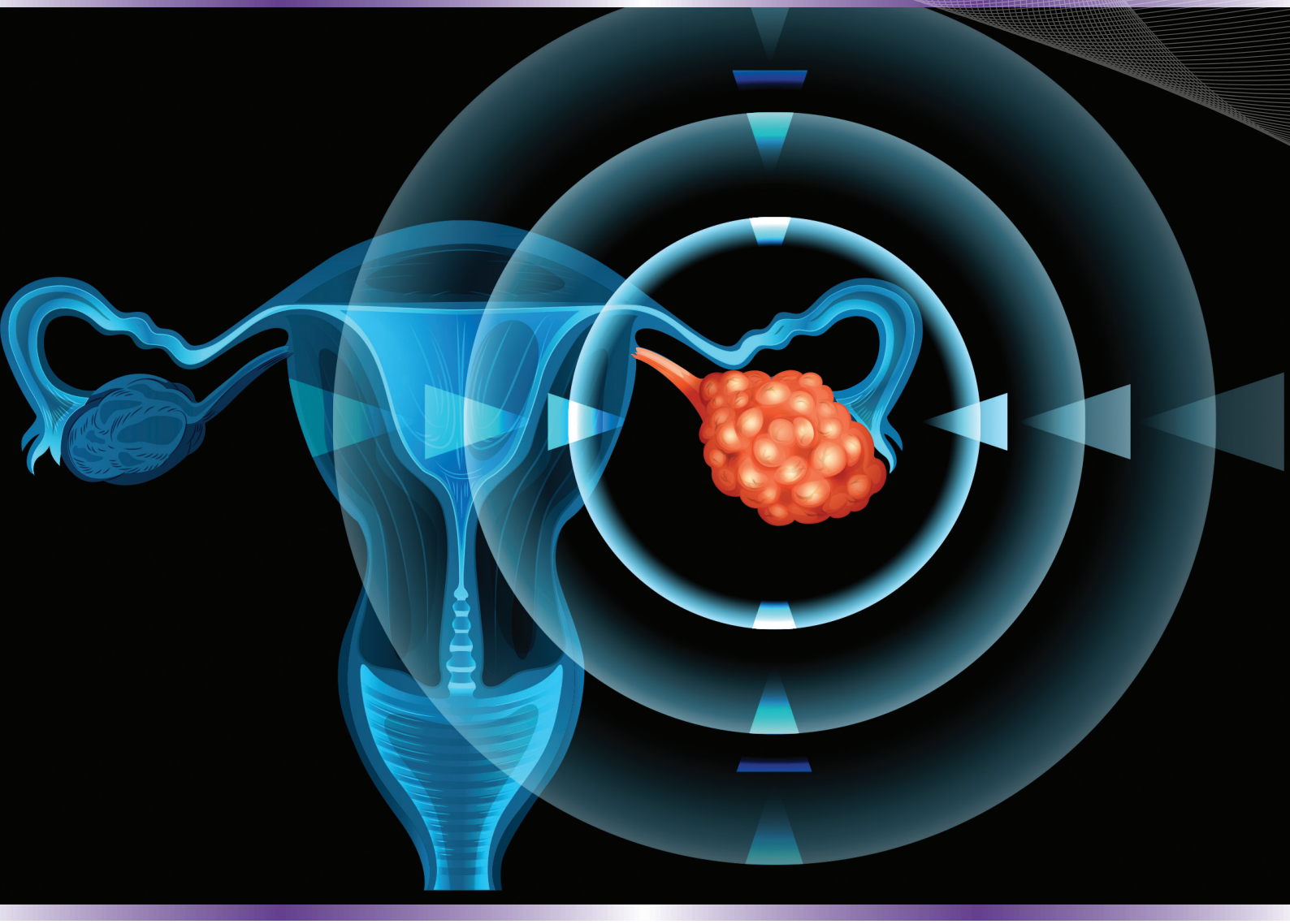
PARP inhibitors – a new treatment option for ovarian cancer



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1. Introduction

Every year, approximately, 200,000 women around the world are diagnosed with ovarian cancer [1]. There are usually no early signs or symptoms of the disease, and there is still no effective screening method available for its early detection [2].

Currently, the standard treatment options for ovarian cancer involve a combination of surgery and chemotherapy [3]:

- Primary debulking surgery (PDS) is focused on removing all tumour tissue to achieve no residual disease. The surgery is followed by platinum-based chemotherapy treatment.
- Interval debulking surgery (IDS) is used to treat more advanced stages of ovarian cancer not eligible for PDS. Prior to IDS, the patient is treated with neoadjuvant chemotherapy, which helps shrink tumour before surgical intervention.

Most patients with ovarian cancer initially respond well to chemotherapy; however, the majority of patients (mainly in advanced stages (III and IV)) will relapse and develop resistance to medical treatment [2].

Although there has been limited improvement in 5-year survival for most ovarian cancer patients over the past three decades, the introduction of poly-ADP ribose polymerase (PARP) inhibitors as maintenance therapy in ovarian cancer has resulted in improvements in progression-free survival and a trend toward improved overall survival [2].

2. About

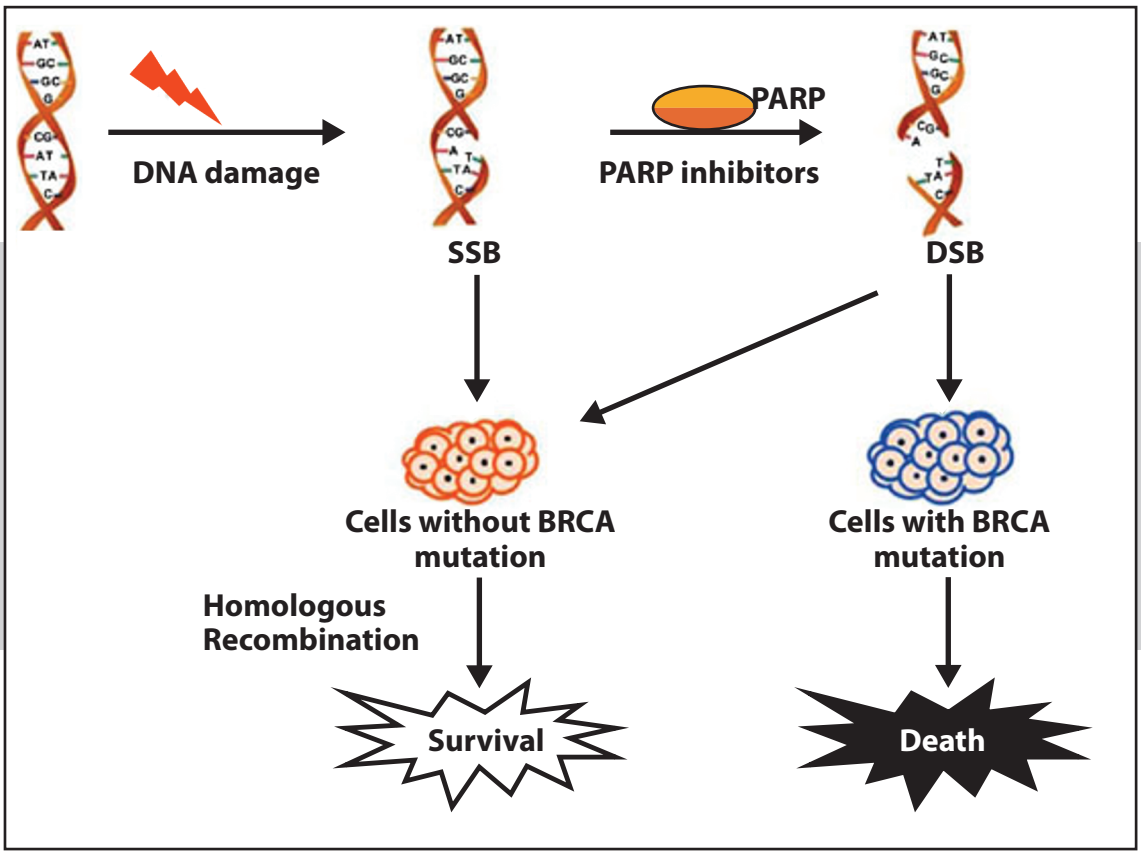
2.1 How do PARP inhibitors work?

Inhibition of the enzyme poly-ADP ribose polymerase (PARP) causes an accumulation of single-and double-stranded DNA breaks [4], and cells with an impaired DNA repair pathway (so called homologous recombination deficiency (HRD)) are unable to repair this amount of DNA damage, resulting in cancer cell death [5].

2.2 Which patients are eligible for treatment with PARP inhibitors?

Approximately 50% of patients with ovarian cancer have defective DNA repair due to genetic and epigenetic alterations of the homologous recombination (HR) pathway [6]. These patients often respond well to treatment with PARP inhibitors and chemotherapy, with an an improved survival [2].

PARP inhibitors show the best results in patients with mutations in the tumour suppressor genes BRCA1 and BRCA2, which are most commonly associated with hereditary breast and ovarian cancer, so testing for these mutations is very important for all patients diagnosed with ovarian cancer [2,3].



Currently, PARP inhibitors are used as a standard of care in both the first line and recurrent treatment of ovarian cancer patients with BRCA mutations, as well as those with deficiency of the HR pathway [2,3]. PARP inhibitors have also shown to be helpful when administered as maintenance therapy in patients without HR deficiency if they have had complete or partial response to platinum-based treatment [2,3]. As hopeful as this may seem, the data to support this statement are not that robust. Some countries are not implementing this at all, and some are actually moving backwards from this decision.

GENETIC TESTING FOR OVARIAN CANCER

If you are a patient with ovarian cancer, it is important to request a genetic test at the time of diagnosis. It can provide valuable information for your treatment, particularly in case of a relapse of the disease.

Genetic testing can help identify the presence of any genetic mutations, which may influence treatment options and guide personalized care decisions. Therefore, it is advisable to discuss the possibility of a genetic test with your healthcare provider, as it can be beneficial for your overall management and treatment of ovarian cancer.

2.3. What are the potential side effects of PARP inhibitors?

All treatments can cause side effects. The most common side effects of PARP inhibitors include weakness, fatigue, nausea, vomiting, diarrhea, indigestion, headaches, dizziness, changes in taste, and liver and kidney problems, but their severity is typically lower than compared with standard chemotherapy. In most cases, these side effects can be quickly alleviated by temporarily reducing the dose of the drug.

In rare cases, bone marrow activity may decrease temporarily, leading to anaemia, decreased white blood cell count resulting in an increased risk of infection, bleeding problems, tiredness, and breathlessness. Overall, the administration of PARP inhibitors is considered safe when appropriate precautions are followed (all patients who take PARP inhibitors are closely monitored with frequent blood tests and regular computer tomography scans.)

2.4. What's the difference between PARP inhibitors and chemotherapy?

Classical chemotherapy exerts its effect primarily by damaging or inhibiting the regeneration of DNA, or by targeting other essential mechanisms in the cell cycle. Chemotherapy causes damage not only to cancer cells but also to healthy cells, leading to most of the treatment's associated side effects. The basic idea of chemotherapy is that healthy cells can repair damage more effectively and precisely than fast-dividing tumour cells, thus causing death of the tumour cells.

In contrast, PARP inhibitors do not directly damage cells. Instead, their mode of action is based on inhibiting a specific DNA repair pathway that leads to the accumulation of DNA defects and stopping the tumour cell from repairing the damage in other ways. This process primarily causes the death of tumour cells due to severe damage to their genetic material.

It is important to note that PARP inhibitors also affect the DNA repair pathway in healthy cells; however, because DNA in healthy cells is intact and cell division is properly regulated, the likelihood of cell death in healthy tissues is lower than compared with tumour cells.

2.5. What types of PARP inhibitors are currently available?

Several PARP inhibitors have been approved or are in clinical trials. Niraparib, olaparib, and rucaparib are already on the market, while talazoparib and velaparib are being studied at various stages. It is important to note that although the mechanism is similar for each product, there may be differences in potency and side effects.

2.6. How are PARP inhibitors administered?

In contrast to most chemotherapeutic agents, PARP inhibitors can be taken orally once or twice a day depending on the particular inhibitor being used and its side effects. The oral administration of PARP inhibitors makes them practical and well-tolerated for long-term use.

PARP inhibitors are considered maintenance treatment for patients who have responded to previous platinum-based chemotherapy and are taken for 2-3 years (depending on the PARP- inhibitor) after the completion of chemotherapy. Clinical studies have shown that this length of treatment sufficiently reduces risk and causes few long-term side effects.

Patients in other countries may be prescribed PARP inhibitors for a longer period of time, as not all different inhibitors may be available, the cost of treatment is not always covered by health insurance, and some countries have their own regulations.

2.7. What happens if the cancer recurs despite PARP inhibitor treatment?

Unfortunately, ovarian cancer can relapse even while using a PARP inhibitor. However, it is important to emphasize that the likelihood of recurrence is significantly reduced compared to not using a PARP inhibitor.

If the cancer recurs, the next step is typically a course of platinum-based chemotherapy. If the disease responds well to chemotherapy, either partially or completely, there may be an opportunity to undergo maintenance treatment with another PARP inhibitor. Consult with your oncologist for more information about treatment options.

CLINICAL TRIALS

There are many ongoing trials for ovarian cancer patients at ESGO. Learn more at https://engot.esgo.org.

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ENGAGe recommends contacting your local patient association!

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