2024

Poly adenosine diphosphate-ribose polymerase (PARP) Inhibitors versus Traditional Therapy in BRCA positive HER2 Negative Breast Cancer

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by

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2024

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Acknowledgements

I am grateful for all the support I had while working on this scholarly project. I would like to express appreciation and gratitude to my advisor Kristen Carr, MPAS, PA-C, DipACLM for her advice, time, and guidance for the project. I would also like to thank Megan Denis and Dr. Marilyn Klug for their expertise, assistance, and time. I would also like to thank Chelsea Scheil for her peer review. Finally, I would like to thank my family for their patience and support.

Abstract

Of the women diagnosed with breast cancer, approximately 5% will be found to have a germline breast cancer gene mutation (BRCA). This mutation increases the risk for developing a triple negative breast cancer, of which treatment options are limited. PARP inhibitors are a new pharmaceutical that act on the PARP enzyme to stop repair for cancer cells in BRCA mutations (Robson et al., 2017). The purpose of this literature review is to compare efficacy and safety of PARP inhibitor pharmaceuticals to traditional therapy for treatment of BRCA positive HER2 negative breast cancers. A literature review was preformed using the electronic search database PubMed. Both keywords and mesh terms were used to define a set of the literature discussing PARP inhibitor safety and effectiveness in patients with BRCA positive HER2 negative breast cancer. Eight phase two or phase three clinical trials that considered BRCA status were selected for the review, and information was sorted based on early, locally advanced, or metastatic breast cancer stage.

Regardless of stage, most clinical trials supported the use of PARP inhibitors for treatment of breast cancer in BRCA positive participants. The one clinical trial that did not show PARP inhibitor benefit did not consider BRCA status for the trial. Most participants tolerated the medication with hematologic deficits, nausea, and vomiting being the most common side effects. This research supports the use of PARP inhibitors in practice with careful monitoring of blood counts in patients with a known BRCA mutation.

Keywords: PARP inhibitors, BRCA mutation, early breast cancer, locally advanced breast cancer, metastatic breast cancer, and triple negative breast cancer.

Introduction

Approximately 5% of women diagnosed with breast cancer will be found to have a germline BRCA mutation. These BRCA mutations cause damage to DNA, and the poly(adenosine diphosphate-ribose polymerase) (PARP) enzyme is released to repair the damage. However, cancer cells can also utilize the PARP enzyme to grow. Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors are a class of medications that target the PARP enzyme and stop the DNA repair. By stopping the DNA repair, cancer cells are unable to thrive (Robson et al., 2017). BRCA mutations can predispose women to triple negative breast cancers, where treatment options are currently limited. The purpose of the review is to compile a comprehensive literature review comparing safety and efficacy of PARP inhibitors to the current standard of therapy for treatment of women with BRCA positive HER2 negative breast cancer. Hormone receptor positive and negative markers were both considered in the review, but patients were limited to being HER2 negative. Information was categorized depending on early, locally advanced, or metastatic staged BRCA positive, HER2 negative breast cancers.

Statement of the Problem

Women with germline BRCA mutations have a higher chance of developing a triple negative breast cancer. With no positive estrogen, progesterone, or HER2 markers, treatment options are limited. Traditional therapies for triple negative breast cancer currently include surgery, chemotherapy, and radiation. While triple negative therapy is limited, hormone receptor positive cancers have more options. The traditional therapies for estrogen receptor positive cancers include hormone suppressors such as Tamoxifen, Arimidex, and Femara.

Research Question

In breast cancer patients with BRCA positive mutations and HER2 negative breast cancer, are PARP inhibitors as safe and effective as traditional breast cancer therapies?

Methods

A literature review was preformed using the electronic search database PubMed. Both keywords and mesh terms were used to define a set of the literature discussing PARP inhibitor safety and effectiveness in patients with BRCA positive HER2 negative breast cancer. Keywords included PARP inhibitors, BRCA mutation, early breast cancer, locally advanced breast cancer, metastatic breast cancer, and triple negative breast cancer. The search yielded approximately 869 results. These results were narrowed to clinical trials which yielded 78 results. Of the 78 results 60 trials were chosen based on date and relevancy to the PICO question. Duplicate, phase one, and trials not considering BRCA were eliminated. The BrightNess trial was still considered for the review, because BRCA status was considered with data analysis, but not criteria for trial eligibility. Eight studies met the final criteria of being either a phase two or three clinical trial with consideration of BRCA status that fit the PICO question.

Literature Review

Theme 1: Early Stage BRCA Positive HER2 Negative Breast cancer

Tutt et al. (2021) conducted a phase three randomized double-blind clinical trial comparing the efficacy of PARP inhibitor Olaparib 300 mg BID vs a placebo BID for 52 weeks, both in conjunction with chemotherapy and local therapy. AstraZeneca was a sponsor of the study and provided the pharmaceutical. To account for bias, sponsors were not involved in the first draft of the literature (Tutt et al., 2021).

Participants were followed for a median of 2.5-3.5 years in this clinical trial named the OlympiA trial. Data was collected from 2014-2019. The population for this trial was specific to participants with BRCA 1 or BRCA 2 gene mutations that were diagnosed with early HER2 negative breast cancer with local treatment 2-12 weeks prior to the trial and chemotherapy either before or in conjunction with the medication trial. Treatments including radiation therapy, which needed to be completed 2-12 weeks before the trial to avoid interactions with the pharmaceutical. The trial excludes participants with chemotherapy after completion of pharmaceutical therapy, specifically the chemotherapy capecitabine as it was not in use during the time of data collection (Tutt et al., 2021).

Other participation requirements included ensuring no cancer remained after completion of chemotherapy before the trial. The clinical trial was studied at over 420 clinical sites and 23 countries. The trial enrolled 1,836 eligible participants. Participants were allowed to be either estrogen/progesterone receptor positive or triple negative, with most participants being triple negative. Of the 1,836 participants, 1509 were triple negative and 325 were hormone receptor positive. Six men were included in the population. Strict p values were utilized for limited error. The greatest was a p value of 0.02 with findings that participants who received olaparib had fewer deaths than the placebo group. Fifty-nine deaths were reported in the test group and 86 deaths were reported in the placebo group. The majority cause of death in both the olaparib group and placebo group was breast cancer, causing 55 deaths in the test group and 82 deaths in the placebo group. Cardiac arrest was reported in one individual, and another individual died due to an unknown cause. (Tutt et al., 2021).

Adverse reactions and side effects were shared in the safety data. Of the 1836 total participants, 21 did not start either medication or placebo for unstated reasons. As a result, 1815

were considered for the safety analysis. Of the 1815 participants 911 were in the olaparib test group and 904 were in the placebo group. Side effects severity was assessed by a grading system, with grade three or above being the most severe. The three most common side effects experienced by the test group were nausea, vomiting, and anemia. Nausea was experienced by 56.9% (518) of test group participants. Of those 518 participants, 390 experienced nausea at a grade one, 121 experienced nausea at a grade two, and seven experienced nausea at a grade three or higher. Fatigue was experienced by 40.1% (365) of test group participants. Of those 365 participants, 240 experienced fatigue at a grade one, 109 at a grade two, and 16 at a grade three or more. Anemia was experienced by 23.5% (214) of test group participants. Of those 214 test group participants, 68 experienced grade one anemia, 67 experienced grade two anemia, and 79 experienced grade three or higher. Neutropenia and leukopenia were also noted in the test group. Neutropenia was experienced by 16% (146) of test group participants. Of the 146 participants, 36 experienced grade 1 neutropenia, 66 grade 2 neutropenia, and 44 grade 3 or higher neutropenia. Neutropenia and anemia were the two side effects in the test group where more participants experienced grade 3 or higher side effects than grade 1. Leukopenia was experienced in 15.7% (143) of test group participants. Of the 143 participants, 41 experienced grade 1 leukopenia, 75 experienced grade 2 leukopenia, and 27 experienced grade 3 leukopenia (Tutt et al., 2021).

The primary result was measured by how many participants remained cancer free. This endpoint was measured by the STEEP system. These primary endpoints included the first sign of an invasive breast tumor on the same or opposite breast, the cancer returning in the primary spot or to lymph nodes, recurrence in distant organs or tissues, findings of another invasive cancer, or death. Secondary outcomes measured distant disease-free survival, which is metastatic free. The trial found participants in the olaparib test group had longer invasive-disease free and distant

disease-free survival than the placebo group (99.5% CI, $p<0.001$). The olaparib test group had 106 participants who experienced invasive disease or death. This compares to 178 participants in the placebo group who experienced invasive disease or death. At a three year follow up, 85.9% of olaparib test group participants were alive and free of invasive disease. This compares to 77.1% of participants in the placebo group who were alive and free of invasive disease at the three-year follow up (95% CI, $p <0.001$). Kaplan Meier curves were used to visualize these results in the study (Tutt et al., 2021).

Loibl et al. (2018) conducted the BrightNess Trial. This trial is a phase III randomized double-blind placebo-controlled trial that took place at 145 clinical sites in 15 countries. The study required participants to be at least 18 years old with a previous stage two or three triple negative breast cancer. The triple negative had to be untreated and confirmed by either histology or cytology. The participants in this study were candidates for surgery treatment. The study enrolled 634 participants. The goal was to compare the combination of paclitaxel plus carboplatin plus veliparib vs carboplatin plus paclitaxel versus paclitaxel alone. The endpoint of the trial was determined after completion of treatment with a complete response in the breast or lymph nodes. The response was determined by an onsite pathologist (Loibl et al., 2018).

The trial split these 634 participants to three different groups at random in a 2:1:1 ratio. One group that consisted of 316 participants received paclitaxel plus carboplatin plus veliparib. Another group that consisted of 160 participants received paclitaxel plus carboplatin and a veliparib placebo, and the third group consisted of 158 participants who received paclitaxel and carboplatin and veliparib placebo. The response rates and side effects were both evaluated in the trial (Loibl et al., 2018).

The addition of the PARP inhibitor veliparib to the chemotherapy regimen had mixed results. The group with the PARP addition did show a better response than the group with paclitaxel, but the group combining carboplatin and paclitaxel had best results. The veliparib/carboplatin/paclitaxel group showed a response rate of 53% (168 participants of the 316) with a $p < 0.0001$. Paclitaxel alone showed a response of 31% (49 out of 158 participants) with a $p<0.0001$. The group that showed the best response was paclitaxel plus carboplatin. The response rate for this group was 58% (92 out of 160 participants) with a $p=0.36$ (Loibl et al., 2018).

Both groups who received carboplatin had the greatest side effects. These side effects included grade three or four toxicity levels. The group that had the addition of veliparib did not show an increase in toxic effects. Nine deaths occurred during the study; however, no deaths were related to paclitaxel, carboplatin, or veliparib. There was not a significant increase in neutropenia, anemia, leukopenia, or thrombocytopenia with the addition of veliparib. In the group given paclitaxel, carboplatin, and veliparib 40 participants developed neutropenia at grade one or two (13%), 138 patients developed neutropenia at a grade three (44%) and 41 participants developed neutropenia at grade four (13%). This compares to the paclitaxel/carboplatin group results, which showed that 13 participants developed neutropenia grade 1 or 2 (8%), 66 developed neutropenia grade three (42%), and 18 participants developed neutropenia grade four (11%). There was no significant increase in gastrointestinal side effects such as nausea, constipation, diarrhea, vomiting, or decreased appetite with the addition of veliparib in comparison to the group with paclitaxel and carboplatin (Loibl et al., 2018).

Theme 2: Locally Advanced BRCA Positive HER2 Negative Breast Cancer

Litton et al (2020) conducted the EMBRACA trial. The EMBRACA trial is a phase III open label randomized clinical trial comparing safety and efficacy of the PARP inhibitor talazoparib to traditional chemotherapy. Participants had to be at least 18 years old with a confirmed BRCA positive mutation and HER2 negative breast cancer. This study considered both locally advanced and metastatic disease. The study allowed participants to have up to three prior chemotherapies including taxanes such as paclitaxel, and/or an anthracycline such as doxorubicin. The study selected 431 participants who were randomly placed into groups in a 2:1 ratio. One group of 287 participants received talazoparib 1 mg orally once daily. The other group of 144 received a chemotherapy agent such as capecitabine, eribulin, gemcitabine or vinorelbine. The talazoparib group had more participants with decreased activity or more self-care limitations according to the ECOG status scoring. The talazoparib group also had more participants who experienced disease progression within a year of breast cancer diagnosis. Disease progression or toxic effects were two reasons for participants to stop talazoparib treatment. Participants were followed every 12 weeks for survival status and additional cancer treatment (Litton et al., 2020).

Overall survival was evaluated between the talazoparib and chemotherapy groups. The median follow-up of the talazoparib group was 44.9 months. The median follow-up of the chemotherapy group was 36.8 months. The results were made with a 95% confidence interval for both groups. Survival was illustrated with a Kaplan Meier curve. These percentages were made with a 95% CI. Overall survival rates for the talazoparib group were 71% at one year, 42% at two years, and 27% at three years. Overall survival for the chemotherapy group was 74% and one year, 38% at two years, and 21% at three years (Litton et al., 2020).

Side effects between the two groups were also assessed. In the talazoparib group anemia, fatigue, nausea, neutropenia, and headache were the most common side effects occurring in

greater than 30% of the participants. Grade three or four side effects occurred in 69.9% of participants in the talazoparib group. Hematologic side effects were the most common grade three or four occurring in 56.6% of participants. Anemia occurred in 54.9% of participants in the talazoparib group. 5.9% of participants in the talazoparib group needed to discontinue the medication due to side effects. The most common side effects in the chemotherapy group included neutropenia, nausea, and fatigue. Grade three or four side effects occurred in 64.3% of participants in the chemotherapy group. Hematologic side effects were the most common grade three or four occurring in 38.9% of participants. Anemia occurred in 19.0% of participants in the chemotherapy group. 8.7% of participants in the chemotherapy group needed to permanently discontinue treatment due to side effects (Litton et al., 2020).

Palacova et al. (2020) conducted the BROCADE3 clinical trial. The BROCADE3 trial is a randomized double blind, placebo-controlled study. The study took place at 147 clinical sites in 36 countries. Participants were required to be at least 18 years of age and have a confirmed BRCA1 or BRCA2 mutation with locally advanced or metastatic HER2 negative breast cancer. Participants had to have been given at most two prior treatments of chemotherapy. Of 2,202 participants screened between 2014 to 2018, 513 participants meet criteria and were selected for the study. Three hundred thirty-seven participants were randomly selected to be treated with veliparib plus carboplatin- paclitaxel and were called the veliparib group. One hundred seventy-two participants were randomly selected to be treated with placebo plus carboplatin and paclitaxel and were considered the control group. Permuted blocks were used to randomly assign participants into groups in a 2:1 ratio. Groups were given carboplatin 6 mg/mL per min IV on day one and paclitaxel 80mg/mL IV on days one, eight, and 15. These medications were given in combination with 120 mg bid oral veliparib on days two to five or placebo. The medication cycle

was 21 days long. If carboplatin and paclitaxel needed to be stopped due to progression of disease, participants were able to increase dose of veliparib to 300 mg bid or 400 mg twice daily. If participants who needed to discontinue the carboplatin and paclitaxel were in the placebo group, they could start monotherapy veliparib as open label. Groups were organized based on previous chemotherapy use, history of central nervous system metastases, and hormone receptor status. Investigator-assessed progression free survival was reported according to the Response Evaluation Criteria and determined the primary endpoint of the study. The side effects and response rate were reported in the study (Palacova et al., 2020).

The side effects of the study were compared between the two groups. In the veliparib group (336 total participants) 3% (10 participants) experienced grade one or two, 52% (174) experienced grade three, and 43% (144) experienced grade four. Grade five side effects were reported in 2% (six) of participants. The control group (171 total participants) 5% (eight participants) experienced grade one or two side effects, 55% (94) experienced grade three, 39% (66 participants) experienced grade four, and 2% (three participants) experienced grade five side effects. The most common adverse effect was neutropenia. Neutropenia grade one to four was experienced by 89% of the veliparib group and 92% in the control group. Thrombocytopenia grade one to four was reported in 81% of the veliparib group and 71% of the control group. Anemia grade one to four was reported in 80% of veliparib group and 70% in the control group. The most common side effect reported in veliparib monotherapy was nausea. Nausea grade one to four was reported in 52% of veliparib monotherapy group vs 11% in placebo. Overall, there were no reported study related pharmaceutical deaths (Palacova et al., 2020).

Progression-free survival was reported between the groups. The veliparib group reported a median of progression free survival of 14.5 months (95% CI). The control group reported a

median disease-free survival of 12.6 months (95% CI, p=0.0016, hazard ration 0.71). Kaplan Meier curves were utilized to demonstrate the improved outcomes of the veliparib group (Palacova et al., 2020).

Theme 3: Metastatic BRCA Positive HER2 Negative Breast Cancer

Xu, B. et al. (2023) conducted a clinical trial looking into the PARP inhibitor pamiparib. This was an open-label phase II multi-center study in China. This study enrolled 88 participants into two different cohorts. One cohort called the TNBC cohort included participants with triple negative breast cancer. The TNBC cohort included 62 participants. In this group, 75.8% of participants had BRCA1 mutations and 24.2% of participants had BRCA 2 mutations. The other cohort was called the HR+/HER2- cohort and included participants with that form of breast cancer. This cohort included 26 participants. In this group 65.4% of participants had BRCA2 mutations, and 34.6% had BRCA1 mutations. The study allowed for prior platinum chemotherapy or two or less previous lines of chemotherapy. Of the 88 participants 42 participants had received prior platinum therapy, and 60 had received two or less previous lines of chemotherapy. The platinum therapy was only allowed if the disease did not continue to worsen while on treatment. Common treatments of chemotherapy included previous anthracycline and taxane. Sixty-six of the participants (75%) had metastasis of two or more locations prior to the study. Participants were required to be at least 18 years old. The median age of participants was 45 years old with age ranging from 27-67 years old. Participants also needed to have a confirmed metastatic triple negative breast cancer or hormone receptor positive/HER2 negative breast cancer. The participants also needed a confirmed BRCA 1 or 2 mutation. All the participants were female. Pamiparib 60 mg orally twice daily was given to participants in 28-day cycles. Disease progression, toxicity, death, participant withdrawal of

consent, or sponsor trial termination all were reasons for participants to stop treatment. Dose reductions to 40 mg orally twice daily or 20 mg orally twice daily were allowed (Xu et al., 2023).

The results showed a better overall response rate in participants who had not received platinum chemotherapy prior to the study and who had less lines of prior chemotherapy. In the triple negative group participants with no prior chemotherapy had an overall response rate of 66.7%, one prior line 34.5%, and two prior lines 9.1%. In this triple negative group participants with no prior platinum therapy had a 50% response rate compared to a 24% response rate in participants who had platinum therapy. In the hormone receptor positive group, no prior lines had an 88.9% response, one prior line 44.4% response, 2 prior lines 33.3% response. In this group participants with no prior platinum therapy had a 75% response rate and the participants who had prior platinum therapy had a 44.4% response rate. These results were reported with a 95% confidence interval. The study reported the overall response rate of the triple negative group to be 38.2% (p=0.0210). The overall response rate of the hormone positive group was 61.9% (Xu et al., 2023).

Safety and adverse effects were also reported in the study. Anemia, neutropenia, and leukopenia were the most common treatment emergent adverse effects. Due to these emergent adverse effects 66 participants needed a dose adjustment of either a dose interruption and/or a dose reduction. Of these 66 participants, 63 had dose interruptions and 57 had a dose reduction. Only one patient in each cohort needed to fully stop treatment due to treatment emergent adverse effects. There was one death in the triple negative group, however this was found to not be due to the PARP inhibitor (Xu et al., 2023).

Turner et al. (2019) conducted the ABRAZO clinical trial. The ABRAZO trial was a phase II, two cohort, two stage clinical trial that assessed the safety and efficacy of the PARP inhibiter talazoparib in BRCA positive participants with triple negative metastatic breast cancer. The goal of the study was to compare the effect of prior treatment with talazoparib. A total of 84 participants were enrolled in the study. All participants were given talazoparib 1 mg once daily orally. The participants were checked every 21 days. This included visit assessments the on day one, eight, and 15 for the initial two cycles. After the first two cycles, visit assessments were days eight and 15 of the 21-day cycle. Cohort one was to include participants who had prior platinum chemotherapy with the cancer shown to be sensitive to the platinum therapy. Cohort two included participants treated prior to the study, but not with platinum chemotherapy. Forty-nine participants were enrolled in cohort one and 35 participants were enrolled in cohort two. The median age of participants was 50 years old, with ages ranging from 31 to 75 years. Cohort one had 59% of participants with triple negative breast cancer and cohort two had 17% of participants with triple negative breast cancer. The participants in cohort one had a median value of two chemotherapy treatments prior to the study, while cohort two had a median value of four chemotherapy treatments prior to the study for metastatic breast cancer. One participant in cohort needed to stop pharmaceutical treatment due to poor liver function tests that worsened., Eighty three participants were included in the safety analysis (Turner et al., 2019).

Adverse effects were documented in the study. Three participants needed to stop talazoparib due to side effects. These side effects included anemia for one patient and abnormal liver function tests for two participants. Cohort one had two participants that needed to stop talazoparib and cohort two had one patient. Overall anemia was a common hematologic adverse effect in both cohorts, and the most common reason for dose reduction of talazoparib. Anemia

occurred in 40 out of 48 participants in cohort one, and 34 out of 35 participants in cohort two. In some cases, blood transfusions were needed for the anemia. In cohort two 37% of participants received a blood transfusion due to anemia, and in cohort one 21% of participants received a blood transfusion. Fatigue, nausea, and diarrhea were common non-blood related side effects. Fatigue occurred in 32 participants in cohort one and eight participants in cohort two. Nausea occurred in 22 participants in cohort one and 15 participants in cohort two. Diarrhea occurred in 18 participants in cohort one and 10 participants in cohort two. (Turner et al., 2019).

Efficacy was also reported in the study. Objective response rate was determined by an independent radiology facility with a confidence interval of 95%. These findings showed a 21% overall response rate in cohort 1, and a 37% overall response rate in cohort 2. Overall response rate was also evaluated in subgroups of each cohort. The overall response rate in participants with a BRCA 1 mutation was 23% and with a BRCA 2 mutation was 33%. Overall response rate in participants with a triple negative breast cancer was 26% and HER2 positive was 29%. Median survival rate was also assessed. The median follow-up time was 13.7 months for each cohort. In cohort one median overall survival was 12.7 months. In cohort two median overall survival was 14.7 months (Turner et al., 2019).

Turner et al. (2019) noted limitations. First, the open label structure of the study can introduce bias. The authors attempted to the control this by utilizing an independent radiology facility to determine overall response rate. Second, the study wanted to enroll 70 participants in each cohort but needed to stop enrollment due to the EMBARCA trial as participants had to meet similar criteria for both trials (Turner et al., 2019).

Robson et al. (2017) conducted an open-label randomized phase three trial to compare olaparib to traditional therapy in patients with BRCA positive HER2 negative metastatic breast

cancer. This trial was called the OlympiAD trial. Participants could not receive more than two chemotherapy treatment regimens prior to starting the trial. Three hundred and two participants were divided into two cohorts, at random in a 2:1 ratio. The first cohort, made of 205 participants, was given olaparib 300 mg BID. The second, made up of 97 participants, received standard therapy with a single chemotherapy agent of the provider's choice between capecitabine, eribulin, or vinorelbine (Robson et al., 2017).

Olaparib participants had a longer progression free survival in comparison to the group who was given standard therapy. The median progression free survival for the olaparib group was seven months, compared to 4.2 months in the standard therapy group. Both groups had participants who died during the study prior to primary statistical analysis. The olaparib group had a total of 94 participant deaths (45.9%) and the standard chemotherapy group had a total of 46 participant deaths (47.4%) (Robson et al., 2017).

Hormone receptor status was considered for the trial. In the olaparib group 103 participants were hormone receptor positive and 102 were triple negative. In the chemo group 49 participants were hormone receptor positive and 48 were triple negative (Robson et al., 2017).

Side effects were also assessed in the study. Anemia, neutropenia, leukopenia, and nausea were the four most common side effects. The olaparib had a higher percentage of side effects, but less grade 3 side effects in comparison to the chemo group. In the olaparib group 97% of participants had any side effects, while 36.6% experienced grade three or higher. In the chemotherapy group 96.7% of participants experienced any side effect, while 50.5% experienced grade three or higher. Anemia grade three or higher occurred in 16.1% of olaparib group and 4.4% of the chemotherapy group. Neutropenia grade three or higher occurred in 9.3% of the olaparib group and 26.4% of chemo group. Decreased white blood cell count grade three or

higher occurred in 3.4% of olaparib group and 9.9% of the chemotherapy group. No olaparib group participants experienced grade 3 or higher nausea, while one patient experienced grade three or more nausea in chemo group. The study reported one death due to adverse effects in the PARP inhibitor group in which the participant died due to sepsis (Robson et al., 2017).

Gelmon et al (2021) conducted the LUCY Trial. This trial was an open label, single arm study looking at the effectiveness of olaparib in participants with BRCA positive HER2 negative metastatic breast cancer. This trial was a phase IIIb extension of the OlympiA trial (Tutt et al., 2021). The study included 252 participants who had BRCA mutations and HER2 negative metastatic breast cancer. Either hormone receptor positive or negative cancers were both included in the population. Prior platinum chemotherapy was allowed for early disease. Median age of participants was 45 years old with ages ranging from 22-75 years old. Participants were given Olaparib 300 mg BID over a median of eight months, with a range of 0.2-20 months. Treatment was continued until September 2019 or until discontinuation criteria was met. Discontinuation criteria included disease progression and harmful side effects (Gelmon et al., 2021).

Of the 252 participants, 240 had a treatment emergent adverse effect from olaparib. General statistics were reported in the study. Of the 240 participants who experienced adverse effects, 69 participants had grade one severity, 107 participants had grade two, 61 participants had grade three, and three participants had grade four severity. Nausea, anemia, asthenia, vomiting, and fatigue of any grade were the most common adverse effects, which occurred in more than 20% of participants. Grade one anemia occurred in 26 participants. These participants did not require blood transfusion. Grade two or higher anemia occurred in 71 participants, with 40 participants requiring a blood transfusion. Neutropenia grade three or higher was reported in

11 participants. Of the 252 participants, 11 had to stop treatment due to side effects from the medication. None of the participants died because of the adverse effects. (Gelmon et al., 2021).

The effectiveness of Olaparib was also reported in the study results as investigator assessed progression free survival and clinical response rate. Median progression free survival was 8.11 months with a 95% confidence interval. Progression free survival based on hormone receptor status, line of therapy, and prior platinum chemotherapy was illustrated in a Kaplan-Meier curve and reported in the study. Eighty-one participants had prior platinum therapy and a median progression free survival of 6.70 months with a 95% confidence interval. This compares to the 47 participants who received neoadjuvant/adjuvant therapy, who had a median progression free survival of 5.19 months, with a 95% confidence interval. Median progression free survival in 131 participants with hormone receptor positive metastatic breast cancer was 7.95 months, with a 95% confidence interval. In the trial 119 participants showed clinical response to the treatment. The median duration of clinical response reported in those 119 participants was 6.6 months (CI=95%). The median time to study treatment discontinuation or death was 6.90 months (CI=95%). The median time to first subsequent treatment or death was 9.66 months. Of the 119 participants, 69 had continued disease progression or death (Gelmon et al., 2021).

Discussion

Eight total clinical trials were reviewed to compare the efficacy and safety of PARP inhibitors in comparison to standard therapy for the treatment of HER2 negative breast cancer in patients with BRCA positive mutations. PARP inhibitors olaparib, talazoparib, pamiparib, and veliparib were compared to standard therapy in patients with early, locally advanced, and metastatic breast cancer.

The clinical trials that evaluated PARP inhibitors for treatment in early breast cancer offered opposing data. The OlympiA trial supports the use of PARP inhibitor olaparib 300 mg twice daily in clinical practice for BRCA positive patients with early-stage breast cancer versus traditional therapy alone (Tutt et al., 2021). The BrightNess trial reported opposing findings, as this study did not favor the addition of PARP inhibitors to traditional therapy. However, this trial did not compare the PARP inhibitor as monotherapy but rather compared the PARP inhibitor to traditional therapy versus traditional therapy alone. The BrightNess trial did not show an increase in response rate when the PARP inhibitor veliparib was added to therapy. (Loibl et al., 2018).

Because the BrightNess trial included stage 2 breast cancer as part of their participants, this trial seemed most appropriate to compare to the OlympiA trial for use of PARP inhibitors in early breast cancer. With the different findings, the OlympiA trial has stronger evidence. The trial was specific to participants with BRCA 1 or BRCA 2 gene mutations and separated results depending on hormone receptor status (Tutt et al., 2021). The BrightNess Trial was more specific to hormone receptor status, as participants were required to have a triple negative breast cancer, but the trial did not require a BRCA mutation. This could have impacted results, as the PARP inhibitor targets the area of the gene affected by the BRCA mutation (Loibl et al., 2018). The studies also used different PARP inhibitors. While the strongest argument for comparing the trials is BRCA status, the different PARP inhibitors may also have an impact. Olaparib was used for OlympiA trial and veliparib was used for the BrightNess trial. Overall, olaparib was found to be effective treatment for BRCA positive participants with HER2 negative early-stage breast cancer.

The Brocade3 trial, EMBARCA, and China trial evaluated PARP inhibitors in comparison to traditional therapy in participants with locally advanced BRCA positive HER2

negative breast cancer. All three trials used a different PARP inhibitor. The Brocade3 trial was conducted by the same sponsors as the BrightNess trial and used the same PARP inhibitor veliparib. Similar to the BrightNess trial, the addition of the veliparib to traditional therapy was assessed in comparison to traditional therapy alone. In the Brocade3 trial BRCA status was considered, and results favored the addition of veliparib to standard treatment. Dosing was different between the two studies and may have impacted outcomes. Veliparib 120 mg BID was administered during the Brocade3 trial (Palacova et al., 2020). While the BrightNess trial used veliparib 50 mg BID (Loibl et al., 2018).

Talazoparib and pamiparib showed an increase response in patients with locally advanced and metastatic breast cancer. Findings were not isolated between locally advanced and metastatic disease, however both stages were included in two studies. Both the EMBARCA and China trial compared the PARP inhibitors to standard therapy in patients with locally advanced and metastatic breast cancer. EMBARCA used talazoparib 1 mg once daily (Litton et al., 2020). While the China trial used pamiparib 60 mg twice daily (Xu et al., 2023).

Olaparib and talazoparib offered longer progression free survival than standard therapy alone in participants with BRCA positive mutations and HER2 negative metastatic breast cancer. The LUCY trial, OlympiAD trial, and ABRAZO trial were all specific to metastatic breast cancer. The LUCY and OlympiAD trial both evaluated the PARP inhibitor olaparib. The ABRAZO trial evaluated the PARP inhibitor talazoparib (Turner et al., 2019).

In consideration of hormone receptor status, both olaparib and pamiparib had slightly improved outcomes in patients with hormone receptor positive cancer. The LUCY and China trial gave the best isolation of results. The LUCY trial results were similar based on hormone receptors. In the olaparib group of the LUCY trial, the hormone receptor positive participants

had a longer progression free survival by less than 2 months, in comparison to the triple negative participants who received olaparib (Gelmon et al., 2021). The China trial reported similar results. The hormone receptor positive group had a greater objective response rate in comparison to the triple negative group. However, progression free survival was comparable between the two groups. (Xu et al., 2023).

Side effects and safety of the PARP inhibitors were reported in the clinical trials. Anemia and neutropenia were the most common hematologic side effects. Prior platinum chemotherapy treatments may impact the severity of the hematologic side effect, as less blood transfusions were needed for patients who received prior platinum therapy (Turner et al., 2019). In some cases, more instances of anemia occurred in the PARP inhibitor group than traditional therapy (Litton et al., 2020). However, not all studies came to this same conclusion. In the BrightNess trial, patients in which the PARP inhibitor was added to traditional therapy did not have any more side effects than traditional therapy alone (Loibl et al., 2018). The Brocade3 trial supported this finding as well. In the Brocade3 trial neutropenia percentages were relatively similar between the group with the veliparib addition compared to standard therapy alone (Palacova et al., 2020). One death from sepsis was reported due to adverse effects of PARP inhibitors (Robson et al., 2017).

The studies had limitation and strengths. The OlympiA trial included a well-rounded demographic with little error and would be sufficient data to use for research. The trial size seemed appropriate and beneficial that the study was worldwide, allowing for a wide demographic including men. To strengthen the data, it would be beneficial to extend the follow up duration to assess the longevity of the drug and efficacy in prevention of reoccurrence. It was difficult to fully assess death as preexisting conditions were not reported in the trial (Tutt et al, 2021). The BrightNess trial had result limitations due to the p value of 0.36. Future

considerations would be to consider a group that had paclitaxel and veliparib with carboplatin placebo. While participants with BRCA positive mutations were included, this study did not require BRCA mutated breast cancers. The results would have been strengthened if BRCA status would have been considered as part of the eligibility criteria (Loibl et al., 2018).

The BROCADE3 favored the addition of veliparib to paclitaxel and carboplatin. Overall results showed decreased disease progression with no significant adverse effects. The same sponsor also sponsored the BrightNess trial which did not favor the addition of veliparib in the results. BRCA status was considered in the eligibility criteria, which may have increased favorable results for the PARP inhibitor (Palacova et al., 2020).

Limitations of study conducted by Xu et al., 2023 include one patient demographic of Asian women. Opening the study to more demographics would allow the result to be applied other ethnicities. Strengths of the study include separating BRCA 1 and 2 gene mutations and separating triple negative and hormone positive advanced cancers. This study favors PARP inhibitors without prior chemotherapy especially in participants in hormone receptor positive HER2 negative BRCA mutated breast cancer (Xu et al., 2023).

Limitations of the LUCY study include compensation to the researchers of the study by the pharmaceutical company AstraZeneca. AstraZeneca also funded the study. To strengthen the study a double-blind design could be considered versus the open label design. Another consideration to strengthen the study would be to report the side effects in a table instead of a bar graph. The data seemed general, and more specific statistics would strengthen the study. In conclusion this study favored the treatment, but with conflicts of interest (Gelmon et al., 2021).

Overall, all but one clinical trial support the PARP inhibitor either as monotherapy or in addition to tradition therapy in comparison to standard therapy alone. The one study that did not

support the PARP inhibitor therapy did not require BRCA positive mutation for participants and had a lower dose than comparing studies. Additional studies are needed to understand the full impact of prior chemotherapy with the efficacy of the PARP inhibiters, however prior platinum therapy may improve side effects. Hematologic side effects of anemia and neutropenia were most common of the PARP inhibitors, with one death due to adverse effects. When hormone receptor status is considered, hormone receptor positive cancer has slightly better outcomes with PARP inhibitors.

Conclusion

PARP inhibitors were supported in the studies for treatment of HER2 negative breast cancers in patients with BRCA positive germline mutations as being both safe and effective when used with traditional therapy or as monotherapy. While using PARP inhibitors in clinical practice, careful blood count monitoring with a CBC would be beneficial as neutropenia and anemia were common side effects. The PARP inhibitors were not shown to be effective in patients without a BRCA mutation, therefore genetic testing would be necessary before considering the PARP inhibitor treatment. Future considerations and research could include PARP inhibitors as prophylactic treatment for high-risk women carrying the BRCA germline mutation. Other areas for research would include if the knowledge of PARP inhibitor therapy decreases prophylactic mastectomy rates, as many women with BRCA positive mutations opt for prophylactic surgery.

Applicability to Practice

While an oncology provider in oncology would likely be managing the medication, it is applicable for family practice providers to be aware of management as well. According to the research side effects, the family medicine provider would want to monitor blood counts with a

CBC to check for neutropenia and anemia and consider these side effect deficits when taking the patient's history. Knowledge of family history of BRCA mutations with genetic testing would also be beneficial prior to the patient starting the medication.

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