**PARP inhibitors in the treatment of Pancreatic Cancer- A Review of literature**

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**Abstract**

**Introduction**

Pancreatic cancer is one of the most aggressive cancers. It occurs in men more often than women. The primary therapy for these cancers is surgery; chemotherapy, radiation therapy, hormone therapy, or immunotherapy are also used. More and better treatments are being sought for this disease. The use of PARP inhibitors in the treatment of pancreatic cancer has shown good results, so in this article we have done a review of the results of various studies on this topic. In this review, the results of studies on the use of various PARP inhibitors in pancreatic cancer of different hormonal status are presented.

**Purpose**

This article aims to give you an overview of the trials that have looked at the effects of different PARP inhibitors in the treatment of pancreatic cancer. PARP inhibitors are a relatively new cancer therapy with good results, so it is important to pay attention.

**State of Knowledge**

In this article, I used the PubMed database and considered papers from the last 10 years, but most of the information in this review comes from papers published after 2020. I have also taken into account the recommendations of the FDA and the European Medicines Agency on the use of PARP inhibitors.

**Conclusions**

PARP inhibitors have shown significant effects on pancreatic cancer outcomes. The differences in outcomes depending on the type of cancer, the PARP inhibitor used, and the previous therapies used in a given patient tell us how important it is to individualize therapy in oncology. The findings of the studies presented in this review also point to the need for further research that could focus on identifying patients who may best benefit from treatment with PARP inhibitors, as well as studying synergistic effects in combination with other forms of therapy, such as immunotherapy or chemotherapy. The changes in treatment outcomes that these drugs can bring underscore the importance of exploring new therapeutic strategies in oncology.

**Keywords**

PARP inhibitors; pancreatic cancer; pancreatic cancer treatment.

**PARP inhibitors**

The PARP inhibitor family comprises 17 distinct proteins involved in various biological functions, including DNA repair, apoptosis, stress responses, and transcription regulation. Among them, PARP1 and PARP2 play crucial roles in the DNA repair process. The first protein in this group was identified in 1963 during research on a DNA-dependent enzyme activated by nicotinamide mononucleotide (NMN). It was initially observed that PolyA was not generated in the reaction, and the resulting molecule exhibited unexpected properties. Further investigation in 1967 led to the identification of the product as poly(ADP-ribose) (PAR). PARP inhibitors represent an emerging category of cancer treatment therapies. Several of these inhibitors have received approval for treating cancers such as breast, ovarian, and pancreatic cancers associated with BRCA mutations. Research is ongoing to explore their potential in enhancing chemotherapy and radiotherapy. Additionally, some studies focus on using these inhibitors as standalone treatments to selectively target cells with impaired DNA repair mechanisms, such as those involving BRCA1/2 mutations.[1][2][3]

Clinical trials to date have demonstrated a benefit in tumor response and/or disease progression-free survival (PFS) following use of the orally active PARP inhibitor olaparib, as well as other PARP inhibitors in breast and ovarian cancer associated with BRCA1/2 mutations in the germline.[15-18]

Loss-of-function mutations in the BRCA1, BRCA2 or both (BRCA) genes are associated with an increased risk of ovarian and breast cancer; such mutations are also associated with an increased risk of pancreatic cancer. [11]

The BRCA1 and BRCA2 genes function as tumor suppressors, coding for proteins that facilitate the repair of DNA double-strand breaks via homologous recombination. In contrast, enzymes in the poly(adenosine diphosphate-ribose)-polymerase (PARP) family play a key role in fixing single-strand DNA damage. Laboratory studies have demonstrated that cells lacking functional BRCA1 or BRCA2 genes are more vulnerable to PARP inhibitors. This heightened sensitivity is likely due to mechanisms such as synthetic lethality, where uncorrected DNA damage and replication stress occur as a result of replication forks being stalled by trapped PARP complexes.[1][4]

**Pancreatic Cancer**

Pancreatic cancer (PC) is a very aggressive malignancy, and it occurs more often in men than in women. The 5-year survival rate is less than 10%. Early pancreatic cancer usually produces no symptoms, which is why the cancer is most often detected in an advanced state. As the disease progresses, there are various symptoms such as light stools or dark urine, jaundice, pain in the upper or middle abdomen and back, among others. Unfortunately, the incidence of pancreatic cancer has been increasing in recent years. Risk factors for this disease include smoking, obesity, a family history of pancreatic cancer, and certain genetic disorders (such as those related to the BRCA1 and BRCA2 genes). Surgical resection remains the main form of treatment; the results of this treatment modality depend on the location of the tumor and the stage of the disease. Post-operative chemotherapy improves treatment outcomes for it, while chemoradiotherapy remains controversial. [5][6][7]

 4-8 [%] of patients with pancreatic adenocarcinoma have germline mutations in BRCA1 or BRCA2. [8,9] Pancreatic tumors with such mutations show a better response to platinum-based therapies. [10] Several PARP inhibitors have been approved for the treatment of patients with advanced ovarian and breast cancer with BRCA1/BRCA2 mutations and are being actively investigated for the treatment of patients with pancreatic adenocarcinoma with BRCA1/BRCA2 mutations.[5][6][7]

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##### **Olaparib**

Maintenance treatment with olaparib is considered in patients who meet conditions such as the presence of a germline BRCA1/BRCA2 mutation and metastatic pancreatic adenocarcinoma and the occurrence of a response to platinum-based first-line treatment for more than 4 months. [5][6][7]

POLO study (Pancreas Cancer Olaparib Ongoing)

The study included patients who were 18 years of age or older and had histologically or cytologically confirmed pancreatic adenocarcinoma. Participants had to have a documented deleterious or potentially deleterious germline mutation in the BRCA1 or BRCA2 genes. Eligible patients underwent at least 16 weeks of platinum-based first-line chemotherapy for metastatic pancreatic cancer. Therapy could be continued as long as no disease progression was observed. However, if treatment-related toxicities occurred, the platinum component of chemotherapy could be discontinued after the completion of the required minimum treatment period. Prior to study initiation, side effects of prior treatment had to be reduced to Grade 1 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0). [11]

The POLO study, a double-blind, randomized phase 3 trial with a placebo control group, was conducted at 119 study sites located in 12 different countries. Participants were randomly assigned in a 3:2 ratio to the group taking olaparib 300 mg twice daily or placebo. Stratification of patients was not used. Maintenance treatment was initiated between 4 and 8 weeks after completion of chemotherapy, and continued until radiologically confirmed disease progression or unacceptable side effects. Disease progression was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) [12]. The primary endpoint of the study was progression-free survival time, calculated from the time of randomization to the occurrence of radiologically confirmed progression. [11]

The study included regular follow-up with CT or MRI scans, initially every 8 weeks for 40 weeks and then every 12 weeks. After progression, patients were monitored every 8 weeks for survival and subsequent lines of treatment. Quality of life was assessed using the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire, which patients completed at the beginning of the study, every 4 weeks until progression, and after completion of study treatment. [11]

Of the 3315 subjects tested, a BRCA germline mutation was identified in 247 (7.5%). Finally, 154 patients were randomized: 92 to the olaparib group and 62 to placebo. At the time of analysis (January 15, 2019), 30 patients were still receiving olaparib, and eight were receiving placebo. Median progression-free survival was 7.4 months in the olaparib group and 3.8 months in the placebo group. (table 1) After 6 months, the percentage of patients without disease progression was more than twice as high in the olaparib group as in the placebo group. [11]

The conduct of this study and the results obtained in it led to The U.S. Food and Drug Administration (FDA) approval of olaparib for maintenance treatment of pancreatic cancer. [13]

|  |  |
| --- | --- |
| Table 1. | Median progression-free survival |
| Olaparib group | 7.4 months |
| Placebo group | 3.8 months |

Next study

This was a forward-looking, multicenter, phase II clinical trial conducted without randomization. The study targeted individuals diagnosed with advanced solid tumors and harboring a confirmed germline mutation in the BRCA1 or BRCA2 genes. Participants were administered oral olaparib at a dose of 400 mg twice daily in capsule form. Treatment continued until the disease showed signs of progression. If toxicity or adverse effects were observed, dose adjustments were permitted, with reductions to 200 mg twice daily or 100 mg twice daily if required. In cases of severe toxicity, treatment could be completely discontinued. [14]

Eligible participants were adults with an established germline mutation in BRCA1 or BRCA2. These mutations were considered either harmful or potentially harmful based on local diagnostic criteria before the patient provided consent. Participants needed to have advanced solid tumors and meet the following eligibility criteria: at least one measurable or evaluable lesion based on RECIST version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 2, and a life expectancy of at least 16 weeks. [14]

To qualify, patients also had to fall into one of several defined subgroups based on their cancer type and prior treatment history:

* Ovarian, primary peritoneal, or fallopian tube cancer that was resistant to platinum therapy, defined as recurrence within six months of receiving platinum-based treatment, or where further platinum therapy was deemed unsuitable.
* Breast cancer that had progressed despite undergoing three or more prior lines of chemotherapy.
* Pancreatic cancer with disease progression during gemcitabine treatment in the advanced stage or cases where gemcitabine therapy was no longer considered appropriate.
* Prostate cancer that was refractory to hormone therapy, showing disease progression after at least one cycle of systemic treatment, and with no anti-androgen therapy in the six weeks leading up to enrollment.
* Other solid tumor types that had progressed following at least one course of metastatic treatment.

This inclusive approach allowed the study to evaluate the potential of olaparib across a wide spectrum of advanced cancers associated with BRCA1/2 mutations, offering valuable insights into its efficacy and tolerability across various patient groups. [14]

The main objective of the study was to determine the percentage of patients in whom a tumor response was observed, according to the RECIST. The response was confirmed at least 28 days after the previous evaluation. Tumor examinations were performed at the beginning of the experiment, and then after the completion of each two cycles of treatment (each cycle lasted 28 days), until the final visit associated with the end of therapy. [14]

Secondary endpoints included: objective response rate (for patients with measurable tumor lesions at the beginning of the study), time free of disease progression (PFS) and duration of treatment response. Safety and tolerability of therapy were assessed by analyzing adverse effects (AEs) and changes in laboratory results. Evaluation criteria were according to version 3 of the National Cancer Institute's Common Terminology Criteria for Adverse Events. [14]

A total of 317 patients with advanced cancers and confirmed germline mutations in the BRCA1 or BRCA2 genes were enrolled in the study, of whom 298 (94%) met the inclusion criteria and received at least one dose of olaparib. Among the 23 patients with advanced pancreatic cancer, 17 patients (74%) had a BRCA2 mutation, and one patient was found to have mutations in both BRCA1 and BRCA2. [14] The average number of previous lines of treatment was two. Almost all but one patient had been previously treated with gemcitabine, and 65% had a history of exposure to platinum drugs such as cisplatin (35%), carboplatin (9%) or oxaliplatin (30%). [14]

Stabilization of the disease, lasting at least eight weeks, was noted in 41.6% of patients. Rates of stabilization were: 40.4% for ovarian cancer, 46.8% for breast cancer, 34.8% for pancreatic cancer, 25% for prostate cancer and 58.3% among other cancers. The median duration of response was 208 days, including each cancer in table 2. In contrast, the median time to the appearance of a response was 56 days, with differences depending on the type of cancer- table 3. [14]

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| Table 2. | The median duration of response |
| For ovarian cancer | 225 days |
| For breast cancer | 204 days |
| For pancreatic cancer | 134 days |
| For prostate cancer | 327 days |

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| --- | --- |
| Table 3. | The median time to the appearance of a response |
| For ovarian cancer | 56.5 days |
| For breast cancer | 54.5 days |
| For pancreatic cancer | 113 days  |
| For prostate cancer. | 54.5 days |

The results of the study showed that response rates were comparable between patients with a mutation in the BRCA1 gene and those with a mutation in BRCA2, regardless of cancer type. There were also no significant differences in treatment efficacy between patients with pancreatic cancer who had previously been treated with platinum-containing regimens and those who had not received such therapy.

For patients with pancreatic cancer, the median disease progression-free time was 4.6 months. After 6 months of treatment, the disease had not progressed in 36.4% of patients in this group. The median overall survival (OS) in the pancreatic cancer group was 9.8 months. In contrast, the 12-month survival rate was: 64.4% for ovarian cancer patients, 44.7% for breast cancer, 40.9% for pancreatic cancer and 50.0% for prostate cancer.

The study showed that among patients carrying germline mutations in the BRCA1/2 genes, tumor response to treatment was prolonged regardless of the type of cancer, including ovarian, breast, pancreatic and prostate cancer. These results support the hypothesis that genetic targeting therapy can be effective regardless of the primary anatomical location of the cancer. The presence of a germline mutation in the BRCA1/2 genes identifies a group of patients who may benefit from treatment with PARP inhibitors. [14]

**Rucaparib**

Badanie II fazy przeprowadzone w Abramson Cancer Center na Uniwersytecie Pensylwanii

The study was designed to evaluate whether maintenance treatment with rucaparib, a PARP inhibitor, in patients with advanced pancreatic cancer sensitive to platinum-based chemotherapy and with a pathogenic or likely pathogenic mutation in the BRCA1, BRCA2 or PALB2 genes (both in the germline and somatic line) can achieve a disease progression-free survival rate of at least 60% at 6 months (PFS6). [19]

Patients meeting the following criteria were eligible for the study: being at least 18 years old, a diagnosis of locally advanced or metastatic pancreatic cancer (excluding neuroendocrine tumors), and the presence of a confirmed pathogenic or likely pathogenic mutation in the BRCA1, BRCA2 or PALB2 genes. All participants had to have received at least 16 weeks of platinum-based chemotherapy for advanced disease or metastasis. At the same time, they could not show signs of platinum resistance, which was defined as an increase in tumor size, the appearance of new lesions or a systematic increase in tumor markers during or within 8 weeks of platinum therapy. However, subjects who could not complete the full 16 weeks of platinum therapy for medical reasons were allowed into the study, provided the principal investigator deemed their eligibility reasonable. It was also a requirement to have adequate organ function, good general status defined as 0-1 on the Eastern Cooperative Oncology Group scale, and a life expectancy of at least 12 weeks. Patients who had previously received treatment with PARP inhibitors were excluded from participation in the study. [19]

Patients were treated with rucaparib at a dose of 600 mg administered orally twice daily in 28-day cycles. Therapy was continued until intolerable side effects or disease progression occurred. However, if patients continued to benefit clinically despite diagnosed progression, they were allowed to remain in the study at the discretion of their treating physician. [19]

The primary objective of the study was to determine progression-free survival (PFS), measured from the start of rucaparib therapy until disease progression or death from any cause. Patients who were alive at last follow-up and had not experienced progression were censored on the day of last imaging. [19]

The study's secondary objectives included: objective response rate (ORR), defined as confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 criteria; disease control rate (DCR), meaning CR, PR or stable disease sustained for at least 16 weeks; duration of response (DOR), calculated from first response to disease progression or death; overall survival, meaning time from start of treatment to death or last follow-up; and assessment of treatment toxicity. [19]

Follow-up imaging studies were performed every 8 weeks, and patients were examined every 4 weeks, at the end of each treatment cycle. Over time, the protocol was modified to allow patients who had been in the study for at least 12 cycles to undergo clinical evaluations every other cycle (i.e., every 8 weeks), while laboratory tests were performed every 4 weeks. [19]

All patients who took at least one dose of the study drug were included in the safety analysis. From September 2017 to October 2019, 46 patients were included in the study and started treatment. In the end, 42 patients were evaluated for efficacy, according to the protocol, for various reasons. Of these patients: 27 had a gBRCA2 mutation, 7 a gBRCA1 mutation, 6 a gPALB2 mutation, and 2 a BRCA2 mutation (table 4). Forty had adenocarcinoma, one patient had had acinar carcinoma, and one had squamous cell carcinoma (table 5). [19]

|  |  |
| --- | --- |
| Table 4. | number of people |
|  had a gBRCA2 mutation |  27 |
| had a gBRCA1 mutation |  7 |
| had a gPALB2 mutation |  6  |
| had a BRCA2 mutation |  2 |

|  |  |
| --- | --- |
| Table 5. | number of people |
| had adenocarcinoma | 40 |
| had acinar carcinoma | 1 |
| had squamous cell carcinoma | 1 |

The study evaluated 46 patients, 42 of whom qualified for primary endpoint analysis. By the time data collection was completed, disease progression had been observed in 28 patients, and 20 patients had died. The median potential PFS follow-up time was 18 months, and the median progression-free survival was 13.1 months. The percentage of PFS6 was 59.5% and at 12 months (PFS12) was 54.8%. The lower limit of the 95% confidence interval exceeded the null hypothesis of 44%, meaning that the study achieved its primary objective. [19]

There were no significant differences in age, disease location, length of prior platinum treatment or type of treatment regimen used between patients with BRCA1 and BRCA2 mutations. The results of the Phase II trial confirmed the efficacy of rucaparib (PARPi) as maintenance treatment in patients with advanced pancreatic cancer and germline or somatic BRCA1, BRCA2 and PALB2 mutations who did not experience progression after platinum therapy. [19]

The observed effects differed from the results of the Phase III POLO study, which may be explained by differences in the designs of these studies. The POLO study included only patients with metastatic disease, while this study also included patients with locally advanced disease, who may have had a lower disease burden. [19]

There were also no significant differences in PFS or OS between the 34 patients who completed at least 16 weeks of platinum therapy and the 8 patients who did not. This suggests that a full four months of platinum treatment may not be necessary before starting PARPi maintenance therapy. This is particularly important because platinum toxicity may preclude longer treatment in some patients. [19]

Patients with BRCA1 mutations showed poorer responses to treatment than those with BRCA2 mutations. Subgroup analysis revealed a significant difference in median progression-free survival between patients with BRCA1 and BRCA2 (3.7 months vs. 18 months, respectively). [19]

**RUCAPANC**

RUCAPANC is an international Phase II clinical trial that was conducted at seven research centers in the United States and Israel. Eligible for participation were women and men 18 years of age or older with histologically confirmed locally advanced or metastatic pancreatic adenocarcinoma with measurable lesions and a known deleterious germline or somatic BRCA1/2 mutation confirmed by local testing. Patients could have had up to two prior lines of chemotherapy used to treat locally advanced or metastatic cancer, but could not have previously received PARP inhibitors. As part of the study, participants were treated with oral rucaparib 600 mg twice daily continuously until disease progression or other reasons for discontinuing therapy. If side effects occurred, it was possible to reduce the dose or temporarily stop treatment. [20]

All but four patients underwent local laboratory testing to confirm the presence of BRCA1/2 mutations in the germline before entering the study. The primary endpoint in the study was tumor response rate, assessed using RECIST version 1.1 criteria. Imaging studies to assess the tumor were performed at the start of the study, within seven days before the start of every third treatment cycle, and at the end-of-therapy visit. Secondary endpoints were related to treatment efficacy and included duration of response, progression-free survival and overall survival. Safety analysis was based on the occurrence of adverse events, which were assessed according to the Common Terminology Criteria for Adverse Events version 4. [20]

The safety assessment included all patients who received at least one dose of rucaparib. Efficacy results are presented for the full analysis group. The study was completed in April 2016. To be included in the objective response rate (ORR), a complete response or partial response according to RECIST criteria had to be confirmed at least 28 days after the first response was recorded. Responses not confirmed within that time were classified as unverified. [20]

The study included 19 patients who received at least one dose of rucaparib. The mean age was 57 years. The majority were men (57.9%, or 11 of the 19 participants). The mean number of prior chemotherapy regimens used for locally advanced or metastatic disease (excluding follow-up treatment if progression occurred more than 6 months after the end of therapy) was two (range 1 to 3). A performance status according to the Eastern Cooperative Oncology Group scale of 1 was reported in 78.9% of patients (15 of 19). Also, 78.9% of patients (15 of 19) had a BRCA2 mutation. Somatic BRCA2 mutations were detected in three patients, while the remaining mutations were germline mutations. [20]

Confirmed responses lasted 36 weeks (PR), 19 weeks (CR) and five weeks (PR), respectively. Of the four patients with confirmed or unconfirmed responses, three had been previously treated with only one therapy regimen. None of these patients had tumors showing progression after previous treatment with platinum. The rate of disease control (including CR, PR or disease stabilization [SD] lasting at least 12 weeks) was 31.6% for all study participants and 44.4% in the group of patients who had previously received only one line of chemotherapy for locally advanced or metastatic disease. As stipulated in the protocol, recruitment to the study was halted after no response in the first 15 patients evaluated. However, three confirmed responses were observed in the last four patients included in the study. [20]

Adverse effects occur during the use of PARP inhibitors, the incidence of which varies depending on a number of factors. In this study of the use of rucaparib as monotherapy in patients with pancreatic cancer with a BRCA mutation, every patient experienced some sort of side effect. Among the most common were nausea, anemia, fatigue, and ascites. Adverse effects that required dose reduction included elevations in ALT or AspAT levels, fatigue, neutropenia, and thrombocytopenia, each of which occurred in 5.3% of patients (1 in 19 patients). Treatment was discontinued by one patient due to fatigue and thrombocytopenia, which the investigator believed were related to rucaparib. [20]

Discussion

Pancreatic cancer (PC) is estimated to be the second most common cause of cancer-related deaths by 2020.[21] Most cases of PC are diagnosed at an advanced stage, making surgical, potentially curative treatment unfeasible. For advanced-stage disease, the standard treatment options include FOLFIRINOX (a combination of folinic acid [leucovorin], fluorouracil, irinotecan, and oxaliplatin) and gemcitabine paired with nab-paclitaxel. Both regimens have shown superior overall survival rates compared to gemcitabine used as a monotherapy. [22-23]

For second-line treatment, data from prospective studies show limited efficacy, with chemotherapy response rates typically below 20%. This is true for both second-line chemotherapy with FOLFIRINOX and fluorouracil in combination with the nanoliposomal irinotecan. [24-28]

Pancreatic cancer (PC) is one of the most aggressive and difficult-to-treat cancers, with a poor prognosis and limited efficacy of available therapies. PARP (poly(ADP-ribose) polymerase) inhibitors are emerging as a promising therapeutic strategy for treating cancers associated with defects in DNA repair mechanisms, particularly in patients with BRCA1/2 mutations. Further research in this area is key to improving treatment outcomes and understanding resistance mechanisms and the potential benefits of combination therapy.

Although the use of PARP inhibitors has beenO successfully used in the treatment of ovarian and breast cancer, its potential in the treatment of pancreatic cancer requires further study. [29-31]

**Why is further research necessary?**

Low survival rate: Pancreatic cancer remains one of the most difficult cancers to treat, with a 5-year survival rate of less than 10%. Further research on PARP inhibitors may bring breakthroughs in improving treatment outcomes, especially in the subgroup of patients with BRCA1/2 mutations.

Genetic diversity: Although BRCA1/2 mutations are well studied, many other defects in DNA repair mechanisms, such as PALB2 mutations, may also respond to PARP inhibitor therapy. It is necessary to identify and better understand these biomarkers.

Mechanisms of resistance: Currently, little is known about why some patients stop responding to PARP inhibitors. Research into mechanisms of resistance may help develop new therapeutic strategies, such as drug combinations or new generations of PARP inhibitors.

Optimizing treatment regimens: Further research is needed to determine whether PARP inhibitors are more effective as monotherapy or in combination with other drugs, such as immunotherapies, platinum-based chemotherapy or checkpoint inhibitors.

To date, results from phase II and III trials, such as the POLO study, provide preliminary evidence for the efficacy of PARP inhibitors in the treatment of pancreatic cancer with BRCA mutations. However, differences in study designs and patient populations point to the need for further validation of results in larger clinical trials.

**Summary**

Further studies of PARP inhibitors for the treatment of pancreatic cancer are needed to improve outcomes for this deadly disease. They can contribute to the development of personalized therapy, a better understanding of the genetic underpinnings of the disease and the efficacy of combination therapies. With advances in this area, it will be possible to develop more effective treatment strategies and improve the quality of life for pancreatic cancer patients. [29-31]

**Disclosure**

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