Breast Cancer Tumor Board

Anita Aggarwal, DO, PhD; Russell Crawford, BPharm, BCOP; Joann Manning, MD; and Vicke L. Venne, MS

CASE PRESENTATION

This case represents a composite of many different patients and is not meant to represent an individual. Any resemblance to an actual patient is coincidental.

A 32-year-old African American woman presented with a self-palpated left breast mass (axillary tail at 9 o'clock position). The patient was a nonsmoker, was otherwise healthy, and had no family history of breast or any other cancer. She had never used oral contraceptives or hormones, was never pregnant, her menarche was at age 12 years, and she had regular menstrual periods. On physical examination she had a 1-cm left breast mass and a palpable left axillary lymph node. A complete diagnostic workup revealed a 2-cm left breast mass. An ultrasound-guided biopsy of the axillary lymph node was positive for invasive ductal carcinoma (IDC). The final diagnosis was left breast cancer, stage IIB IDC, T1N1M0, ER+, PR+, HER2 *2+ by immunohistochemistry, fluorescence in situ hybridization (FISH) was 2.4, confirming a* HER2+ *tumor.*

Anita Aggarwal, DO, PhD. What is the role of genetic counseling and testing in this young patient who does not have a family history of breast cancer?

Vickie L. Venne, MS. This patient absolutely would be a candidate for counseling and testing. From a genetic counseling perspective, one of the first points has to do with what "no family history of cancer" means. Typically, in a fast-paced clinic, a patient will be asked "Does anybody else in your family have cancer?" And it's not uncommon to get the answer "no." Genetic counselors collect specific information on at least the first- and second-degree relatives, so we end up with 3 generations. This includes both the maternal and the paternal histories. We find that people who initially report no family history of cancer are often just thinking of breast cancer, even if the provider's question is broad. When we start digging, we often find other cancers because cancer is common.

The other issue is that she was diagnosed at a young age. Clearly, 32 years is much younger than we typically see in breast cancer, and we know that individuals with hereditary cancers often have an earlier age of onset. With no other information, her a priori risk of having a *BRCA1/2* mutation would be < 2.5%.

Regardless, based on current National Comprehensive Cancer Network (NCCN) guidelines, she would be a testing candidate. We would also recommend testing for more than just *BRCA1/2.* In the last few decades, there have been many genes identified that are associated with an increased susceptibility to cancer. Many of these genes are part of syndromes, so if you had a mutation, that also would increase the risk for a cancer in another organ. If this woman's mother and father lived into their 70s or 80s and she had a number of aunts on both sides who never developed breast cancer, it would be less likely to be *BRCA1/2*. However, *P53* also can present in young women and as a de novo mutation. Therefore, we would offer her a panel of actionable genes. Genes that if, in fact, we identified a mutation in one of them, would mean we could do something different for this young lady.

JoAnn Manning, MD. Let's say she does have testing, and she comes back *BRCA*+. Then what would be the recommendations or guidance?

Ms. Venne. Women (and men as well!) with mutations have an increased risk for a second primary breast cancer as well as cancer in other organs. Focusing first on the breast story and all the media around *BRCA1/2* mutations and surgery, this is a woman who may consider a more aggressive surgery, including prophylactic contralateral mastectomy, if she is concerned. She is young, so we also would explore her fertility plans. While her next few months will be filled with breast cancer treatment choices, women with *BRCA* mutations also are at an increased risk to develop ovarian cancer, so that might be a decision she makes as well. Her health care team may also eventually discuss chemotherapeutic options available specifically to women with mutations.

However, we often see young women who are extremely nervous because there is a sense that if you're younger, your cancer *must* be inherited. Part of the pretest counseling is to explore psychosocial issues and help these young

ladies understand that, especially if she does not have a family history of cancer and the only indication is her age, then it's highly likely that we're *not* going to find an identifiable mutation. And in that circumstance, she probably could consider a more conservative surgical decision.

Dr. Aggarwal. How common is a *BRCA1* or *BRCA2* mutation in African American females?

Ms. Venne. I have not paid attention to the prevalence of mutations based on ethnicity, so I don't know. While many of the initial mutations were discovered in women of European ancestry, there are large cohorts of women with African ancestry whose specimens are now available for identifying genetic markers that will improve breast cancer risk assessment in them.[1] However, because those mutations are still being characterized, it is more common to find a variant of uncertain significance (VUS) in African American women. A VUS is an alteration—a change in the gene—that we simply don't know what it means yet. Clinicians don't have enough information to know if that alteration is pathogenic or benign. The problem is that people try to make sense out of everything in their lives, so they also will try to make a VUS mean something. We try hard to help people understand that a VUS is really no more significant than if we had not tested in the first place, and they should not act on that information. They should use their family history, their age, their other psychosocial concerns about their experiences with cancer as they make their treatment decisions. But they also should check back periodically with their genetic counselor because VUSs can be reclassified. And if that happens, the information might be more useful for not only them, but their family members.

Dr. Manning. Would you consider this patient for any neoadjuvant chemotherapy?

Dr. Aggarwal. The patient is a young female with a small tumor that is *HER2*+. The indication for neoadjuvant chemotherapy is typically a big tumor or inoperable disease. Neoadjuvant chemotherapy is considered the standard of care for patients with inflammatory breast cancer and may confer a survival benefit in these patients. Of all the breast cancer subtypes, triple negative and *HER2*+ are considered the most chemosensitive and may benefit from neoadjuvant therapy. This patient has a small tumor, and I don't think she's a candidate for neoadjuvant chemotherapy unless the patient wants to see if her tumor is chemosensitive or not.

Dr. Manning, What's the role and benefit of lumpectomy vs mastectomy?

Dr. Manning. Historically, mastectomy would have been considered the standard of care, but luckily, in the 1970s and the 1980s, we had a significant number of randomized controlled trials that demonstrated that certain women with particular characteristics would get the same overall survival if they chose mastectomy vs lumpectomy, the removal of the tumor with negative margin and whole-breast radiation. The key thing to understand is that breast-conserving surgery is now very well established with more than 20 years of data to support it. And that breast irradiation after breast-conserving surgery is essential to maximizing the local control and the overall survival (OS).

There have been a lot of major studies, but the one with the greatest follow-up now is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 protocol, which was the only trial to compare mastectomy to lumpectomy and radiation or lumpectomy alone. It required negative margins. With 20 years of follow-up, the data still support that mastectomy or lumpectomy with radiation offers equivalent OS and local control. It's really about patient preference if they are candidates.

Who is a candidate? Clearly, there are contraindications. We tend to look primarily at the size of the tumor. However, removing an average-sized tumor (< 2 cm) with a margin may not have a good cosmetic result for a patient with very small breasts. That patient may opt to go forward with a mastectomy instead. Young patients who are

Discussion Participants

Anita Aggarwal, DO, PhD, is an oncologist/hematologist at Washington DC VA Medical Center with expertise in breast cancer and a former president of the Association of VA Hematology/Oncology. She is an associate professor at George Washington University and Georgetown University.

Russell Crawford, BPharm, BCOP, is president of the Association of VA Hematology/Oncology. Mr Crawford is a clinical pharmacy specialist in hematology/oncology and PGY2 program director for pharmacy residency at the Southern Arizona VA Healthcare System in Tucson, Arizona.

Joann Manning, MD, is the section chief, radiation oncology at the Veterans Affairs Medical Center Washington, DC.

Vicke L. Venne, MS, is the senior genetic counselor for VA Genomic Medicine Service, a national specialty care service that uses the VA's telehealth infrastructure to provide genetic counseling to over 80 VAMCs around the country.

candidates must have to have negative margins. If they have persistently positive resection margins after excision or reexcision, then they need to go forward with mastectomy.

A patient who has imaging evidence of multicentric disease with 2 or more primary tumors in separate quadrants would not be a candidate for breast-conserving therapy. Diffuse malignant-appearing microcalcifications on a mammogram also would suggest multicentric disease. And a patient with a prior history of radiation therapy to the breast or chest wall cannot go through breast-conserving therapy.

In the case we are discussing, we also should make sure this young lady is not pregnant. If the patient is adamant about breast-conserving surgery and pregnant, especially in the third trimester, radiation could be deferred until after delivery. Another relative contraindication is for patients who have connective tissue disorders. Sometimes if they are given whole-breast radiation, the cosmetic result is poor. So if you're doing this procedure to save the breast, then having a good cosmetic result is an important consideration for many patients.

When you look at the size of the tumor for this patient, she seems to be a good candidate for breast-conserving surgery. I would recommend that she go forward with lumpectomy followed by whole-breast radiation.

Ms. Venne. Although the numbers aren't nearly as large as they were in the original trials looking at the lumpectomy vs mastectomy, there are now survival data for women with *BRCA1/2* mutations. With all of the caveats that Dr. Manning mentioned, even if you have an identifiable mutation, you may not necessarily need that more aggressive surgery.[2] Clearly, individuals with identifiable mutations would have a higher chance of a contralateral breast cancer, a second primary, so some individuals consider a prophylactic bilateral mastectomy. But from a survival perspective, there are a fair amount of data now available that say that lumpectomy vs mastectomy should really be the conversation based on all of the information that Dr. Manning outlines rather than using primarily the mutation status.

Dr. Manning. I agree.

Dr. Aggarwal. This patient had a lumpectomy and axillary lymph node dissection. Pathology reported 1.5-cm mass, grade 3 IDC; the margins were negative. There was no skin involvement, 27 lymph nodes removed were all negative. Dr. Manning, can you please discuss the role of radiation in early stage breast cancer in patients like this case?

Dr. Manning. One of the questions that is always controversial for radiation in these early stage breast cancer cases is what do you do with the nodal irradiation? Previously, radiation oncologists based treatment plans on retrospective data, but in 2015, there were 2 major studies, 1 from Canada, and 1 from the European Organisation for Research and Treatment of Cancer (EORTC).[3,4] Both studies tried to determine whether there was an advantage to doing regional nodal irradiation in early breast cancer cases. That encompassed axillary, supraclavicular, and internal mammary nodes. The studies showed that there was no survival advantage, but there was a statistically significant improvement in disease free survival and in local regional recurrence and distant mets.

Unfortunately, there are still a lot of unanswered questions, like what group potentially would benefit the most? In the MA.20 Study, some observers questioned that maybe the ER-/PR- women had the most benefit, but then, in the other study the benefit wasn't clear.[4,5] One question is which lymph node group is having the most impact? Was the benefit from radiating the supraclavicular nodes or was it from radiating the internal mammary nodes? Determining the answer is important from a technical point of view because when you radiate the internal mammary nodes, you have the potential to expose more heart and lung to radiation. You have to put all these together and make a recommendation.

Clearly, for a patient with negative nodes there is no question: You would not treat the regional nodes. However, for a patient with positive nodes you really have to individualize the approach and consider age, anatomy, tumor location, and burden of axillary disease.

I would sit down and have a discussion with this young woman to weigh the risks and the benefits. There is a slight increased risk of lymphedema in these patients, and radiation pneumonitis increases, but not significantly. A key concern is to minimize the total dose of radiation to the heart. There have been great developments in radiation oncology technology and capabilities, so the cardiac dose is now less. But when you think about a 32-year-old patient and weigh the benefit of a 2% to 3% decrease in the incidence

of distant metastases and no OS advantage, then you really need to have a conversation about how to safely treat her. At a minimum, I would treat the high axilla and the supraclavicular nodes because she had a pretty extensive lymph node dissection with more than 20 nodes, and then with her getting systemic therapy, that should be more than adequate.

Dr. Aggarwal. Is there any cutoff for age or size of the tumor where you would not do any radiation to the breast?

Dr. Manning. In this particular patient absolutely not because of the lymph node. She had breast-conserving therapy, and she's only 32-years-old. The PRIME 2 study offered lumpectomy alone vs lumpectomy and radiation for women aged ≥ 65 years with tumors ≤ 3 cm, low grade.[6] The study participants had to have negative lymph nodes, be ER+, and low grade. It was a very select group. The lumpectomy patients had a recurrence rate around 4%, and the other was closer to 1.3%.

You have to look at the whole picture. Is this a healthy 70-year-old woman? Is it an inconvenience for her to get treatment? Is she going to get hormone therapy and will she be adherent? There's a very small group of women who underwent breast-conserving surgery that I would feel safe about not offering radiation.

Dr. Aggarwal. About 15% to 20% of all breast cancers are HER2 over expressors, which used to be a poor prognostic characteristic. However, the development of anti-HER2 therapies has changed the picture of *HER2* prognosis. After the initial discovery of activity, the pivotal study by Slamon et al showed benefit in terms of progression-free survival (PFS) and OS with chemotherapy and trastuzumab. The NCCN guideline recommends anti-HER2 antibody trastuzumab in combination with chemotherapy.[7]

Patients with tumor < 0.5 cm who are *HER2*+ and ER+ may not benefit from trastuzumab, but those who are ER- and *HER2*+ will still benefit from trastuzumab. The combination is adriamycin/cyclophosphamide followed by a taxane with trastuzumab and to complete 1 year of trastuzumab or trastuzumab in combination with carboplatin and taxanes.

Pertuzumab, in combination with trastuzumab and docetaxel (PHT) has been FDA-approved in neoadjuvant and metastatic *HER2*+ disease, but is not FDA approved yet in the adjuvant setting. However, these are expensive drugs, and we don't know how long these drugs should be given.

Mr. Crawford, What are the adverse effects (AEs) of an anti-HER2 or trastuzumab treatment, and what is the cost of trastuzumab?

Russell Crawford, BPharm. The anti-HER2 antibodies have certainly changed treatment plans and outcomes for patients with breast cancer who test *HER2*+. There are actually 3 of these anti-HER2 drugs on the U.S. market, and they can be used in a variety of settings. Trastuzumab and pertuzumab are indicated in women or patients who have *HER2*+ disease, and they work by binding to the extracellular domain of the *HER2* proteins and mediate antibody-dependent cellular toxicity by inhibiting proliferation of the cells that overexpress *HER2*.

In this patient, we would be looking at using adjuvant trastuzumab to complete a 1-year course of therapy while she's getting her dose-dense doxorubicin and cyclophosphamide (AC) on a weekly basis for the first 12 weeks. Trastuzumab is dosed with an initial loading dose of 4 mg/kg as the first dose, and then it's 2 mg/kg/wk until adjuvant chemotherapy is completed. We usually extend the dosing out to 6 mg/kg every 3 weeks to complete the year of treatment.

These drugs are fairly well tolerated. They are monoclonal proteins, so a lot of the AEs that patients experience are the things that we're used to seeing with other monoclonal proteins like the infusion-related reactions and some flulike symptoms. The biggest concern with these patients is that being on the drug for a year, there is a risk of decreasing the left ventricular ejection fraction (LVEF) of the heart. That risk is increased when these drugs are combined with anthracyclines that we know are cardiotoxic. As a single agent, the impact on left ventricular function is not significant, but when it is combined with chemotherapy, it does become a problem. Usually, we recommend routine and periodic monitoring of the LVEF with a multiple-gated acquisition or an echocardiogram to make sure that we're not causing harm related to this treatment.

The cost of these drugs depends on the frequency, is it every week, every 2 weeks, or every 3 weeks? There are different ways to give trastuzumab, but for most patients, we prefer the every 3-week dose. And it's estimated that for a 70-kg patient, a dose of trastuzumab at

6 mg/kg at the rate of every 3 weeks costs about $2,500 per dose. The VA pays about $6 a milligram, but it's certainly money well spent because it has changed the playing field and the outcomes for these patients.

The cost of pertuzumab is dosed a little bit differently. It's a flat dose not a weight-based dose. Patients get an initial loading dose of 840 mg and a continuation dose of 420 mg every 3 weeks. The cost of the 420-mg dose of pertuzumab is just under $3,000, so that first-time loading dose would be a $6,000 dose, and the continuing doses are about $3,000 per dose every 3 weeks. The AE profile is no different from what you would expect with trastuzumab. There is a similar toxicity profile for these 2 drugs. It does not appear that there is any additional cardiotoxicity if you are using the combination in the neoadjuvant setting.

The third targeted agent that goes after the HER2 is ado-trastuzumab, but it is only used in the metastatic setting, so we'll reserve that for down the road for this patient should we ever need it.

Dr. Aggarwal. The patient received adriamycin/cyclophosphamide followed by paclitaxel weekly for 12 weeks with trastuzumab. After the 12 weekly doses, she went on trastuzumab every 3 weeks. Because she was ER+, she was a candidate for additional endocrine ablation therapy. She was started on tamoxifen and leuprolide acetate for complete hormonal ablation.

Tamoxifen was the first targeted therapy for breast cancer. In women with ER+ breast cancer, with tamoxifen given for 5 years as adjuvant treatment, the odds of recurrences decreased by 39%, and death decreased by 30% in both pre- and postmenopausal women.[8] Then the ATLAS data came, which randomly allocated patients to continue another 5 years of tamoxifen vs placebo, for a total of 10 years of treatment with tamoxifen. With a mean of 7.6 years of further follow-up after entry at year 5 in this trial showed that recurrence and breast cancer mortality during the second decade after diagnosis are reduced more effectively by 10 years of adjuvant tamoxifen than by 5 years.[9] The current recommendation for pre- and postmenopausal is 10 years of tamoxifen.

In addition we have 3 aromatase inhibitors (AIs), anastrozole, letrozole, and exemestane, which block the production of estrogen in postmenopausal females. Anastrozole and letrozole are nonsteroidal, and exemestane is steroidal. There are countless big randomized trials using all of these drug in different combinations. In most of these trials, AIs are shown to be equal to tamoxifen when they are compared with each other, but their AE profile is different.

The recommendation by the American Society of Clinical Oncology and NCCN guidelines is to use only AIs for 5 years. There are different combinations: You can give tamoxifen for 2 to 3 years, followed by 5 years of an AI, or 5 years of tamoxifen and 5 years of an AI. Some patients wants to stop because of AEs, but others want to continue. Patients can develop osteoporosis and arthritis from an AI and hot flashes from tamoxifen.

Mr. Crawford, How would you manage of these AEs from these treatments?

Mr. Crawford. Because this woman is young, age 32, and premenopausal, tamoxifen would be the recommended endocrine therapy for her being ER+/PR+. But the role of the leuprolide acetate is to induce a chemical oophorectomy. We are putting her into ovarian ablation by using the leuprolide acetate.

The tamoxifen is relatively well tolerated, but as an ER blocker, it has a different AE profile than does an estrogen production decreaser. With tamoxifen patients tend to complain about hot flashes, edema, fluid retention, altered menses, spotting vaginal discharge, vaginal bleeding, and dryness. These medications also increase the risk of venous thromboembolism (VTE), and there is some concern about increased risk of developing endometrial cancers with these medications. We can give it either once or twice daily. There's nothing that really says 10 mg twice daily vs 20 mg once daily is any different. So we may play with dosing to see if patients tolerate it better one way or the other.

There are medications that we can offer to help manage the hot flashes. These medications don't necessarily make the hot flashes go away, but they can decrease the hot flash intensity or and/or frequency. Many medications have been evaluated for hot flashes. The best data are for venlafaxine, which is usually given once a day at bedtime (dosage 37.5-75.0 mg). There has been success with gabapentin titrated up to a dose of about 300 mg 3 times daily. They are fairly similar for decreasing hot flash scores and intensities, but the patient preferences were more favorable toward the venlafaxine than for the gabapentin.

The AIs, on the other hand, have a different AE profile. With tamoxifen we see vaginal discharges, bleeding, endometrial cancer risk, and VTE risk,

but these are not significant problems with any of the AIs. The AE profiles for AIs include hot flashes, but more often it is complaints of bone pain, arthralgias, and myalgias. Probably the top reason why most patients discontinue taking AIs is arthralgia and myalgia.

Because we have shut off estrogen production with the AIs, and estrogen is an important component of maintaining good bone health and bone homeostasis, patients are at an increased risked of losing or declining bone mineral density (BMD). It is recommended that these patients get placed on routine calcium and vitamin D supplementation with routine dual-energy X-ray absorptiometry scans, so we know whether we will need to initiate osteoporosis treatment, whether with oral bisphosphonates, intravenous bisphosphonates, or subcutaneous rank ligand inhibitors.

With bisphosphonates there may be a slight increase in fracture rates. But we have to balance that with the BMD concerns. If the patient progresses into the metastatic setting and we know that there's a fair chance that there's going to be some skeletal involvement, those people are also at an increased risk of fracture. While there is a slight concern about the increased risk of fractures with bisphosphonates, I tend to believe that the benefits outweigh the risks.

Go to www.fedprac.com/AVAHO for a discussion of the next steps in the treatment for the patient after she returned 2 years later with nausea, vomiting, acute onset headache, and 2 brain lesions that were about 2 cm.

AUTHOR DISCLOSURES

The authors report no actual or potential conflicts of interest with regard to this article.

DISCLAIMER

REFERENCES

1. Feng Y, Rhie SK, Huo D, et al. Characterizing genetic susceptibility to breast cancer in women of african ancestry. *Cancer Epidemiol Biomarkers.* 2017;26(7):1016-1026.
2. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol.* 2018;19(2):169-180.
3. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med.* 2015;373(4):317-327.
4. Whelan TJ, Olivotto IA, Parulekar WR, et al; MA.20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med.* 2015;373(4):307-316.
5. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014;383(9935):2127-2135.
6. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266-273.
7. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687-1717.
9. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet.* 2013;381(9869):805-816.