

## CLINICAL VIGNETTE

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# Special Consideration in the Adjuvant and Neoadjuvant Systemic Treatment of BRCA-associated Breast Cancer

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### Case Report

A 39-year-old woman palpated a left breast mass at the end of a pregnancy. Mammography revealed a 3 cm left breast mass in the upper outer quadrant with abnormal pleomorphic calcifications extending over 8 cm, while ultrasound demonstrated a 6 cm left upper outer quadrant mass. No adenopathy was seen on imaging. Ultrasound-guided biopsy revealed a high grade invasive ductal carcinoma, Estrogen Receptor (ER) positive, Progesterone Receptor (PR) positive, high ki-67 at 70%, and HER2 negative. One week after her diagnosis, she delivered a healthy daughter by vaginal delivery.

She had a strong family history of malignancy, with her mother developing breast cancer at age 37, and two maternal aunts with breast cancer at ages 34 and 50. Genetic testing demonstrated a *BRCA2* germline mutation.

She received neoadjuvant docetaxel and carboplatin chemotherapy followed by bilateral mastectomies, with residual 3.8 cm ductal carcinoma in situ (DCIS), two negative sentinel nodes, and no residual invasive disease. The radiation oncologist did not advise adjuvant radiation therapy. She began adjuvant endocrine therapy with leuprolide and anastrozole, and planned to have a prophylactic bilateral salpingo-oophorectomy (BSO) in the near future. Given the pathologic complete response to neoadjuvant chemotherapy with only residual DCIS, based on the OlympiA trial eligibility criteria<sup>1</sup> she was not treated with an adjuvant poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor.

### Discussion

Although most breast cancers are sporadic, germline pathogenic mutations in *BRCA1* and *BRCA2* occur in approximately 5% of patients with breast cancer, and in 15% of women with breast cancer who have a family history of breast cancer. Inherited in an autosomal-dominant pattern, these mutations significantly increase the risk of breast and ovarian cancers, as well as other cancers such as pancreatic cancer, prostate cancer, and melanoma. There are some clinical differences between *BRCA1* and *BRCA2* carriers. *BRCA1* confers a higher risk of ovarian cancer than does *BRCA2* (44% vs 17%). The age of onset of breast cancer is younger in *BRCA1* carriers than in *BRCA2*, and triple negative disease is more common in *BRCA1* compared to *BRCA2* related breast cancers.

This patient had her breast cancer diagnosed at the end of her pregnancy, and therefore was able to initiate breast cancer treatment shortly after her diagnosis was made. Given the high-grade nature of her cancer and the elevated ki67, along with the large size, the decision was made to treat her with neoadjuvant chemotherapy for what was felt to be luminal B breast cancer. There are a number of neoadjuvant chemotherapeutic regimens that can potentially be used in this setting. Anthracyclines were not administered given the node negative, hormone sensitive disease. Carboplatin was selected due to the *BRCA2* mutation, although with the understanding that the data on neoadjuvant platinum therapy is based mainly in BRCA associated triple negative breast cancer. The TNT trial<sup>2</sup> compared first line carboplatin to docetaxel in the treatment of triple negative metastatic breast cancer. In this trial of patients with a known *BRCA1/2* mutation, the response rate (68% vs 33%) and progression free survival (6.8 months vs 4.4 months) were higher in the carboplatin arm. Other randomized trials of the neoadjuvant treatment of triple negative breast cancer have demonstrated an increased pathologic complete response rate with the addition of carboplatin to standard anthracycline and taxane chemotherapy in both BRCA carriers and non-carriers, but with increased toxicity. One other study of neoadjuvant treatment of triple negative breast cancer evaluated docetaxel with carboplatin and demonstrated excellent 3-year disease free survival and overall survival in this non-anthracycline regimen.<sup>3</sup> Although this patient did not have triple negative disease, given her BRCA mutation, carboplatin was used based on extrapolation of the data from the TNT study and the other trials discussed above. This patient did obtain a complete pathologic response with only residual non-invasive disease.

Given her *BRCA2* mutation and the increased risk of ovarian cancer, this patient decided that she would proceed with prophylactic BSO, but did want to wait for a number of months after chemotherapy was completed before having surgery. For premenopausal women with higher risk hormone sensitive breast cancer, such as tumor size over 5 cm, node positive disease, or high-risk features requiring chemotherapy, disease free survival can be improved with the addition of ovarian suppressive therapy to tamoxifen or aromatase inhibitors.<sup>4</sup> This patient will continue on leuprolide with anastrozole until she has her BSO, at which point the anastrozole will be continued.

Women with *BRCA2* mutations on average develop ovarian cancer 8-10 years later than those with *BRCA1* mutations. Risk-reducing BSO is advised for BRCA 1 carriers at age 35 to 40, after completion of childbearing. *BRCA2* carriers can often safely wait to do this risk-reducing surgery until age 40-45, although it is advised to be done earlier if there is a family history of ovarian cancer at a younger age. For this patient BSO is not only prophylactic but is also a therapeutic intervention for her hormone-sensitive breast cancer.

Breast cancers with *BRCA1* and *BRCA2* mutations have evidence of deficiency in homologous recombination DNA repair. PARP inhibitors can selectively kill tumor cells that have such a deficiency. In the treatment of metastatic breast cancer in BRCA carriers, PARP inhibitors are effective therapies that are generally less toxic than chemotherapy. Recently, the use of PARP inhibitors in the adjuvant treatment of BRCA-associated breast cancer was evaluated in the OlympiA trial.<sup>1</sup> In this study, patients with high risk HER2 negative *BRCA1* and *BRCA 2* early breast who completed neoadjuvant or adjuvant chemotherapy and finished local treatment were randomized between one year of the PARP inhibitor olaparib or placebo. Three-year invasive disease-free survival was improved by 8.8% and distant disease-free survival was improved by 7.1% with the use of olaparib. The patients with hormone sensitive disease eligible for this trial had 4 or more involved axillary nodes, or residual disease after neoadjuvant chemotherapy and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score  $\geq 3$ .

This patient has a good prognosis based on the complete pathologic response of invasive disease after neoadjuvant chemotherapy. She does not have high enough risk disease to qualify for adjuvant PARP inhibition. Her future treatment will consist of BSO and adjuvant anastrozole therapy.

## REFERENCES

1. **Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, Gelber RD, de Azambuja E, Fielding A, Balmaña J, Domchek SM, Gelmon KA, Hollingsworth SJ, Korde LA, Linderholm B, Bandos H, Senkus E, Suga JM, Shao Z, Pippas AW, Nowecki Z, Huzarski T, Ganz PA, Lucas PC, Baker N, Loibl S, McConnell R, Piccart M, Schmutzler R, Steger GG, Costantino JP, Arahani A, Wolmark N, McFadden E, Karantza V, Lakhani SR, Yothers G, Campbell C, Geyer CE Jr; OlympiA Clinical Trial Steering Committee and Investigators.** Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. *N Engl J Med.* 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848.
2. **Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Barrett-Lee P, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Wynne C, Hatton MQ, Hoadley KA, Parikh J, Parker P, Perou CM, Roylance R, Shah V, Shaw A, Smith IE, Timms KM, Wardley AM, Wilson G, Gillett C, Lanchbury JS, Ashworth A, Rahman N, Harries M, Ellis P, Pinder SE, Bliss JM.** Carboplatin in *BRCA1/2*-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med.* 2018 May;24(5):628-637. doi: 10.1038/s41591-018-0009-7. Epub 2018 Apr 30. PMID: 29713086; PMCID: PMC6372067.
3. **Sharma P, López-Tarruella S, García-Saenz JA, Khan QJ, Gómez HL, Prat A, Moreno F, Jerez-Gilarranz Y, Barnadas A, Picornell AC, Monte-Millán MD, González-Rivera M, Massarrah T, Pelaez-Lorenzo B, Palomero MI, González Del Val R, Cortés J, Fuentes-Rivera H, Morales DB, Márquez-Rodas I, Perou CM, Lehn C, Wang YY, Klemp JR, Mammen JV, Wagner JL, Amin AL, O'Dea AP, Heldstab J, Jensen RA, Kimler BF, Godwin AK, Martín M.** Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel. *Clin Cancer Res.* 2018 Dec 1;24(23):5820-5829. doi: 10.1158/1078-0432.CCR-18-0585. Epub 2018 Jul 30. PMID: 30061361; PMCID: PMC6279513.
4. **Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, Láng I, Gómez HL, Tondini C, Ciruelos E, Burstein HJ, Bonnefoi HR, Bellet M, Martino S, Geyer CE Jr, Goetz MP, Stearns V, Pinotti G, Puglisi F, Spazzapan S, Climent MA, Pavesi L, Ruhstaller T, Davidson NE, Coleman R, Debled M, Buchholz S, Ingle JN, Winer EP, Maibach R, Rabaglio-Poretti M, Ruepp B, Di Leo A, Coates AS, Gelber RD, Goldhirsch A, Regan MM; SOFT and TEXT Investigators and the International Breast Cancer Study Group.** Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. *N Engl J Med.* 2018 Jul 12;379(2):122-137. doi: 10.1056/NEJMoa1803164. Epub 2018 Jun 4. PMID: 29863451; PMCID: PMC6193457.