NIEWIADOMSKA, Jagoda, BONDOS, Borys, STĘPIEŃ, Aleksandra, PALUCH, Alicja, SKRZYPEK, Jakub, NIEKRA, Aleksandra, FUSSEK, Łukasz, KOCHAN, Robert, WIECZOREK, Ewelina and LEE, Kacper. A PARP inhibitors in the treatment of breast cancer - A Review of literature. Journal of Education, Health and Sport. 2024;71:56024. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.71.56024
https://apcz.umk.pl/JEHS/article/view/56024

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received:06.11.2024. Revised:20.11.2024. Accepted:21.11.2024. Published:21.11.2024.

PARP inhibitors in the treatment of breast cancer- A Review of literature

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Abstract

Introduction

Breast cancer is the most common malignancy in women in developed countries. It also occurs in men. 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 breast cancer has shown good results, so in this article we have done a review of the results of various studies on this topic. [1] In this review, the results of studies on the use of various PARP inhibitors in breast 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 breast 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 15 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 breast 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; breast cancer; breast cancer treatment.

Introduction

PARP inhibitors

The PARP inhibitor group includes 17 different proteins that are involved in various processes such as DNA repair, apoptosis, stress response and transcription regulation. PARP1 AND PARP2 are involved in DNA repair. The first protein belonging to this group was discovered in 1963. The protein was discovered during the study of DNA-dependent nicotinamide mononucleotide (NMN)-activated enzyme, then it was found that PolyA was not produced during the reaction; the resulting molecule had different characteristics than expected. In 1967, the enzyme was further studied, and the reactant product was identified as poly(ADP-ribose)(PAR). PARP inhibitors can be said to be a new class of cancer treatment therapies. Several PARP inhibitors have been approved to treat cancers such as breast cancer, ovarian cancer, pancreatic cancer with BRCA mutation.

Many studies are being conducted on the use of PARP inhibitors in augmenting chemotherapy and radiation therapy, but there are also studies in the use of inhibitors as single drugs that selectively kill cells with defects in DNA repair pathways (BRCA1 /2 mutations).[2][3]

There is a clear link between BRCA mutations and hormone receptor (HR) status in breast cancer. Mutations in the BRCA1 gene are most commonly associated with triple-negative breast cancer (TNBC), characterized by the absence of hormone receptors and HER2 receptors. [4][5], Mutations in the BRCA2 gene are usually associated with breast cancer with positive hormone receptors, such as estrogen receptor (ER) or progesterone receptor (PgR).[6] Homologous recombination HR is a key factor in choosing a treatment strategy for breast cancer. At an advanced stage, HR+ patients may be eligible for hormone therapy, potentially in combination with cyclin-dependent kinase 4/6 inhibitors, before chemotherapy is considered. For patients with triple-negative breast cancer, options are typically limited to chemotherapy, although recent studies indicate a benefit of adding immune checkpoint inhibitors for certain subgroups of patients. [7][8]

BRCA1 and BRCA2 genes act as tumor suppressor genes, encoding proteins involved in the repair of DNA double-strand breaks through a homologous recombination mechanism. Enzymes of the poly(adenosine diphosphate-ribose)-polymerase (PARP) family, on the other hand, are crucial for repairing single-strand DNA damage. In vitro studies have shown that cells lacking functional BRCA1 or BRCA2 genes show increased susceptibility to PARP inhibitors, most likely due to several mechanisms, including so-called synthetic lethality. This process results from uncorrected DNA damage and replication blockage caused by the arrest of replication forks by blocked PARP complexes. [9]

Two PARP inhibitors, olaparib and talazoparib, have been approved by the FDA and the EMA for the treatment of HER2-negative breast cancer patients with a gBRCA mutation, due to positive results from phase III trials (OlympiAD and EMBRACA) . Olaparib is approved by the FDA for the treatment of metastatic breast cancer, and by the EMA for the treatment of locally advanced or metastatic breast cancer. Talazoparib, on the other hand, is approved by both agencies for the treatment of locally advanced or metastatic breast cancer. Of the three other PARP inhibitors (niraparib, rucaparib and veliparib), veliparib is in phase III clinical trials for HER2-negative gBRCA-mutated breast cancer at the locally advanced or metastatic stage. Veliparib has shown promising results in combination with platinum-based chemotherapy (BROCADE3 trial). [10][11][12][13]

OLAPARIB

Olaparib belongs to the PARP inhibitors and is oral. It has been approved for the treatment of patients who have recurrent ovarian cancer and have a BRCA mutation, and has been proven to show clinical benefit in these patients. Olaparib is also promising in the treatment of patients with metastatic breast cancer with a BRCA mutation.[9]

OlimpiAD Study

The OlympiAD trial was a phase 3, multicenter, randomized, international study in which the idea was to compare the efficacy of treatment and compare the safety of olaparib therapy and standard therapy with single-drug chemotherapy selected by the physician.

Patients who were 18 years of age or older and had HER2 negative metastatic breast cancer were eligible for this study. These patients had hormone receptor-positive breast cancer (positive for estrogen receptor or progesterone receptor, both) or were triple-negative. Randomization was performed taking into account three stratification criteria: prior use of chemotherapy to treat metastatic disease (yes or no), hormone receptor status (hormone receptor positive or triple negative), and prior treatment based on platinum compounds (yes or no).
In patients, BRCA mutation was confirmed during BRCAanalysis (myriad genetics) in 297 patients, and by local testing in 167 patients (confirmation by central testing in all but 5 patients). Patients had normal baseline organ and bone marrow functional scores and measurable lesions, which meant they had at least one lesion suitable for assessing disease progression both at the start of the study and at later stages, according to the modified RECIST criteria for solid tumors. Participants were randomly assigned in a 2:1 ratio to the group receiving olaparib (300 mg twice daily) or to the group receiving standard chemotherapy, according to one of three established regimens: capecitabine administered orally at a dose of 2,500 mg/m² per day (in two divided doses) for 14 days in cycles of every 21 days; eribulin administered intravenously at a dose of 1.4 mg/m² on days 1. and day 8, also every 21 days; or vinorelbine intravenously at a dose of 30 mg/m² on days 1 and 8, repeated every 21 days.
The primary objective of the study was to estimate the time to disease progression-free survival, defined as the time from randomization to radiological confirmation of progression (according to RECIST, version 1.1) or death from any cause. After collecting data on at least 230 events, an analysis of outcomes for the primary endpoint was conducted. Data were also collected for the pre-specified secondary endpoints, which included safety outcomes, overall survival time, time from randomization to second progression event or death after first progression (as assessed by the investigator), objective response to treatment (as assessed by a blinded, independent central evaluation based on the modified RECIST) and health-related quality of life outcomes.
The primary endpoint was assessed after progression or death in 234 of 302 patients (77.5%), based on a blinded, independent central assessment. Median progression-free survival time was 7.8 months in the olaparib-treated group and 3.8 months in the standard treatment group. The median time from randomization to second progression or death after first progression was 13.2 months in the olaparib group and 9.3 months in the standard therapy group. Overall survival between the groups showed no significant differences.
Although there were no significant differences in overall survival between the olaparib-treated group and the standard treatment group, the study did not have sufficient power to accurately assess differences in overall survival. In addition, the overall survival results may have been biased by treatment after the assigned regimen ended: more patients in the standard group later received PARP inhibitors, platinum-based therapy or cytotoxic chemotherapy after disease progression than in the olaparib-treated group.[9] Phase 1 and 2 trials have shown that PARP inhibitors have monotherapy activity in patients with metastatic breast cancer who have a germline mutation in the BRCA gene. [14]-[18]

I-SPY2 study

This article examines the results from the neoadjuvant segment of the I-SPY2 adaptive trial for patients with stage II/III breast cancer. The study investigated the efficacy of the combination of durvalumab and olaparib with weekly neoadjuvant paclitaxel (DOP) treatment, seeking to establish whether this approach enhances pathologic complete response (pCR) rates compared to chemotherapy alone in patients identified with HER2-negative stage II and III breast cancer. Molecular markers, including both previously identified and novel markers, were also evaluated to establish predictors of treatment response.

The primary endpoint of the study was pCR evaluation, and molecular markers were analyzed for their usefulness as biomarkers predicting response to therapy. The I-SPY trial, with a multiarm design and adaptive randomization, is designed to rapidly detect new drug combinations with higher pCR rates compared to standard chemotherapy for different breast cancer subtypes, as defined by biomarkers. The pCR rates are monitored in real time, and patients are randomly allocated to arms with higher pCR rates through adaptive Bayesian randomization, enhancing the trial's efficiency.

Adding durvalumab and olaparib to standard chemotherapy increased the pCR rate in HER2-negative tumors from 20% to 37%. In the TNBC subtype, the pCR rate increased from 27% to 47%, and in HR-positive/HER2-negative cancers from 14% to 28%. Importantly, even in patients who did not achieve a complete response, the combination of an immune checkpoint inhibitor with a PARP inhibitor reduced the number of remaining tumor cells across a range of RCB scores, covering all HER2-negative subtypes.

Early imaging plays a key role in I-SPY, but presents some challenges, as some patients drop out of further participation due to anxiety over lack of response in the early stages of therapy. [19]

PETREMAC

TNBC is a specific type of cancer characterized by the absence of ER and PgR, as well as the lack of overexpression of the HER2 protein. TNBC accounts for about 15% of all breast cancer cases. Although this type of cancer usually responds well to chemotherapy, the prognosis for patients is worse compared to other breast cancer subtypes. Early studies suggest that immune checkpoint inhibition may help treat selected cases of TNBC, but so far no significant improvement in survival has been achieved for either early-stage or metastatic disease. Currently, there are no targeted therapies with proven efficacy in primary TNBC.

It is worth mentioning that secondary mutations that arise during platinum therapy can restore BRCA1/2 gene function and cause resistance to further treatment with platinum or PARP inhibitors in patients with breast and ovarian cancer. If carboplatin or cyclophosphamide treatment leads to resistance against PARP inhibitors, this might account for the restricted effectiveness of olaparib in individuals with advanced metastatic breast cancer. Notably, PARP inhibitors have shown efficacy in patients with metastatic prostate cancer who have not previously been treated with DNA crosslinking agents.

In the phase II PETREMAC trial, patients with stage II and III breast cancer were divided into eight different treatment groups based on ER, PGR and HER2 receptor status and TP53 gene mutation. The aim of the study was to develop optimal neoadjuvant therapies for high-risk cases and to identify biomarkers that can predict response to different treatment strategies.

Patients with TNBC received olaparib in monotherapy at a dose of 300 mg twice a day for up to 10 weeks, regardless of the presence of BRCA and TP53 mutations, to reduce tumor size prior to chemotherapy.
Olaparib was administered for the planned 10 weeks, but chemotherapy was introduced earlier if the tumor did not respond to treatment. Combined clinical evaluation and MRI scans showed one complete response and 17 partial responses in 32 patients (overall response rate was 56.3%). The results suggest that the response to olaparib did not depend on tumor size. In the group without gBRCA1/2 and gPALB2 mutations, an objective response was noted in 14 of 27 patients (51.9%). Olaparib was well tolerated, and only one patient developed toxicity higher than grade 2 (fatigue), which required a dose reduction. Monitoring patients and adjusting dosage in response to side effects were key to ensuring the safety of therapy.
The study's conclusions point to the need for further research, which could focus on identifying patients who may best benefit from talazoparib treatment, as well as exploring synergistic effects in combination with other forms of therapy, such as immunotherapy or chemotherapy. [20]

TALAZOPARIB

Talazoparib Beyond BRCA

The open-label Phase II trial was designed to evaluate the efficacy of talazoparib in patients with advanced HER2-negative breast cancer who were previously treated (13 patients), and in patients with other types of solid tumors (7 patients) having mutations in genes associated with HR, excluding the BRCA1 and BRCA2 genes. This study was open-label, non-randomized and single-center. The primary objective of the study was to determine the overall response rate (ORR), with additional objectives to determine the clinical benefit (CBR), progression-free survival (PFS) and safety profile.
Results from the OlympiAD and EMBRACA clinical trials, which looked at the use of olaparib and talazoparib in patients with advanced breast cancer with a BRCA1/2 mutation, showed that both drugs prolonged disease PFS by about 3 months compared to physician-selected chemotherapy. These results contributed to FDA approval of these drugs for this group of patients.
The Talazoparib Beyond BRCA trial evaluated the hypothesis that triple-negative breast cancers with high HRDs (cohort A) or other solid tumors with germline or somatic mutations in HRD genes (beyond BRCA1/2) may be suitable for selecting patients for talazoparib monotherapy. We present results on 20 patients from cohort B who had mutations in HR genes (except gBRCA1/2) by germline sequencing or next-generation somatic sequencing (NGS). In this group, breast cancer patients had a 31% overall response rate, while there were no objective responses among those with other cancers. Breast cancer patients showed favorable responses associated with mutations in the PALB2 gene (the coding and localization partner of BRCA2), which correlated with high HRD scores. The results suggest that it is worthwhile to continue studying PARP inhibitors in patients with metastatic or advanced breast cancer with mutations in HR genes other than BRCA1/2.
Between August 2015 and December 2018, 20 patients underwent genetic testing and began treatment with talazoparib (dose of 1 mg orally per day).

Of this group, 13 patients had HER2-negative breast cancer (11 with hormone receptor-positive breast cancer and 2 with triple-negative breast cancer) and 7 patients with other cancers, such as pancreatic, colorectal, uterine, testicular and parotid gland cancers. The mean age was 53.9 years, and patients had undergone an average of two lines of prior therapies.
The ORR rate among patients with breast cancer was 31%, and the CBR rate was 54%. In the cohort without breast cancer, the CBR rate was 29%. Among patients with the gPALB2 mutation, the ORR rate was 50%, and the median progression-free survival time for patients with breast cancer was 5.6 months, compared to 2.6 months in the cohort without breast cancer.
Additionally, it is important to mention that the study evaluated not just serious side effects, but also the overall effect of talazoparib on the quality of life of patients. Gathering information on patients' quality of life related to treatment is crucial as it enables a deeper understanding of how therapy influences everyday functioning.
The research offers proof of the efficacy of talazoparib in addressing breast cancer associated with BRCA mutations. The rise in PFS and the proportion of patients responding to treatment suggest the possible advantages of its application in clinical settings. Talazoparib is becoming a promising option for patients with disease recurrence or those unresponsive to conventional therapies. This research has significant consequences for clinical practice, as talazoparib could become the standard treatment for breast cancer patients with BRCA mutations. Greater awareness of the drug's effectiveness might result in its more extensive application in practice, potentially enhancing treatment results and the quality of life for patients. Comprehending how talazoparib functions and its impact on various cancer cell types will create new therapeutic options and advance the progress of personalized medicine in oncology. As studies on this medication continue to broaden, its significance in breast cancer treatment is bound to increase, potentially resulting in further progress in the battle against this intricate and frequently lethal illness. [21][22]

EMBRACA

The study was a multicenter study involving patients with advanced breast cancer and documented BRCA1 or BRCA2 mutations. Study participants were randomly assigned to a group receiving talazoparib or a control group with standard oncology treatment. The key endpoints of the study were PFS and overall survival (OS), as well as an assessment of the drug's safety.
The study included patients who had previously received various therapies, including chemotherapy. This allowed the efficacy of talazoparib to be assessed in different clinical contexts, which is important for better understanding the potential benefits of its use.
The research indicated that the effectiveness of talazoparib was linked to significant enhancements in quality of life and extended time to deterioration (TTD) of patient-reported functional and symptom scores. In comparison to the PCT (physician's choice chemotherapy) group, there were no results that benefited this group, further supporting the positive profile of talazoparib, which does not have an adverse impact on patients' quality of life.
The EMBRACA trial was designed to evaluate the efficacy and safety of talazoparib as a PARP inhibitor, compared to physician's choice chemotherapy, in patients with HER2-negative advanced breast cancer and mutations in the BRCA1/2 gene (gBRCA1/2m).

This randomized, international phase III trial was conducted on a group of patients assigned 2:1 to the talazoparib group (1 mg daily) or to the group receiving capecitabine, eribulin, gemcitabine or vinorelbine. The entire ITT population included 431 patients - 287 assigned to the talazoparib group and 144 to the PCT group.
The overall change from baseline was based on an interpretation with a 95% CI, analysis of change from baseline showed statistically significant improvements in physical functioning [2.9 (95% CI 0.9; 4.9)] and emotional functioning [6.1 (95% CI 3.8; 8.4)] in patients treated with talazoparib, while the PCT group experienced deterioration in physical functions, social roles and cognitive functions, among others. Thalazoparib significantly delayed the time to deterioration in functional scale scores compared to the PCT group, especially in areas such as fatigue, pain, insomnia and lack of appetite, and improved patients' body image. In contrast, there were no significant differences between the groups in terms of sexual function, sexual pleasure and future prospects. [23]

VELIPARIB

Veliparyb is a potent, orally bioavailable poly(adenosine ribose diphosphate) polymerase (PARP) inhibitor that crosses the blood-brain barrier and has been shown to potentiate the effects of radiation in preclinical studies and early clinical trials. [24] Veliparyb is also being studied for the treatment of ovarian tumors and for the treatment of brain metastases of non-small cell lung cancer.[24][25][26][27]

BROCADE3 study

Veliparib is a potent oral inhibitor of PARP1 and PARP2 enzymes with good bioavailability and selectivity of action. Preclinical studies indicate that veliparib may enhance the efficacy of platinum compound-based chemotherapy. [28] In phase 1 and 2 studies, veliparib demonstrated antitumor activity and a favorable safety profile in patients with advanced BRCA-mutated breast cancer, both used as monotherapy and in combination with carboplatin and paclitaxel. The first phase 3 study, BROCADE3, investigated the efficacy of PARP inhibitor combination therapy with platinum-based chemotherapy in patients with HER2-negative breast cancer and BRCA mutation. BROCADE3 is a double-blind, randomized, placebo-controlled trial conducted at 147 centers worldwide. [29]
The research assessed the effectiveness of veliparib for treating advanced breast cancer in patients over 18 years old with BRCA1 and BRCA2 mutations, specifically those with HER2-negative metastatic or advanced cancer. Patients who had earlier undergone a maximum of two lines of chemotherapy and had not been given PARP inhibitors were randomly allocated to a group receiving veliparib or placebo together with carboplatin and paclitaxel. The main goal of the study was median progression-free survival (mPFS), which was observed based on established criteria.
Patients were randomized to form groups receiving veliparib or placebo to compare the efficacy of the therapies. The study showed that the addition of veliparib improved median PFS in patients with both BRCA1 and BRCA2 mutations, as well as in patients with different hormone receptor statuses (HR+ and TNBC). In the HR+ group, median PFS was 13.0 months for patients treated with veliparib, compared to 12.5 months in the placebo group, which was statistically significant.

In the TNBC group, the results were similar, with a median PFS of 16.6 months for the veliparib group and 14.1 months for placebo, indicating the durability of the treatment benefit.
Additionally, a higher percentage of patients in the veliparib group remained progression-free after two and three years compared to the placebo group. For the HR+ group, the percentages were 27.5% and 17.5% after two and three years, respectively, for patients taking veliparib, compared to 15.3% and 8.6% in the placebo group. For TNBC, the corresponding values were 40.4% and 35.3% with veliparib, compared to 25.0% and 13.0% with placebo.
In conclusion, veliparib significantly increased progression-free survival time in the entire study population, in both the BRCA1 and BRCA2 mutation and HR+ and TNBC subgroups, confirming the benefit of its use as an adjunct to carboplatin and paclitaxel. [30]

BrighTNess Study

The BrighTNess trial was conducted to evaluate the efficacy of the PARP inhibitor, veliparib, added to a regimen of carboplatin and standard neoadjuvant chemotherapy, in patients with triple-negative breast cancer. The multicenter phase 3 study, involving 145 centers in 15 countries, enrolled patients with clinically confirmed stage II-III breast cancer who were previously untreated and eligible for surgery. The participants, randomly divided into three groups, received different treatment regimens based on paclitaxel, carboplatin and veliparib or placebo. Randomization took into account factors such as BRCA mutation and cancer stage.
The study's primary endpoint, pCR in breast and lymph nodes, was assessed after completion of neoadjuvant treatment by a pathologist. A total of 634 patients were randomly assigned to three treatment regimens: 316 women received paclitaxel with carboplatin and veliparib, 160 patients received paclitaxel with carboplatin, and 158 received paclitaxel with placebo. The results showed that the group of patients treated with paclitaxel, carboplatin and veliparib achieved a higher percentage of pCR (53%) compared to the group receiving paclitaxel alone (31%). However, there was no significant difference between the group receiving paclitaxel with carboplatin and veliparib and the group with carboplatin and paclitaxel alone. Although the addition of veliparib and carboplatin to paclitaxel, followed by doxorubicin and cyclophosphamide, increased the proportion of patients with triple-negative breast cancer who achieved a complete pathologic response, the presence of veliparib alone in combination with carboplatin and paclitaxel did not result in such an improvement. The increased toxicity associated with carboplatin (with or without veliparib) was controllable and did not significantly affect the administration of paclitaxel or further treatment with doxorubicin and cyclophosphamide. [31]

S1416 study

The S1416 study, a randomized, double-blind, phase 2 trial with a placebo control group, was conducted at 154 clinical and academic centers in the United States.
Patients enrolled in the study were 18 years of age or older who had metastatic or recurrent triple-negative breast cancer or breast cancer associated with an inherited BRCA1/2 mutation. Participants had to meet the Eastern Cooperative Oncology Group 0-2 performance status criterion and could have previously received one line of chemotherapy for metastasis.

Patients were randomly assigned in a 1:1 ratio to a group receiving intravenous cisplatin (75 mg/m², day 1) along with veliparib or the corresponding placebo (300 mg orally twice daily, days 1-14) in 21-day cycles. The randomization process was conducted via the National Clinical Trials Network's interactive system with dynamic balancing of the number of prior cytotoxic regimens.

The main objective of the study was to determine the time to disease progression-free survival, assessed by the investigators separately in three predefined biomarker groups with predefined α values for each group. Efficacy analyses were performed according to the intention-to-treat principle, including all eligible patients. A total of 320 patients were included in the efficacy study, including 162 receiving cisplatin therapy in combination with veliparib (all women) and 158 patients treated with cisplatin and placebo (157 women and one man). Among the 247 patients, three groups of biomarkers were distinguished: those with BRCA1/2 germline mutation (n=37), BRCA-like (n=101) and BRCA-unlike (n=109). For the remaining 73 patients, biomarkers could not be assigned due to lack of data.

The results indicate that the addition of veliparib to cisplatin significantly prolonged progression-free survival in patients with BRCA-like metastatic triple-negative breast cancer, but this benefit was not observed in patients in the non-BRCA-like group. The results suggest that it is worthwhile to continue studying the use of PARP inhibitors in combination with platinum chemotherapy for BRCA-like triple-negative breast cancer.[32][33]

Conclusion

Role of PARP inhibitors in cancer treatment

PARP inhibitors have been shown to be an effective tool in the treatment of cancer, particularly in patients with defects in the BRCA genes, as clearly demonstrated in the OlympiAD trial, in which HER2-negative breast cancer patients with confirmed BRCA mutations received olaparib. In this case, median disease progression-free survival was significantly longer in the olaparib-treated group compared to standard chemotherapy, confirming the drug's potential as an effective therapeutic option. Equally important are the results of the EMBRACA trial, which confirm the efficacy of talazoparib, particularly in prolonging time to disease progression and improving patients' physical and emotional functioning.

Efficacy of PARP inhibitors in groups with different receptor statuses

In the OlympiAD study and other studies analyzed, it was noted that the efficacy of PARP inhibitors varies according to breast cancer receptor status. For example, mutations in the BRCA1 gene are typically associated with triple-negative breast cancer, which is characterized by the absence of hormone receptors and HER2 receptors, limiting the available therapeutic options to chemotherapy. BRCA2 mutations, on the other hand, are more common in hormone receptor-positive breast cancer, which opens up the possibility of treatment with PARP inhibitors in combination with hormone therapy or CDK4/6 inhibitors. In TNBC, the lack of receptor expression leaves chemotherapy as the only option, but the findings suggest that the addition of immune checkpoint inhibitors may increase treatment efficacy.

Effectiveness of olaparib and talazoparib in breast cancer treatment

Olaparib and talazoparib have demonstrated efficacy as monotherapy for breast cancer in patients with BRCA1/2 mutations.

The EMBRACA trial showed that talazoparib prolonged progression-free survival and improved patients' quality of life compared to traditional therapies, which is particularly important for the advanced breast cancer group. In the OlympiAD trial, the median time from disease progression was significantly longer in the olaparib-treated group of patients compared to the control group, demonstrating the efficacy and usefulness of this drug in clinical practice. The results of this study demonstrate that PARP inhibitors may become the standard of treatment for patients with BRCA1/2 mutations, which could improve treatment outcomes and quality of life for breast cancer patients.

Challenges of PARP inhibitor treatment

Despite the promising results of PARP inhibitor therapy, the treatment comes with challenges. One study (PETREMAC) found that resistance to PARP inhibitors can result from secondary mutations that restore BRCA1/2 gene function during platinum treatment, which can lead to the development of therapy resistance. The study also showed that patients who develop resistance to platinum-containing drugs may have limited treatment efficacy with PARP inhibitors. These findings point to the need for further research into the mechanisms of resistance to develop coping strategies and maximize the benefits of therapy.

Potential combination therapies with PARP inhibitors

An interesting line of research is the potential combination of PARP inhibitors with other therapies, such as immunotherapy. The I-SPY2 trial showed that adding durvalumab to olaparib and standard chemotherapy increased the rate of pathologic complete response in patients with HER2-negative cancer compared to chemotherapy alone. These results suggest that combination therapy may improve the efficacy of TNBC patients by increasing the number of tumor cells that respond to treatment. Thus, further research into combinations of PARP inhibitors with immune therapies and chemotherapy is warranted, as they may offer additional clinical benefits.

Prospects for developing targeted therapies using PARP inhibitors

The studies analyzed indicate the potential for PARP inhibitors to be used effectively as part of targeted therapy for patients with advanced breast cancer, especially those with BRCA1/2 mutations. Advances in research on these inhibitors are contributing to the development of personalized medicine, in which the selection of therapy is based on the individual molecular characteristics of the tumor. Further research into the mechanisms of action and efficacy of various PARP inhibitors may contribute to the introduction of new treatment strategies and further advances in the fight against breast cancer.

Summary

PARP inhibitors, including olaparib and talazoparib, represent important advances in the treatment of advanced breast cancer with BRCA mutations. Clinical trials confirm their efficacy both in monotherapy and in combination therapy. Although the efficacy of these drugs varies according to receptor status, their role in cancer therapy is undeniable, and further research may lead to more personalized and effective treatment strategies, which is of great clinical importance.

Disclosure

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All authors have read and agreed with the published version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Funding Statement: No external funding was received to perform this review.

Board Statement: Not applicable – this review included an analysis of the available literature.

Statement of Informed Consent: Not applicable.

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