BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Expanding the Use of PARP Inhibitors in Breast Cancer

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H&O Which patients with breast cancer are currently eligible for poly(ADP-ribose) polymerase (PARP) inhibition?

TT For this question, I refer to the National Comprehensive Cancer Network guidelines,[1] which address patients with both early and advanced breast cancer. Patients with early breast cancer are eligible for 1 year of adjuvant olaparib (Lynparza, AstraZeneca) if they have a germline pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2*, human epidermal growth factor receptor 2 (HER2) negativity, and high-risk clinicopathological factors following local treatment and neoadjuvant or adjuvant chemotherapy. Patients with early triple-negative breast cancer (TNBC) are eligible if they have either residual disease after neoadjuvant chemotherapy, or T2 tumors or tumors involving the lymph nodes if they did not receive neoadjuvant therapy. Patients with estrogen receptor–positive early breast cancer are eligible if they have extensive lymph node involvement or residual disease, plus a CPS+EG score—which estimates the probability of relapse based on clinical and pathological stage, estrogen receptor status, and histologic grade—of 3 or higher. Patients in all these groups experience better invasive disease–free survival, better distant disease–free survival, and a decrease in distant recurrences with 1 year of adjuvant olaparib, based on results from the phase 3, double-blind, randomized OlympiA trial.[2]

Patients with advanced breast cancer are eligible for PARP inhibitor treatment if they have a germline *BRCA1* or *BRCA2* mutation, based on data from the OlympiAD[3] and EMBRACA[4] studies. Both phase 3 randomized studies examined the use of PARP inhibition for patients with HER2-negative breast cancer: olaparib in the OlympiAD study and talazoparib (Talzenna, Pfizer) in the EMBRACA study. Patients were randomly assigned to PARP inhibition or the physician's choice of chemotherapy, excluding platinum chemotherapy. In both studies, progression-free survival (PFS) was longer with PARP inhibition than with chemotherapy. In addition, the OlympiAD study showed that quality of life was better with PARP inhibition than with chemotherapy. This finding makes sense because PARP inhibition is a simple pill that is administered orally, making it highly convenient, whereas with chemotherapy, patients need to return to the chemotherapy unit or clinic for regular intravenous treatments, many of which lead to side effects such as alopecia, myelosuppression, nausea, and vomiting. Although neither of the studies was powered to show a survival benefit, survival was numerically longer with olaparib than with chemotherapy in the OlympiAD study. The studies also showed that PARP inhibitors seem to be more efficacious when used in earlier lines of treatment.

Emerging evidence is pointing to the value of other biomarkers that may predict benefits with the use of PARP inhibitors. For example, the phase 2 TBCRC 048 study[5] showed that olaparib was able to benefit patients with HER2-negative metastatic breast cancer who had somatic *BRCA1* or *BRCA2* mutations or germline *PALB2* mutations; all 3 of these genes are necessary for homologous recombination repair (HRR).

H&O Could you further discuss the role of homologous recombination deficiency (HRD) status in predicting which patients will benefit from PARP inhibition?

TT Homologous recombination is the mechanism that

our cells have developed to repair double-stranded DNA damage, which is highly lethal to cells. In homologous recombination, the intact sister chromatid is used as a template to resynthesize the DNA sequence and repair the areas that are broken. This type of repair is very important to the integrity of our genome.

When patients have HRD, such as a mutation in *BRCA1* or *BRCA2*, their cells are unable to repair double-stranded DNA breaks. As a result, their cells become unstable genomically, leading to cellular death. When patients have this vulnerability, it gives us an excellent target because we know that these tumor cells are exquisitely sensitive to DNA-damaging agents, such as platinum chemotherapy or PARP inhibition. There are many ways to define HRD, but I would argue that it should be defined phenotypically because it gives tumor cells a vulnerability that we can target via DNA-damaging agents.

Oncologists have been making an increasing effort to identify more patients with breast cancer who have HRD. Only 2% or 3% of all breast cancers are associated with a germline mutation in *BRCA1* or *BRCA2,* but multiple other genes are involved in the homologous recombination pathway. The question is, how do we identify more cases of HRD?

We have a couple of ways to assess for HRD. One way is to look for specific mutations in genes such as germline *BRCA1*, *BRCA2*, or *PALB2,* or silencing of *BRCA1* through promoter hypermethylation of the *BRCA1* gene. Another way is to use an assay that looks at genomic scars, such as the MyChoice CDx HRD assay from Myriad Genetics or the FoundationFocus CDxBRCA assay from Foundation Medicine, or a weighted model that looks at mutational signatures, such as HRDetect. The advantage of looking at genomic scars and mutational signatures is that these approaches capture patients with HRD, regardless of the underlying mechanism or the specific homologous recombination. One major disadvantage is that these scars or signatures represent what was present at one point of the tumor evolution, and do not necessarily reflect the phenotypic state the tumor is in. Therefore, it is not surprising that the current data evaluating different HRD assays are somewhat mixed regarding the best way to predict which patients will benefit from PARP inhibition.

H&O What recent studies have looked at the use of HRD status to predict which patients will benefit from PARP inhibition?

TT There are 2 studies of special interest: RIO[6] and PETREMAC.[7] The RIO study, which was a phase 2 window of opportunity study, looked at biomarkers for PARP inhibition following 2 weeks of neoadjuvant PARP inhibition in unselected patients with TNBC. Mutational signature analysis revealed that in this unselected cohort of patients with TNBC, 69% of patients had HRD and more than two-thirds of HRD tumors were attributed to underlying mutations in *BRCA1/2*, *PALB2*, or promoter hypermethylation of *BRCA1*/RAD51C. Of note, direct measurement of epigenetic changes through assessment of DNA methylation in gene promoter regions is not currently included in clinically available next-generation sequencing panels. The authors highlighted the potential for mutational signatures based on whole genome sequencing to identify patients suited for trials incorporating PARP inhibition.

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In the phase 2 PETREMAC study, patients with stage II or III TNBC received olaparib for up to 10 weeks before chemotherapy. There were 17 complete and partial responses among the 32 recruited patients with TNBC. Somatic or germline mutations affecting homologous recombination were observed in 10 of 18 responders vs 1 of 14 nonresponders. Among the patients not harboring any mutations, 6 out of 8 responders were found to have *BRCA1* promoter hypermethylation, again pointing to PARP inhibitor activity in treatment-naive TNBC who had HRD beyond germline *BRCA1/2* or *PALB2* mutations.

In the advanced breast cancer setting, a noteworthy study is the phase 2 S1416 study from the Southwest Oncology Group.[8] In this study, patients with metastatic TNBC who had received no more than 1 prior line of systemic treatment were randomly assigned to intravenous cisplatin combined with either the experimental PARP inhibitor veliparib or a placebo. Patients were classified into 1 of 3 predefined biomarker groups: (1) germline *BRCA1/2*-mutated; (2) non-BRCA; and (3) BRCA-like, based on any one of the following biomarkers: genomic instability score of 42 or more, somatic *BRCA1/2* mutations, *BRCA1* promoter methylation, or non-*BRCA1/2* homologous recombination germline mutations. Of the more than 300 patients who were enrolled, 13% had a

germline *BRCA1/2* mutation. Of the remaining 257 patients with negative germline *BRCA1/2* mutations who were eligible for biomarkers, approximately half were classified as BRCA1/2-like. The researchers found that the addition of PARP inhibition to platinum chemotherapy improved PFS in the BRCA-like group but not in the germline *BRCA1/2*-mutated or non-BRCA groups.

H&O What approaches are being investigated to increase the response rate to PARP inhibition in breast cancer?

TT Multiple studies are looking at combining PARP inhibitors with other agents, such as chemotherapy. A major problem with this approach is the overlapping toxicities between the agents. For example, both PARP inhibitors and chemotherapy can lead to cytopenia. As mentioned earlier, the S1416 study showed that veliparib, which is not as potent at PARP trapping as other PARP inhibitors, can be used successfully in combination with chemotherapy. Another example comes from patients in the phase 3 BROCADE3 study.[9] In this study, patients with HER2-negative advanced breast cancer and a germline *BRCA1* or *BRCA2* mutation had longer PFS if they received veliparib vs placebo in addition to carboplatin and paclitaxel. Patients in this trial were allowed to continue veliparib even if they needed to discontinue chemotherapy because of toxicities. The Kaplan-Meier curves continued to separate over time, suggesting that maintenance therapy with a PARP inhibitor may be beneficial. It will be interesting to see how newer PARP inhibitors, which are more selective for PARP1—thus sparing cytopenic toxicities—will compare when they are combined with cytotoxic agents.

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Researchers are looking at other combination strategies, such as PARP inhibition plus immune checkpoint blockade. Two of the studies that come to mind are TOPACIO[10] and MEDIOLA.[11] TOPACIO, also known as KEYNOTE-162, was a phase 1/2 study of niraparib (Zejula, GSK/Janssen) plus pembrolizumab (Keytruda, Merck) for patients with advanced or metastatic TNBC. MEDIOLA was a phase 1/2 basket study of olaparib plus durvalumab (Imfinzi, AstraZeneca) for patients with germline *BRCA*-mutated, HER2-negative metastatic breast cancer. Both studies suggested that the combination of a PARP inhibitor and an immune checkpoint inhibitor was safe and had promising antitumor activity. However, given that these studies were both single-arm studies, we are not able to tease out how much benefit the immune checkpoint inhibitor added.

Ongoing studies are looking at additional combination strategies. One such strategy is PARP inhibition plus a novel antibody-drug conjugate, such as sacituzumab govitecan (Trodelvy, Gilead).[12] Another is PARP inhibition plus a targeted therapy, such as the PIK3CA inhibitor alpelisib (Piqray, Novartis).[13] Antibody-drug conjugates and PIK3CA inhibitors have been shown to increase the indices for DNA damage, which may allow them to work synergistically with PARP inhibitors.

H&O Could you talk about your work on the DORA study?

TT DORA is a phase 2 study of maintenance treatment using olaparib with or without durvalumab for patients with platinum-treated advanced TNBC who had a prior response to platinum chemotherapy.[14,15]

In this small trial, we found that it was feasible for patients to switch from chemotherapy to a chemotherapy-free maintenance regimen that included a PARP inhibitor. We also found that some patients who did not have an identified germline *BRCA* mutation benefited from this strategy. When we went back and looked at the tumors of these patients, we saw similar proportions of patients with *BRCA* mutations as with *BRCA* promoter hypermethylation. We do not currently screen patients for *BRCA* methylation, but screening could potentially be used to identify patients who are eligible for PARP inhibition. Another notable finding was that patients with a *BRCA* mutation do not have *BRCA* methylation, and those with *BRCA* methylation do not have a *BRCA* mutation. We would like to further explore this finding in larger, confirmatory trials.

Disclosures

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References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast cancer. v.4.2023. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated March 23, 2023. Accessed August 9, 2023.
2. Tutt ANJ, Garber JE, Kaufman B, et al; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. *N Engl J Med*. 2021;384(25):2394-2405.
3. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. 2019;30(4):558-566.
4. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol*. 2020;31(11):1526-1535.
5. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol*. 2020;38(36):4274-4282.
6. Chopra N, Tovey H, Pearson A, et al. Homologous recombination DNA repair deficiency and PARP inhibition activity in primary triple negative breast cancer. *Nat Commun*. 2020;11(1):2662.
7. Eikesdal HP, Yndestad S, Elzawahry A, et al. Olaparib monotherapy as primary treatment in unselected triple negative breast cancer. *Ann Oncol*. 2021;32(2):240-249.
8. Rodler E, Sharma P, Barlow WE, et al. Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a acituzuma, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2023;24(2):162-174.
9. Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a acituzuma, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(10):1269-1282.
10. Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. *JAMA Oncol*. 2019;5(8):1132-1140.
11. Domchek SM, Postel-Vinay S, Im SA, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, acituzumab, phase 1/2, basket study. *Lancet Oncol*. 2020;21(9):1155-1164.
12. Yap TA, Hamilton E, Bauer T, et al. Phase Ib SEASTAR study: combining rucaparib and acituzumab govitecan in patients with cancer with or without mutations in homologous recombination repair genes. *JCO Precis Oncol*. 2022;6:e2100456.
13. Batalini F, Xiong N, Tayob N, et al. Phase 1b clinical trial with alpelisib plus olaparib for patients with advanced triple-negative breast cancer. *Clin Cancer Res*. 2022;28(8):1493-1499.
14. Sammons SL, Tan TJ, Im YH, et al. DORA: a phase II, multicenter, international, non-comparator study of olaparib (O) +/- durvalumab (D) as a chemotherapy-free maintenance strategy in platinum treated advanced triple-negative breast cancer (aTNBC) [SABCS abstract PD11-12]. *Cancer Res*. 2023;83(5)(suppl).
15. Tan TJY, Sammons S, Fink JL, et al. Homologous recombination (HR) status of platinum responsive advanced triple negative breast cancers (aTNBC) treated with olaparib as maintenance therapy [ESMO abstract 4MO]. *Ann Oncol*. 2023;8(1)(suppl 4).