CLINICAL VIGNETTE

PALB-2 Associated Metastatic Breast Cancer

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Case

An 80-year-old woman felt a left breast mass. Her last mammogram was three years prior. Examination revealed 4 cm breast mass with erythema, skin thickening, peau d' orange changes and left an enlarged left axillary node.

Mammography revealed 2 malignant appearing left breast masses, skin thickening, and 2 abnormal left axillary nodes. Breast MRI confirmed the mammogram findings. Biopsies of both breast masses revealed identical high grade invasive ductal carcinoma, estrogen receptor (ER) negative, progesterone receptor (PR) 3% positive, HER2 negative, ki-67 elevated. The axillary node biopsy revealed carcinoma.

PET/CT confirmed left breast masses, with metastases to left axillary, left supraclavicular, retrocrural, and retroperitoneal nodes. She met criteria for stage IV metastatic breast cancer at presentation.

Genomic testing revealed both somatic and germline mutations in PALB2. Her family history was notable for a sister with ovarian cancer at age 38, another sister with colon cancer at age 65, and her mother with liver cancer at age 50.

Initially she was treated with 6 cycles of nab-paclitaxel chemotherapy with near complete response of disease in all sites. She had one small residual retrocrural node remaining. Subsequently she was started on the PARP inhibitor olaparib, which she has continued to take for more than 2 years with no evidence of residual disease on examination or imaging.

Discussion

PALB2 is a mutation that carries a high risk of female breast cancer, ranging from 41-60%. Other cancer risks associated with this genetic mutation include a 0.9% risk of male breast cancer, a 3-5% risk of ovarian cancer, and a 2-5% risk of pancreas cancer. Women who carry the PALB2 mutation without a cancer diagnosis, have aggressive cancer screening recommendations: annual mammography and breast MRI, and consideration of salpingo-oophrectomy at age 45-50 to reduce pancreas cancer screening is recommended only if there is a family history of pancreas cancer.

Our patient had sister with ovarian cancer at a young age. She had 9 siblings but no other family history of PALB2 related malignancies. It is recommended that women with a personal history of ovarian cancer undergo genetic testing to evaluate for possible germline mutations. In addition, the current NCCN guidelines recommended genetic testing for ovarian cancer susceptibility genes, which include PALB2 recommend genetic testing for unaffected individuals who have first or second degree relatives with epithelial ovarian cancer diagnosed at any age. Given that medical oncologists usually see patients after their cancer diagnoses, it would be beneficial for primary care physicians and gynecologists to be aware of the importance of obtaining family histories of cancer, identify and refer high risk women for genetic counseling and testing, if indicated.

Metastatic breast cancer is incurable, but treatable, with improved survival with newer systemic therapies. This patient presented with stage IV disease and therefore systemic treatment was initiated rather than local therapy. The systemic therapy options for this patient included chemotherapy, endocrine therapy, and PARP inhibitor therapy.

Because her cancer was ER negative and PR 3% positive, her cancer was only minimally hormonally sensitive and unlikely to have a significant response to endocrine therapy. The value of endocrine therapy in treating patients with hormone receptor low (less than 10% positive) breast cancer is debated. This patient had high grade breast cancer that was ER negative and PR 3% positive. This cancer would likely behave more like a triple negative rather hormone dependent breast cancer and therefore chemotherapy was administered as her first line therapy. Although immunotherapy in combination with chemotherapy is used for first line treatment in metastatic triple negative breast cancer, it is used in patients with a PD-L1 mutation,[1] which she did not have. Therefore, she did not receive immunotherapy. In addition, her cancer was not strictly triple negative given the low PR staining, and immunotherapy is not used in hormone sensitive breast cancer.

As anticipated, she had an excellent response to first-line single agent chemotherapy. Single agent chemotherapy can yield good responses in this setting. For patients with visceral crisis, consideration may be given to administering combination chemotherapy, but often single agent chemotherapy is preferred. After 6 months of treatment with nab-paclitaxel, she had minimal residual disease and has subsequently remained in remission with maintenance therapy on the PARP inhibitor olaparib.

PALB2- named such as a Partner and Localizer of BRCA2-was originally identified as crucial for interacting with BRCA2 to maintain normal genome functioning. It was later found to also interact with BRCA1. The mechanism of action of PARP inhibitors breaks in double strand DNA and inhibit cell recovery from DNA damage. Patients with BRCA mutations have a defect in homologous DNA repair and are sensitive to PARP inhibitors. Clinical studies have demonstrated patients with PALB2 mutations also respond well to PARP inhibitors.[2] Although the FDA approval for the current commercially available PARP inhibitors, olaparib and talazoparib, is for women with HER2 negative, BRCA mutated breast cancer. Given that PARP inhibitors benefit breast cancer patients with PALB2 mutations, our patient was able to obtain insurance approval for treatment with olaparib.

PARP inhibitors are oral medications that are generally well-tolerated, as our patient's experience. She has been able to continue olaparib therapy chronically with no significant toxicities. The most common toxicities attributed to olaparib are nausea, fatigue, anemia, leukopenia, as well as a 1.5% risk of myelodysplasia. Talazoparib may cause similar side effects of nausea, fatigue, and count suppression, as well as a 25% risk of low-grade alopecia, with only a 0.4% reported risk of myelodysplasia. In terms of comparative toxicities, olaparib has a higher risk of nausea and vomiting, while talazoparib has a higher rate of anemia and alopecia. Most women are able to tolerate and maintain a good quality of life on either of these PARP inhibitors.

As genomic and genetic testing have developed, systemic cancer therapies have become more targeted, offering more effective individualized treatments, with improved survival in metastatic breast cancer patients.

REFERENCES

1. **Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Holgado E, Iwata H, Masuda N, Otero MT, Gokmen E, Loi S, Guo Z, Zhao J, Aktan G, Karantza V, Schmid P; KEYNOTE-355 Investigators**. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020 Dec 5;396(10265):1817-1828. doi: 10.1016/S0140-6736(20)32531-9. PMID: 33278935.
2. **Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, Shah PD, Ballinger TJ, Yang ES, Vinayak S, Melisko M, Brufsky A, DeMeo M, Jenkins C, Domchek S, D'Andrea A, Lin NU, Hughes ME, Carey LA, Wagle N, Wulf GM, Krop IE, Wolff AC, Winer EP, Garber JE**. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol*. 2020 Dec 20;38(36):4274-4282. doi: 10.1200/JCO.20.02151. Epub 2020 Oct 29. PMID: 33119476.