CLINICAL VIGNETTE

Breast Cancer Recurrence in a Woman with Two Prior Distinct Bilateral Breast Cancers

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Case Report

At age 44, a woman developed Stage IIB T3N0M0 Estrogen Receptor (ER) positive, Progesterone Receptor (PR) negative, Human epidermal growth factor receptor 2 (HER 2) negative infiltrating lobular carcinoma. She received neoadjuvant chemotherapy with doxorubicin, cyclophosphamide followed by docetaxel, after which she underwent lumpectomy. The pathology at surgery revealed a minor response with residual 4.5 cm invasive disease. Whole breast radiation therapy was administered, followed by adjuvant tamoxifen for 5 years. At age 55, she developed a contralateral breast cancer, stage IA T1aN0M0 triple negative high grade infiltrating ductal carcinoma, for which she underwent lumpectomy, adjuvant chemotherapy with gemcitabine and carboplatin, and whole breast radiation therapy. Three years after completing this treatment, she developed right hip pain and was found to have widespread bone metastases, biopsy of which revealed metastatic breast cancer, ER and PR positive, HER2 negative. She was treated with palliative radiation therapy to her hip and started on letrozole, palbociclib and denosumab.

Discussion

This case brings up a number of interesting issues relevant to the management of breast cancer and demonstrates changing paradigms in breast cancer management through the years. The first is the role of genetic testing in patients with breast cancer. After her initial breast cancer diagnosis at age 44, this woman did undergo genetic testing for BRCA1 and 2. This testing was performed many years ago, and the technology of BRCA testing has improved since then. In addition, many more genes which predispose to breast cancer have been identified, and are now often currently tested with multigene panels. The indications for genetic testing in this woman are her diagnosis of breast cancer before the age of 50, the diagnosis of triple negative breast cancer under the age of 60, and two primary breast cancers in the same individual. Of note is the absence of a family history of breast or ovarian cancer. She did undergo more thorough panel testing for genetic risk which was negative.

Another interesting management point was the minimal response of her initial invasive lobular carcinoma to neoadjuvant chemotherapy. Neoadjuvant chemotherapy has been standard of care for T3 lesions for many years. Retrospective analyses suggest that endocrine sensitive, invasive lobular breast cancers do not derive much additional benefit from chemotherapy when added to endocrine therapy.[1] At the time she was treated for her first cancer, genomic assays were not available to assist in decision making about the use of chemotherapy. Currently, a number of genomic assays are available which can be used to assess recurrence risk based on prognostic features, and the 21-gene RT-PCR assay (Oncotype Dx) can also be used to predict the benefit of chemotherapy. If she presented today with her lobular carcinoma, a genomic assay would likely be utilized to determine if chemotherapy would be of benefit in her management.

Breast cancer patients with prior standard neoadjuvant or adjuvant chemotherapy have complex decision making about adjuvant chemotherapy for a second primary breast cancer, due to the concern about cumulative toxicities and about potential resistance to the prior agents. The second cancer in the patient discussed was a triple negative breast cancer, for which there is some evidence for platinum agents. Platinum agents, when combined with other chemotherapy in the neoadjuvant setting, have been shown to increase pathologic complete response rates,[2] and recent data suggests an improvement in disease free survival. But currently, there is no evidence of an overall survival advantage with platinum agents in the adjuvant or neoadjuvant setting. In the case presented here, the choice of adjuvant gemcitabine and carboplatin was made after long discussion with the patient of the risks and benefits of various potential chemotherapy options. This combination has been studied in the setting of metastatic disease and is not a standard adjuvant regimen.

Fourteen years after her initial hormone sensitive breast cancer, and 3 years after her triple negative breast cancer, this patient developed hormone sensitive metastatic breast cancer to bone. Although the endocrine receptor status and HER2 status of metastatic disease can differ from that of the primary, this recurrence is most likely a late recurrence of her initial ER positive lobular carcinoma. A recent article described the steady increase in breast cancer recurrences in years 5 to 20 after the completion of 5 years of adjuvant endocrine therapy.[3] Biomarkers such as the Breast Cancer Index have been developed for prognosticating late distant recurrences of breast cancer and for predicting the benefit of extended endocrine therapy, in order to determine who might benefit from

continuing adjuvant endocrine therapy beyond 5 years to prevent distant recurrences.

For patients with hormone sensitive bone-only metastasis, endocrine therapy can offer sustained progression free survival. The Paloma 2 trial[4] demonstrated a near doubling of progression free survival when palbociclib, a CDK4/6 inhibitor, was added to letrozole, and when palbociclib was added to fulvestrant in the Paloma 3 trial[5] a similar near doubling in progression free survival was also demonstrated. Other CDK4/6 inhibitors also increase progression free survival when added to endocrine therapy. Therefore, in metastatic endocrine sensitive disease in postmenopausal patients not in visceral crisis (who would require chemotherapy), CDK4/6 inhibitors combined with endocrine therapy are often considered as first line therapy.

The final systemic therapy used in her management was denosumab. This monoclonal antibody, a RANKL inhibitor, can reduce the risk of fractures and skeletal related events from bone metastasis in breast cancer. The intravenous bisphosphonates zoledronic acid and pamidronate can also be used to decrease the complications from bone metastases.

This woman who developed 2 primary breast cancers with different histologies many years apart, followed by late bone metastases demonstrates the evolution of breast cancer management over time.

REFERENCES

1. **Truin W, Voogd AC, Vreugdenhil G, van der Heiden-van der Loo M, Siesling S, Roumen RM**. Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer. *Ann Oncol*. 2012 Nov;23(11):2859-65. doi: 10.1093/annonc/mds180. Epub 2012 Jun 27. PubMed PMID: 22745216.
2. **von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M, Blohmer JU, Jackisch C, Paepke S, Gerber B, Zahm DM, Kümmel S, Eidtmann H, Klare P, Huober J, Costa S, Tesch H, Hanusch C, Hilfrich J, Khandan F, Fasching PA, Sinn BV, Engels K, Mehta K, Nekljudova V, Untch M**. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol*. 2014 Jun;15(7):747-56. doi: 10.1016/S1470-2045(14)70160-3. Epub 2014 Apr 30. PubMed PMID: 24794243.
3. **Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, Peto R, Pritchard KI, Bergh J, Dowsett M, Hayes DF; EBCTCG**. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017 Nov 9;377(19):1836-1846. doi: 10.1056/NEJMoa1701830. PubMed PMID: 29117498; PubMed Central PMCID: PMC5734609.
4. **Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ**. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016 Nov 17;375(20):1925-1936. PubMed PMID: 27959613.
5. **Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Zhang K, Theall KP, Jiang Y, Bartlett CH, Koehler M, Slamon D**. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016 Apr;17(4):425-39. doi: 10.1016/S1470-2045(15)00613-0. Epub 2016 Mar 3. PubMed PMID: 26947331.

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