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# Targeted therapy with Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of solid tumours

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**SUMMARY:**
Introduction: According to the National Cancer Register in Poland, the number of cancers including breast cancers has more than doubled in the past three decades. Poly(ADP-ribose) polymerase (PARP) inhibitors lead to the death of cells with a *BRCA1/2* mutation. The use of PARP inhibitors has increased significantly over the last 5 years.

Objective: This article summarizes the current knowledge about the safety and clinical efficacy of PARP inhibitors in the treatment of solid tumors.

Abbreviated description of the state of knowledge: PARP inhibitors have been used in the standard treatment of ovarian cancer. Three of them: Olaparyb, Rucaparyb and Niraparyb have indications for maintenance treatment in recurrent platinum-sensitive ovarian cancer. Olaparib and Weliparib are used to treat breast cancer patients. Research shows that the use of Olaparib in breast cancer patients has reduced tumours size as much as around 60% of women with *BRCA* mutation. The combination of veloparin with carbolatin and paclitaxel was associated with a longer mean survival period than chemotherapy alone in treatment of non-small cell lung cancer(NSCLC).
In addition, there are studies showing the benefits of PARP inhibitor therapy in prostate cancer. Olaparyb in combination with abiraterone shows greater clinical efficacy in patients with castration-resistant prostate cancer compared alone abiraterone.

Conclusions: FDA approval of new PARP inhibitors is a promising method for more effective treatment of the most common cancers in the world. In the future further research may lead to a better definition of the patient group benefiting most from PARP inhibitor therapy.

**Key words:** Targeted Molecular Therapy; Poly(ADP-ribose) Polymerase Inhibitors, BRCA1 Gene; Triple Negative Breast Neoplasms

**ARTICLE**

1. Introduction

As cancer morbidity is growing, the search for new medicinal therapies constantly elaborates. It is estimated that cancer incidence will be more than 29.5 million cases in 2040. The estimated number of deaths from cancer will be around 63.4% higher compared to 2018 [1]. Oncological treatment is gradually based on personalized methods of diagnosis and treatment. The use of Poly(ADP-ribose) polymerase (PARP) inhibitors is an example of targeted treatment. PARP are enzymes important for various cellular processes, from regulation transcription and cell cycle control to chromatin dynamics, DNA repair, mitosis and cell death. The most active PARP is PARP1, which synthesize more than 90% of cellular PAR [2]. PARP are enzymes involved in DNA repair, activated when DNA is damaged. Tumors that share the molecular characteristics of *BRCA* gene mutations, called "BRCAness" , may also be susceptible to similar therapeutic approaches. *BRCA 1/2* are tumor suppressor genes. Genes *BRCA 1/2* are crucial for repairing *BRCA1/2* by homologous recombination(HR) [3,4]. Inhibition of PARP activity can lead to the death of cells with the *BRCA1 /BRCA2* mutation. Patients with somatic and/or embryonic mutation *BRCA1/2* benefit more from these treatments than other patients [5]. For the first time PARP inhibitors have been approved for the treatment of ovarian cancer and this has completely changed the treatment strategy. Efficacy has also been demonstrated in metastatic breast cancer HER2-negative and advanced prostate cancer with *BRCA1 / 2* or *ATM* mutations [6].

Objective

In recent years, numerous studies have focused on the use of PARP inhibitors in the treatment of solid tumors. In our work, we analysed the available literature in terms of the possibility of using new, already registered medicines as well as assessing their effectiveness and safety.

## 2. The state of knowledge

### 2.1 PARP inhibitors in the treatment of ovarian cancer

Ovarian malignancy accounts for 4.6% of cases in women. The number of deaths in 2016 in Poland was 2639 [7].The use of PARP inhibitors has increased significantly over the last 5 years. Three of them have entered into standard treatment for epithelial ovarian cancer (including ovarian, fallopian tube and primary peritoneal cancer) [8]. *BRCA* mutations occur in about 15% of ovarian cancer patients and have been shown to have a better chance of responding to PARP inhibitors. Olaparyb and rucaparib currently have indications for the treatment of recurrent ovarian cancer with the current *BRCA* mutation.Olaparib, rucaparib and niraparib have indications for maintenance treatment in platinum-sensitive recurrent ovarian cancer after responding to platinum-based treatment. As a maintenance therapy in selected patients with a recurrent, platinum-sensitive disease that reacts to chemotherapy, PARP inhibitors have been shown to improve progression-free survival in patients with *BRCA* mutation and wild *BRCA* disease. Randomised 2018 studies have shown that Olaparib, maintenance therapy in analyte platinum-sensitive ovarian cancer reduced the risk of progression by 65% and almost doubled the total time off from the progression of the disease. It is also worth noting that all PARP inhibitors can cause haematological toxicity. This can be problematic, especially in patients undergoing maintenance therapy who have already been treated in the myelosuppressive regimen. In the case of Niraparib, thrombocytopenia can be a particular problem. In the observations, grade 3 or 4 thrombocytopenia was observed in about one third of patients [9].

### 2.2 PARP inhibitors in the treatment of triple-negative breast cancer.

In Poland, according to statistics published in 2018, breast cancer was the most common malignant cancer in women (21,9%) [7].

The primary treatment for breast cancer is surgical treatment. One of the additional treatments are PARP inhibitors. Olaparib and Weliparib are used to treat breast malignant cancer patients. The worst prognosis is characterized by one of the subtypes of cancer called triple negative cancer (TNBC). This means that there are no receptors on the surface of its cells that could become the site of the handle of the action of many complementary therapies such as chemotherapy and hormonoterapy. On the surface of tumor cells there are no receptors for estrogen, progesterone and HER2. The characteristics of most breast cancers based on the BRCA1 gene genetic mutation are triple negative. Treatment of patients with triple negative breast cancer is limited. PARP inhibitors are the subject of research into the effective treatment of this type of breast cancer [10].

The study conducted by Rugo H.S. et al. included 106 patients with triple negative breast cancer (72 patients were a study group and 44 were a control group). Weliparib in combination with carbolatin included with standard therapy has been shown to result in a higher response rate than standard therapy. On the other hand, in the study Gelmon KA et al. 91 patients with ovarian cancer and 26 patients with triple-negative breast cancer were treated

with Olaparib, 400 mg daily. No treatment effects have been demonstrated in patients with triple negative breast cancer. The study only confirmed a positive outcome for ovarian cancer [11,12].

One study showed a reduction in tumours size in approximately 60% of women with *BRCA*-related metastatic breast cancer who received a Olaparib compared to 29% of patients receive chemotherapy. The median time to progression of the disease was 7 months compared with 4.2 months. These are primary findings to show that a PARP inhibitor can improve progression-free survival in metastatic, hereditary breast cancer.[13].

Cohort study by Rodler ET. et al. showed that the use of Veliparib 300 mg twice daily in combination with cisplatin and vinorelin is well tolerated.The following side effects have been observed: neutropenia (36%), anemia (30%) and thrombocytopenia (12%). A randomized phase II study has been planned to assess veliparib's participation in cisplatin chemotherapy in metastatic breast cancer associated with the *TNBC* and *BRCA* mutations. [14].

Of the available PARP inhibitor preparations in clinical trials, Weliparib is effective against breast cancer with BRCA 1 / BRCA 2 mutation when used with standard therapy. On the other hand, with another preparation Olaparib, no positive effects of treatment were observed. More research is needed involving a larger number of patients to be able to confirm the effectiveness of promising PARP inhibitors in the treatment of breast cancer.

2.3 PARP inhibitors for the treatment of non-small cell lung cancer.

Numerous studies on PARP inhibitors have led to the knowledge of their biology and mechanisms of action. It appears that in addition to the standard use of these medicines in patients with HR deficiency in ovarian and breast cancer, they can be used to treat other cancers, including non-small cell lung cancer(NSCLC). Compared to 2018, this will be 72.5% more cases of this type of cancer [1].NSCLC is the most common (approximately 80%) type of lung cancer [15]. Both the increased trend of the disease and the highest mortality rate among other cancers leads to the search for the most effective therapeutic regimens and methods in NSCLC.

One of the promising therapeutic routes is the use of PARP inhibitors. Due to the frequent occurrence of HR gene mutations in lung cancer patients, the potential use of PARP inhibitors in NSCLC patients with these mutations has been investigated. The results of the study showed that Olaparib successfully induced apoptosis in A549 cells with *BRCA1* or *BRCA2* exhaustion, which supports the good effects of potential NSCLC therapy with HR mutation.

Compared to classical chemotherapeutic agents (platinum derivatives) used in the treatment of NSCLC, PARP inhibitors have less toxicity. Combined PARP inhibitor treatment with gemcitabine has been shown to induce synergistic DNA damage mediated by increased accumulation of single-stranded DNA breaks [15].

According to the latest reports, veliparib efficacy in combination with platinum-based chemotherapy compared to placebo is currently assessed in the Phase III study in advanced squamous lung cancer [16].In the Phase II study, promising results were achieved. The combination of veloparin with carbolatin and paclitaxel was associated with a longer mean survival period than chemotherapy alone. In addition, the association velobarib with chemotherapy was well tolerated [17]. Additionally to the mechanisms described, PARP

inhibitors can modify the cancer microenvironment by increasing the expression of PD-L1. Thanks to this mechanism of action of PARP inhibitors, it would be possible to associate them with immunotherapy. However, no data have been published on this potential combination treatment yet. Nevertheless, it provides a noteworthy point for further research. [16].

2.4 PARP inhibitors in the treatment of prostate cancer.

The National Cancer Register reports that prostate cancer is the most common cancer in men in Poland. It represents around 19% of cancer incidence in men and is characterized by the greatest growth rate of morbidity.[7].

The molecular heterogeneity of this disease is well known, but the treatment has not been molecularly stratified so far. Metastatic castration-resistant prostate cancer can have genomic aberrations that interfere with DNA repair [18].Some of these aberrations have been associated with sensitivity to PARP inhibitors, suggesting that treatment with a PARP inhibitor may use synthetic lethal interaction. [19]. In the study Clar N et al. patients with prostate cancer resistant to castration and HR repair mutations demonstrated a response to Olaparib treatment as opposed to patients without HR mutation. Randomised Phase II (double-blind placebo trials) was conducted in 41 urological oncology facilities in 11 countries in Europe and North America. 171 patients aged 18 years or older with metastatic prostate cancer resistant to surgery were qualified. They had previously received docetaksel and were candidates for abiraterone treatment. Of the 142 patients, randomly assigned to the olaparab and abiraterone group (n = 71) or placebo and abiraterone (n = 71). Olaparb in combination with abiraterone was found to have been clinically effective in patients with castration-resistant prostate cancer compared to alone abiraterone [20]. In another Phase II study, 50 patients previously treated with docetakaxel were enrolled. 49 (98%) of them received abiraterone or enzalutamide, while 29 (58%) received cabazitaxel. All patients received olaparib tablets at a dose of 400 mg twice a day until radiological progression, unambiguous clinical progression, unacceptable side effects, withdrawal of consent or death (n = 1). 16 of 49 patients responded to Olaparib. 12 patients received study medication for over 6 months. Homozygous deletions, harmful mutations in genes *BRCA1/2, ATM, Fanconi anemia genes, CHEK2* were identified in 16 patients who responded to treatment using new generation sequencing. Loss of BRCA2 was presented by 14 of them (88%), the larger 4 present were ATM aberrations. Anemia (20%) and fatigue (16%) were the most common adverse events of Olaparib. The study showed that treatment with Olaparib showed a high response rate in patients who did not respond to standard treatment with prostate cancers with defects in repair genes [21].

3. Summary and conclusions:

The choice of PARP inhibitor in a specific clinical case is largely based on baseline laboratory values, number of previous therapies and the presence of BRCA mutations or the degree of damage to HR mechanisms. The evaluation of biomarkers such as the aforementioned HR is being modernised, so in the future it can be expected to be better determined patient group benefiting most from PARP inhibitor therapy. Clinically available PARP inhibitors are currently undergoing extensive research. Other newer measures, such as thazoparib, veliparib, 2X-121 and CEP-9722, are at earlier stages of research. FDA approval

of new PARP inhibitors is a promising method for more effective treatment of the most common cancers in the world. The more FDA-approved drugs we expect the decision to choose a PARP inhibitor will become more complex.

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