions of vascular endothelium	Endothelial cells	CIS
	Increased production of VEGF	Endothelial cells	CAR

Cancer recurrence: platinum sensitivity and resistance

The most common treatment in the early and advanced stages of cancer is surgery and removal of tumor tissue. However, treatment strategies for advanced cancer in women are controversial. In many cancer cases, chemotherapy is used as the main treatment after surgery or without surgery. Studies have shown that although most patients initially respond to chemotherapy, the disease recurs in many cases **(8, 10, 45, 46)**. One of the most important causes of the disease recurrence is resistance to platinum and consequently ineffectiveness of treatment. Platinum-sensitive ovarian tumors respond positively to chemotherapy drugs, resulting in carcinogenic process reduction, but cancer cells are resistant to chemotherapy drugs in many cases (. Resistance to treatment is associated with increase of resistant cancer cells, inhibition of platinum function, and continuation of cancer cells proliferation **(47)**. Resistance to platinum-containing drugs depends on mechanisms such as lack of drug delivery into the cancer cell, oxidation of the drug by intracellular proteins, and so on. The main purpose of platinum drugs is to damage DNA and prevent cell proliferation. Sensitivity or resistance to these drugs depends on the cell's ability to detect the substance damaging the DNA. Clinical evidence suggests that some cellular pathways are disrupted in tumor cells, inducing a specific pathway that is involved in sensitivity and resistance to platinum-based drugs **(48-50)**

Malignant cases and treatment

One of the most important issues investigated in this article was the study of ovarian cancer recurrence and platinum resistance. In many cases, the tumor recurs after a period of treatment. Highly efficient and long-term treatment is one of the therapeutic challenges in patients with ovarian cancer. Platinum-sensitive patients were studied in many clinical studies. In these studies, it was revealed that these patients' treatment was associated with good outcomes initially, but most cases experienced efficiency reduction and tumor recurrence **(51, 52)**. Tumor recurrence rate and platinum resistance are effective predictors of discovering platinum resistance and therapeutic efficacy **(53)**. Luo, Lee **(54)** evaluated 341 patients at stage IIIV and IV of epithelial ovarian cancer in terms of recurrence after neo-adjuvant treatment and surgery. They yielded that treatment with interval debulking surgery (IDS) was associated with the risk of platinum resistance **(54)**. Numerous studies have revealed that IDS treatment is associated with an increased risk of platinum **(55-57)** and suggested the strategy of using platinum-free interval as one of the good strategies to combat drug resistance **(51, 52, 58-61)**. In various studies on malignant ovarian cancer, offering a platinum-free strategy was effective in chemotherapy **(62-64)**. Studies have revealed that a platinum-free diet is usually the most appropriate method for patients with relapsing cancer and resistance to chemotherapy. Clinical and clinical data have shown that prolonging the platinum-free interval leads to platinum sensitivity restoration in many cases, thus enhancing survival. In fact, these studies suggest that non-platinum-based treatments over a longer period of time lead to platinum sensitivity restoration in cancer cells **(47, 65-67)**. The effectiveness of a non-platinum-based regimen in patients with malignant ovarian cancer also depends on the type of non-platinum-based drug and the period of administration. During a platinum-free interval, the use

of pegylated liposomal doxorubicin (PLD) or trabectedin in a course of treatment has been effective in restoring sensitivity **(68-70)**. A study in Japan divided patients with malignant ovarian cancer into two groups of platinum-sensitive and platinum-resistant. The aforementioned study showed that resistance was significantly increasing by aging in groups receiving either platinum-based chemotherapy or non-platinum-based chemotherapy. They stated that patients with cancer recurrence were more resistant to platinum at an older age **(71)**. Attention to the issue of age is important in drug resistance, and other effective factors should be considered in this regard.

Platinum- and non-platinum-based drugs and treatment

Platinum-containing drugs (oxaliplatin, carboplatin, and cisplatin) are beneficial in reducing tumorigenesis and are widely used to treat various malignancies such as ovarian, lung, head and neck, testicular, and colon cancers. In particular, taxane-platinum therapy is the gold standard in the treatment of epithelial ovarian cancer. EOC is one of the most resistant tumors to chemotherapy that responds well to cisplatin and carboplatin, but long-term chemotherapy causes resistance in patients with this tumor, which makes continuation of their treatment difficult **(39, 48)**. Non-platinum-based drugs include PLD, paclitaxel, and topotecan **(51, 60, 72, 73)**. Fosbretablin is another drug that has been originally used to treat platinum-resistant ovarian cancer. Non-platinum-based combination therapies have also shown satisfactory results. In a study, treatment with combretastatin and paclitaxel resulted in a good response rate in patients with cancer recurrence. In many studies, the combination of these two drugs has resulted in higher response rates as well as greater improvement in patients' outcomes. Ombrabulin is a derivative of combretastatin that has been shown to be effective in malignant ovarian cancer. It appears to have similar toxicity to combretastatin A4. It has also been evaluated in combination with paclitaxel and carboplatin in platinum-sensitive ovarian cancer, and effective results have been observed. Paclitaxel is another agent that is widely used in non-platinum-based chemotherapy **(48, 74-77)**. The standard schedule for administration of this drug is one injection every three weeks for three hours; however, it can also be administered every week **(78)**. Studies in 2013 showed that this drug had great success in the treatment process and reduced resistance in the first week of use **(42)**. A study on platinum resistance has demonstrated that paclitaxel administration once a week is more efficient in treating than its administration once every three weeks **(79)**. Epothilones is another non-platinum-based drug that has been shown to increase the sensitivity and therapeutic efficacy of malignant ovarian cancer **(80, 81)**. Pemetrexed is another non-platinum-based drug that is effective in treating advanced ovarian cancer, provided that standard doses are used **(82)**. Platinum resistance and treatment success are also related to the dosage of administration and duration of drug injection, and it's largely an algorithm and treatment chart for ovarian cancer. Based on the duration of exposure to platinum, better responses to treatment have been observed.

Studies have yielded that patients who have platinum-free interval for longer than six months and then receive a platinum agent or a biological substance containing platinum will experience better clinical outcomes, indicating that better clinical results would be obtained through administrating platinum in platinum-sensitive individuals (six months progression-free interval (PFI)). However, many non-platinum-based chemotherapy treatments are also affected by the PFI parameter, and the time since the last treatment should be considered **(74)**. Nevertheless, the FDA has not officially accepted the role of PFI. For example, while the combination of gemcitabine and carboplatin has been approved for patients with recurrent platinum-sensitive ovarian cancer, non-platinum agents, such as topotcan and liposomal deoxorubicin, have been also identified by the FDA as influential agents in the treatment of these patients, and less attention has been paid to the PFI parameter. In addition, more recently, the non-platinum-based drugs of pegylated liposomal doxorubicin and trabectedin have had significant comparable efficacy in comparison with platinum-based compounds in ovarian patients with PFI over six months. Regarding treatment method, the most important therapeutic mechanism of the combination of these drugs in ovarian cancer is targeted chemotherapy, especially the use of angiogenesis inhibitors. Although it is unclear whether the clinical outcomes and efficacy of these new agents are affected by the duality of chemotherapy-sensitive and chemotherapy-resistant or not, they have the potential to increase treatment efficacy in both chemotherapy-resistant and chemotherapy-resistant phenotypes. Non-platinum-based biological agents, such as bevacizumab have also been shown to be effective in treating platinum-sensitive recurrent diseases. Therefore, the use of anti-angiogenesis agents, such as bevacizumab, is an important research priority to be studied as another non-platinum-based drug **(4, 34, 83)**.

Strategies and recommendation

In the initial evaluation, it is important to identify gaps in previous research on the drugs administered. If they are eliminated, it can have the greatest impact on reducing the complications or mortality due to ovarian cancer among women.

Given that HGSC is the most common and deadly ovarian cancer; its study should be a research priority. Due to the rarity and relative heterogenic nature of ovarian cancers, joint research through a consortium is essential. Another noticeable point is to pay attention to the implementation of timely interventions of interventions, informing process, and diagnostic protocol **(84)**. Researchers and financing organizations

should design and prioritize clinical and population-based research programs. The main priority should be to clarify the cellular origin as well as pathogenesis and identification of each subgroup. The present study proposes first the development of experimental model systems which are able to reveal the effectiveness of a drug in ovarian cancer and second the investigation of the tumor characteristics, clinical progression pathways, and the best treatment with the appropriate dosage. Organizations involved in oncology studies and cancer researchers are recommended to agree on new diagnostic criteria, designations, and pharmacological ideas, and identify the most effective drugs. Organizations involved in oncology studies and cancer researchers are suggested to agree on new diagnostic criteria, appellation, and pharmacological ideas, and identify the most effective drugs. Researchers and financing organizations need to focus on developing and evaluating early detection strategies that go beyond current imaging techniques and biomarkers. It is suggested that innovative strategies for surgery and the use of chemotherapy be implemented. Comparison of platinum-based and non-platinum-based drugs can also help with estimation of drug resistance. Studying new surgical methods can also provide useful strategies for this purpose.

Conclusion

The findings suggested that different subtypes of ovarian cancer in most cases expressed specific genes and markers, many of which are common in ovarian cancer. It is very important to pay attention to the inhibition of these factors as a strategy to reduce resistance to chemotherapy. Understanding the cause of platinum resistance and strategies to reduce drug resistance, especially new drugs, is of paramount importance. Another issue is to pay more attention to recognizing resistance-reducing regimes in cases of disease recurrence, in which related organizations, oncology groups, and ovarian cancer researchers agree on a treatment strategy during drug resistance and continuation of treatment with higher efficiency.

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Conflict of Interest

The authors declare no conflict of interest.

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