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PARP inhibitors – a new direction in the treatment of breast and ovarian cancer

Inhibitory PARP – nowy kierunek w leczeniu raka piersi i raka jajnika

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Abstract

Ovarian cancer, like breast cancer, may either develop spontaneously or as a result of a family history. *BRCA1* and *BRCA2* mutations significantly increase the risk of both cancers at all ages. It is estimated that 3–5% of women are *BRCA* mutation carriers. *BRCA1* mutation carriers have a 65% risk of breast cancer and 39% risk of ovarian cancer. These risks are lower among *BRCA2* mutation carriers, i.e. 45% and 11% for breast and ovarian cancer, respectively. In breast and ovarian cancer with *BRCA* mutations, blocking the function of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, causes an accumulation of DNA damage that ultimately leads to cancer cell death. Based on this mechanism, PARP inhibitors have been used in the treatment of hereditary neoplasms, in which the proper functioning of DNA damage repair systems is disturbed. In clinical trials to date, PARP inhibitors significantly extended the progression-free survival in patients with confirmed *BRCA* mutations. Similar results have been obtained for patients without confirmed genetic background. Currently, PARP inhibitors are increasingly approved for use in the treatment of ovarian and breast cancer. From May 2021, the Ministry of Health has reimbursed maintenance therapy with PARP inhibitors in patients with known *BRCA* mutation status.

Keywords: ovarian cancer, breast cancer, *BRCA* mutation, PARP inhibitors, olaparib

Streszczenie

Rak jajnika, podobnie jak rak piersi, jest chorobą pojawiającą się spontanicznie lub może mieć podłoże rodzinnego występowania. Mutacje w genach *BRCA1* i *BRCA2* istotnie zwiększają ryzyko pojawienia się obu tych nowotworów w każdym wieku. Nosicielstwo mutacji genów *BRCA* stwierdza się u 3–5% kobiet. Ryzyko zachorowania na raka piersi u kobiet z mutacją genu *BRCA1* wynosi 65%, a na raka jajnika 39%. Ryzyko to jest niższe w przypadku potwierdzonej mutacji *BRCA2* – dla raka piersi i raka jajnika wynosi ono odpowiednio 45% i 11%. W przypadku raka piersi i raka jajnika z obecnymi mutacjami w genach rodziny *BRCA* zablokowanie funkcji enzymów polimerazy poli-ADP-rybozy (PARP), w tym PARP1 i PARP2, powoduje kumulacje uszkodzeń DNA finalnie doprowadzające do śmierci komórek nowotworowych. Bazując na tym mechanizmie, zastosowano inhibitory PARP w leczeniu nowotworów o podłożu genetycznym, w których dochodzi do zaburzenia prawidłowego funkcjonowania systemów naprawy uszkodzeń nici DNA. W przeprowadzonych badaniach klinicznych u pacjentek ze stwierdzonymi mutacjami *BRCA* zastosowanie inhibitorów PARP znacząco wydłużało czas wolny od progresji choroby. Podobne wyniki uzyskiwane są u pacjentek bez stwierdzonego podłoża genetycznego choroby. Obecnie coraz więcej inhibitorów PARP uzyskuje rejestrację do stosowania w leczeniu raka jajnika i raka piersi. Od maja 2021 roku Ministerstwo Zdrowia refunduje terapię podtrzymującą opartą na inhibitorach PARP u pacjentek ze stwierdzoną mutacją *BRCA*.

Słowa kluczowe: rak jajnika, rak piersi, mutacja *BRCA*, inhibitory PARP, olaparib

INTRODUCTION

In the 1990s, reports appeared linking *BRCA1* and *BRCA2* genes with breast and ovarian cancer. The presence of mutations in this gene family may also initiate the development of pancreatic, prostate and colon cancer[1]. In 2016, there were 18,615 Polish patients with breast cancer, and 3,717 with ovarian cancer. In Polish population of women breast cancer takes the second place and ovarian cancer – the fourth of diagnosed neoplastic diseases. Breast and ovarian cancers are responsible for 6,000 and more than 2,500 female deaths annually, respectively, in Poland[2]. *BRCA1* and *BRCA2* mutations significantly increase the risk of both these malignancies at all ages. It is estimated that 3–5% of women are *BRCA*-mutation carriers. About 16–20% patients with ovarian cancer are *BRCA*-mutation carriers. *BRCA1*-mutation carriers have a 65% risk of breast cancer and 39% risk of ovarian cancer. These risks are lower among *BRCA2*-mutation carriers, i.e. 45% and 11% for breast and ovarian cancer, respectively. The correlation between genetic mutation and the type of cancer prompted an effective search for novel therapeutic approaches based on the mechanisms underlying tumorigenesis. Attention has been recently drawn to poly(ADP-ribose) polymerase (PARP) inhibitors, including talazoparib, niraparib, olaparib, rucaparib and veliparib[3].

MECHANISM OF ACTION

Poly(ADP-ribose) polymerases (PARP) belong to a family of enzymes involved in DNA repair. PARP1 and PARP2, which are the best known enzymes, play an important role in the repair of single-stranded DNA damage[4]. They bind to the damaged strand, undergo modifications that increase their activity, and by attaching poly(ADP-ribose), they activate and involve proteins responsible for regulating the proper course of repair processes. Inhibition of PARP activity leads to the accumulation of cellular damage and, consequently, cell death. DNA damage repair after blocking PARP enzymes is still possible due to the expression of other genes, including *BRCA1* and *BRCA2*. A mutation in the *BRCA* gene family results in the inability to repair the damaged DNA strand. In the case of breast and ovarian cancer with *BRCA* mutations, blocking PARP1 and PARP2 activity causes accumulation of DNA damage, which ultimately leads to the death of cancer cells. Based on this mechanism, PARP inhibitors have been used in the treatment of hereditary neoplasms with dysfunctional DNA damage repair systems. The first data on the relationships between *BRCA1/2* mutations and the potential effective use of PARP inhibitors were published in 2005. There are two mechanisms of action of PARP inhibitors. The first mechanism involves a suppressive effect on the catalytic activity of PARP enzymes, thus preventing the formation of poly(ADP-ribose) chains, and thus engaging in the repair of damaged DNA of the proteins responsible for this process. The second mechanism, known as the PARP trapping, involves capturing PARP enzymes directly on the DNA strand and blocking their activity. Most likely, this mechanism plays a major role in the effective action of PARP inhibitors such as talazoparib and niraparib. Four of these, with the exception of veliparib, have been approved for clinical use by the Food and Drug Administration (FDA). Olaparib and talazoparib are used in the treatment of HER2-negative *BRCA*-positive breast cancer, while olaparib, rucaparib and niraparib are used in the maintenance therapy of platinum-sensitive ovarian cancer[3]. Nowadays, only olaparib and niraparib have been approved in Poland[5]. The other drugs are still in the clinical trials (Tab. 1).

PARP INHIBITORS AND BREAST CANCER

Depending on the clinical and pathomorphological assessment, breast cancer therapy consists of a combination treatment involving surgery, radiation therapy, chemotherapy and hormone therapy. PARP inhibitors are currently an interesting alternative in the treatment of breast cancer in patients with a confirmed *BRCA* mutation. Both the European Medicines Agency (EMA) and the FDA approved olaparib and talazoparib for the treatment of breast cancer. Rucaparib, niraparib and veliparib are still in clinical development[6]. Olaparib was the first PARP inhibitor drug tested. In 2009, the results of the phase I trial were published. Phase II trial confirmed its efficacy, safety and acceptable tolerability in *BRCA*-mutation carriers with breast cancer. Phase III trial enrolled 302 *BRCA*-mutated patients with HER2-negative breast cancer. In 2017, Robson et al. demonstrated a 2.8-month longer progression-free survival and a 42% reduction in the risk of progression or death with olaparib compared to standard treatment[7].

Talazoparib, another PARP inhibitor, showed the best potential in the treatment of breast and ovarian cancer at the lowest concentration in preclinical trials[6]. The results of phase I and II trials with this agent were published in 2017[8]. A year later, Litton et al. presented a study in which patients were put on talazoparib. Progression-free survival

Phase I	Drug safety assessed in healthy volunteers. The main goal is to identify the most common adverse reactions, as well as explore the pharmacokinetics and pharmacodynamics of the candidate drug
Phase II	Evaluation of drug efficacy in patients diagnosed with the target disease. Continued assessment of safety and adverse reactions
Phase III	Assessment of safety and efficacy depending on the dose, target population and combination therapy
Phase IV	Post-marketing phase. Assessment of the drug's impact on the market and collecting additional data on safety, efficacy and optimal use

Tab. 1. Phases of clinical development

FIGO (2014)	
Stage I	**Tumor confined to ovaries or fallopian tube(s)**
	IA – tumor limited to one ovary or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings IB – tumor limited to both ovaries or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings IC – tumor limited to one or both ovaries or fallopian tubes, with any of the following: IC1 – surgical spill IC2 – capsule ruptured before surgery IC3 – tumor on ovarian or fallopian tube surface or malignant cells in the ascites or peritoneal washings
Stage II	**Tumor involves one or both ovaries or fallopian tubes with pelvic extension or primary peritoneal cancer**
	IIA – extension and/or implants on uterus and/or fallopian tubes and/or ovaries IIB – extension to other pelvic intraperitoneal tissues
Stage III	**Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**
	IIIA1 – positive retroperitoneal lymph nodes only IIIA1(i) – metastasis up to 10 mm in greatest dimension IIIA1(ii) – metastasis more than 10 mm in greatest dimension IIIA2 – microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph nodes IIIB – macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes IIIC – macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
Stage IV	**Distant metastasis excluding peritoneal metastases**
	IVA – pleural effusion with positive cytology IVB – parenchymal metastases and metastases to extra-abdominal organs

Tab. 2. FIGO classification of ovarian cancer (2014)

was shown to be 3 months longer in the treatment group. In 2013, clinical trials in breast and ovarian cancer yielded promising results for niraparib, another PARP inhibitor. Currently, monitoring is continued as part of phase II and III clinical trials to assess the efficacy of this drug in *BRCA* mutation carriers with HER2-negative breast cancer[9].

Interestingly, data showing no effect of rucaparib in breast cancer patients was published in 2016[10]. Research is continued to assess the efficacy in the treatment of patients with breast cancer and metastases to other organs.

Veliparib, the last of the tested PARP inhibitors, is the drug with the lowest toxicity, therefore it may be the best candidate for combination therapy using other anticancer drugs[6]. Phase I trials confirmed good tolerability and satisfactory efficacy in breast cancer patients with *BRCA* mutations who received veliparib in combination with cisplatin and vinorelbine[6].

Currently, studies are underway to assess talazoparib and olaparib as a neoadjuvant therapy in *BRCA*-mutated patients with breast cancer, olaparib in adjuvant therapy and combination therapy of veliparib with carboplatin and niraparib in combination with pembrolizumab[11–14].

PARP INHIBITORS AND OVARIAN CANCER

Combination therapy including radical surgery and chemotherapy is the mainstay of ovarian cancer treatment. Chemotherapy may be avoided only in the case of FIGO stage IA and G1 ovarian cancer (Tab. 2). Chemotherapy is indicated in G2 and G3 tumors. First line treatment combines platinum (carboplatin, cisplatin) and taxoid derivatives (paclitaxel). In recent years, olaparib, an oral PARP inhibitor, which has been shown in clinical trials to significantly extend progression-free survival, and rucaparib, also with proven efficacy, have been introduced for *BRCA1*- and *BRCA2*-mutated patients with recurrent ovarian cancer[5]. In the US, niraparib, which significantly prolongs progression-free survival, has been registered as maintenance treatment[15].

Olaparib was the first PARP inhibitor to undergo clinical trials. In 2009, results confirming the efficacy of anticancer treatment in *BRCA*-mutated patients were published. Of the 19 ovarian cancer patients administered olaparib in phase I clinical trials, 63% achieved clinical benefit from the drug[16]. In 2011, phase II trials assessing olaparib with a favorable therapeutic effect in patients with and without *BRCA* mutation were published[17]. Further studies confirmed the efficacy of this drug in the group with recurrent platinum-sensitive ovarian cancer. In 2012, the beneficial effect of olaparib was shown, with progression-free survival longer by 3.8 months, which was confirmed in 2014 in 31.1% of patients[18]. Based on these data, the FDA has approved olaparib in patients with platinum-sensitive ovarian cancer after 3 prior lines of platinum-based chemotherapy. Phase III trials were conducted in 295 *BRCA* mutated patients with platinum-sensitive recurrent ovarian cancer after at least two previous cycles of platinum-based chemotherapy. A statistically significant difference was found in PFS between olaparib patients (19.1 months) vs. placebo patients (5.5 months)[19]. The obtained results led to the FDA approval of olaparib as maintenance treatment for recurrent ovarian cancer responding to platinum-based chemotherapy. A study in 391 *BRCA*-mutated advanced ovarian cancer patients partially or fully responsive to platinum-based chemotherapy was published in December 2018. Olaparib-treated patients were shown to have a significantly lower risk (70%) of disease progression or death[20]. This led to a recent FDA approval of olaparib as the first-line

Drug	Phase	Type of cancer	Identifier	Status
Olaparib	III	Newly diagnosed advanced *BRCA*-mutated OC	NCT01844986	Ongoing
Niraparib	III	Platinum-sensitive OC	NCT01847274	Ongoing
Olaparib	III	Recurrent *BRCA*-mutated OC	NCT01874353	Ongoing
Niraparib	III	HER2-negative *BRCA1/2*-mutated BC	NCT01905592	Ongoing
Talazoparib	III	*BRCA1/2*-mutated BC	NCT01945775	Ongoing
Rucaparib	III	OC	NCT01968213	Ongoing
Olaparib	III	*BRCA1/2*-mutated metastatic BC	NCT02000622	Ongoing
Veliparib	III	Triple-negative BC	NCT02032277	Ongoing
Olaparib	III	BC	NCT02032823	Ongoing
Veliparib	III	Metastatic BC	NCT02163694	Ongoing
Olaparib	III	Recurrent *BRCA*-mutated OC	NCT02282020	Ongoing
Olaparib	III	Recurrent OC	NCT02392676	Discontinued
Olaparib	III	Recurrent OC	NCT02446600	Ongoing
Veliparib	III	OC	NCT02470585	Ongoing
Olaparib	IV	*BRCA*-mutated OC	NCT02476968	Ongoing
Olaparib	III	OC	NCT02477644	Ongoing
Olaparib	II, III	OC	NCT02502266	Ongoing recruitment
Niraparib	III	OC	NCT02655016	Ongoing
Olaparib	III	BC	NCT02810743	Ongoing recruitment
Rucaparib	III	OC	NCT02855944	Ongoing recruitment
Olaparib	III	Epithelial OC	NCT03106987	Ongoing recruitment
Olaparib	II, III	BC	NCT03150576	Ongoing recruitment
Olaparib	III	OC	NCT03278717	Ongoing recruitment
Olaparib	III	Metastatic *BRCA*-mutated BC	NCT03286842	Ongoing
Olaparib	III	Ovarian cancer with no germline mutation in *BRCA*	NCT03402841	Ongoing
Rucaparib	III	Epithelial OC	NCT03522246	Ongoing recruitment
Olaparib	III	Recurrent OC	NCT03534453	Ongoing
Niraparib	III	Recurrent OC	NCT03598270	Ongoing recruitment
Niraparib	III	OC	NCT03602859	Ongoing recruitment
Talazoparib	III	OC	NCT03642132	Ongoing
Niraparib	II, III	Ovarian sarcoma, endometrial sarcoma	NCT03651206	Planned recruitment
Niraparib	III	Recurrent platinum-sensitive OC	NCT03705156	Ongoing
Niraparib	III	OC	NCT03709316	Ongoing recruitment
Olaparib	III	Advanced OC	NCT03737643	Ongoing recruitment
Olaparib	III	OC	NCT03740165	Ongoing recruitment
Niraparib	IV	OC	NCT03752216	Ongoing recruitment
Niraparib	III	OC	NCT03806049	Planned recruitment
Olaparib	II, III	OC and BC	NCT04024254	Planned recruitment
Olaparib	II, III	Triple-negative BC	NCT04191135	Ongoing recruitment
Rucaparib	III	OC	NCT04227522	Planned recruitment
Olaparib	IV	OC and BC	NCT04330040	Ongoing recruitment
Olaparib	III	OC	NCT04421963	Planned recruitment

BC – breast cancer; **OC** – ovarian cancer.

Tab. 3. Ongoing clinical trials assessing PARP in the treatment of breast and ovarian cancer

maintenance treatment for ovarian cancer. Furthermore, in addition to monotherapy, studies on combined olaparib and bevacizumab (monoclonal antibody binding to vascular endothelial growth factor, VEGF) therapy, chemotherapy based on platinum derivatives and cediranib (oral tyrosine kinase inhibitor) have been published. The obtained data indicated that olaparib used in combined therapy extends progression-free survival, and the efficacy of treatment used[21,22].

The second PARP inhibitor, rucaparib, showed good tolerance and benefits in *BRCA*-mutated ovarian cancer patients in a study published in 2017[23]. Other studies have confirmed that patients with recurrent platinum-sensitive ovarian cancer and a known hereditary mutation put on this

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inhibitor had a longer progression-free survival than those with spontaneous disease[24]. This inhibitor has also been shown to be safe in combination therapy. Phase III trials in 564 patients with advanced platinum-sensitive ovarian cancer showed 11.2 month longer recurrence-free survival in *BRCA*-mutated patients on rucaparib vs. placebo[25]. Based on the above evidence, the FDA has approved rucaparib for the treatment of ovarian cancer in *BRCA* mutation carriers after at least two previous lines of chemotherapy[25]. Another inhibitor, niraparib, showed activity against *BRCA1* and *BRCA2* mutated tumors in preclinical trials, which made it possible to use it in ovarian cancer patients with a defect in the DNA repair mechanisms. Studies that followed assessed its efficacy in combined therapies with pembrolizumab, bevacizumab and temozolomide. The obtained results showed that the use of niraparib in combination therapies is associated with its higher anticancer efficacy[26,27]. An analysis in 553 platinum-sensitive recurrent ovarian cancer patients receiving niraparib showed ya 15.5 months longer progression-free survival in the *BRCA* mutation carrier group compared to 9.9 months in the non-carriers[15]. Based on the published data, niraparib was registered in 2017 as a maintenance therapy in recurrent ovarian cancer patients[28], and in April 2020 as a maintenance therapy in adult advanced ovarian cancer patients partially or fully responsive to platinum-based chemotherapy[29].

Talazoparib, which exhibits an effective antitumor activity, is the PARP inhibitor with the expected activity at the lowest concentration. Phase I clinical trials have shown beneficial effects in the treatment of ovarian cancer[8].

Veliparib is the final described drug in this group. Phase I trials confirmed both its safety and low toxicity in monotherapy and combination therapy. Its use was not limited to ovarian cancer patients[30]. The efficacy of veliparib in combination with carboplatin and paclitaxel, as well as carboplatin and gemcitabine has been demonstrated[31,32]. The median recurrence-free survival was 8.18 months. Phase III trials in OC patients on combination therapy with carboplatin and paclitaxel with veliparib are currently underway[33].

CONCLUSIONS

The anticancer strategy has changed dramatically with the advancement of medicine. Targeted therapy has been successfully used in a significant proportion of cancers in recent decades. The same is true for breast and ovarian cancer with a confirmed *BRCA* mutation. The use of PARP inhibitors in the treatment is an ideal example of therapies targeting a specific mechanism of DNA damage. Recent years have shown that many preclinical and clinical trials have been based on the correlation between the mechanisms of action of PARP inhibitors and the use of their potential in the treatment of cancer.

In April 2020, the FDA approved niraparib as first-line treatment for patients with advanced ovarian cancer[34].

Considering the variety of clinical trials (Tab. 3), which are currently in phase III and IV, we can expect interesting reports in the coming years, which will make it possible to find therapies that will extend progression-free survival while maintaining an acceptable level of quality of life. The topic of PARP inhibitors is also very much up-to-date in Poland. Since May 2021, the Ministry of Health has covered a drug program based on olaparib as a maintenance therapy for *BRCA1* or *BRCA2* mutation carriers with both newly diagnosed and recurrent ovarian, fallopian tube and primary peritoneal cancer. Since January 2022, the Ministry of Health in Poland decided also for refundation of niraparib maintenance therapy in newly diagnosed platinum-sensitive ovarian cancer without genetic background. This new promising direction in the treatment of ovarian cancer, although so far reimbursed only for the group of *BRCA* mutation carriers, brings about an opportunity to improve progression-free and overall survival is all ovarian cancer patients.

Conflict of interest

The authors declare no conflict of interest.

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