Evaluating the Neoadjuvant Treatment of Breast Cancer

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Overview

This activity is designed to aid physicians in assessing new data in the neoadjuvant treatment of breast cancer, including patient-specific treatment regimens and monitoring for adverse events during therapy, and applying these data to their practices.

Target Audience

This activity is directed toward medical oncologists who manage and treat patients with breast cancer. Surgical oncologists, radiation oncologists, pathologists, fellows, nurses, nurse practitioners, physician assistants, and other healthcare providers interested in the treatment of breast cancer are also invited to participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Identify predictors of recurrence in patients who receive treatment in the neoadjuvant setting for breast cancer
- Describe the role of pathologic complete response in evaluating the effectiveness of agents in patients with breast cancer in the neoadjuvant setting
- Identify tumor subtypes in which pathologic complete response rate can be a predictor of disease recurrence in patients with breast cancer who receive neoadjuvant treatments

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Systemic chemotherapy can lower the long-term recurrence and mortality risks to the same extent when given following or prior to breast cancer surgery. Neoadjuvant (preoperative) therapy for breast cancer also aims to reduce tumor size, thereby downstaging the disease and making the options of surgical resection or breast-conserving surgery available, and also aims to monitor the individual patient's response to therapy.[1] Systemic therapy is becoming more common for patients with early-stage, operable breast cancer prior to surgery. This is an evolution from the early practice of reserving neoadjuvant therapy for patients with locally advanced or inflammatory breast cancer that otherwise carried a high mortality rate.[2] Neoadjuvant therapy has expanded beyond chemotherapy to targeted agents and endocrine therapies that are specific to tumor subtypes. However, it remains challenging to predict tumor response to preoperative therapy based simply on systemic therapy selection and tumor biology.

With neoadjuvant therapy for breast cancer, the assessment of residual disease at the time of surgery is important for determining the degree of the patient's response to treatment. Surrogate endpoints for long-term outcomes, in this case, *pathologic complete response* (pCR), typically defined as the absence of invasive cancer in the breast and lymph nodes, are still more useful at the clinical trial level as a predictor of clinical benefit with neoadjuvant therapy rather than at the level of the individual patient. Pathologic complete response and its relation to clinical outcomes was analyzed in 2 pivotal trials: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 trials. NSABP B-18 found that pCR may serve as a surrogate endpoint for disease-free survival (DFS) or overall survival (OS); however, NSABP B-27 did not.[3]

Despite the failure of NSABP B-27 to find pCR rate in the breast to be a surrogate endpoint for drug development, researchers continue to use pCR after neoadjuvant therapy as the primary endpoint in subsequent trials. Subsequent trials have concluded that pCR was a prognostic marker, and that the pCR rates can vary depending on the tumor molecular subtype. For example, tumors with high proliferation rates (luminal B/HER2-negative, HER2-positive [nonluminal], triple-negative) have higher rates of pCR, and the pCR is more closely linked with DFS and OS. Pathologic complete response is not an appropriate surrogate endpoint for patients with luminal B/HER2+ and luminal A tumors.[4] In addition, pCR may not be the optimal study endpoint for all classes of drugs used in the neoadjuvant treatment of breast cancer, such as endocrine therapy.[5]

Although the FDA published a "guidance to industry" on using pCR as a surrogate endpoint for accelerated approval of drugs in the neoadjuvant setting, the challenge remains to find a consistent definition of pCR across studies.[3,4]

Adam Brufsky, MD, PhD, associate chief in the Division of Hematology/Oncology, and director of the Comprehensive Breast Cancer Center, University of Pittsburgh School of Medicine, shared his clinical insights into the current and emerging treatment options in the neoadjuvant setting of breast cancer.

Moderator: *Can you provide an historical perspective on how chemotherapeutic and targeted treatment in the neoadjuvant setting of breast cancer has evolved in the past 5 years?*

Dr Brufsky: I can go back even further, maybe 10 years or so. I think the idea behind neoadjuvant chemotherapy initially arose 15 or 20 years ago when we tried to downstage cancer. The patient would present with inoperable disease, and we would use chemotherapy to downstage it and allow surgical treatment. The first trial, NSABP-18 [National Surgical Adjuvant Breast and Bowel Project 18], tested the concept in the operable setting, where women were randomized to receive AC [doxorubicin and cyclophosphamide] for 4 cycles before surgery or after surgery. Two things came out of that trial when it was announced 12 or 13 years ago: (1) there was really no detriment to giving the chemotherapy first, and (2) you could actually see that the pathologic complete response (pCR) rate was a very good biomarker for disease-free survival (DFS) at 5 years. That study led to a number of other trials, in particular, NSABP-27, which added 4 cycles of docetaxel to the 4 AC cycles and actually doubled the pCR rate. What was interesting about that trial was that even though there was a doubling of pCR rate and the women who did well actually had an over 90% 5-year DFS, there really wasn't any overall survival (OS) increase that was statistically significant. Over the next couple of years following that trial, we tried many different therapies, trying to improve pCR rate, knowing that this potentially could be a surrogate endpoint.

There was a series of trials in Europe that tested a variety of chemotherapeutic agents and targeted therapies such as epirubicin, capecitabine, and gemcitabine, among many other agents. They've been tested with or without bevacizumab. In the United States, many different targeted therapies have been evaluated, again, such as bevacizumab with standard chemotherapy. And one of the NSABP trials [NSABP B-38] tried 4 cycles of AC followed by 4 cycles of docetaxel, or actually paclitaxel with or without gemcitabine. The latest trials are 4 cycles of AC with 4 cycles of trastuzumab plus pertuzumab or docetaxel/carboplatin/trastuzumab plus pertuzumab, which are really now the standards of care, at least for HER2-positive disease. There are also some experimental studies called the I-SPY series of trials, where women are getting chemotherapy plus or minus biological agents as neoadjuvant therapy, with the goal of using improvement in pCR rate to accelerate drug development.

Moderator: *How can pCR be used as a predictor of recurrence in patients who receive neoadjuvant therapy for breast cancer?*

Dr Brufsky: The premise of pCR rate, based on some of these early

trials, is that if you had a good pCR rate you would have a better prognosis. However, the issue is that that has never really translated into improved DFS and OS for the entire trial. The reason that's important now is because the FDA is now using that as an endpoint for the early approval of drugs. So if you have a higher pCR rate in the neoadjuvant setting, it could lead to faster regulatory approval of your compound. The FDA came up with this idea based on data released before the final results of the NeoALTTO [Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation] and the ALTTO [Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation] trials were presented. NeoALTTO was basically a trial of 4 cycles of AC and weekly paclitaxel for 12 weeks with trastuzumab or lapatinib, or both. The idea was that the combination therapy would improve the pCR rate, and it did. In other words, the combination of trastuzumab and lapatinib had a pCR rate of about 50% versus about 25% to 30% in the other 2 arms of the trial. And so in theory, those results should have predicted the results of the ALTTO trial, which is basically the same trial, where patients got chemotherapy upfront, and then got trastuzumab or lapatinib, or both. It turns out that the combination was no better than trastuzumab alone. The results of that trial didn't match the neoadjuvant data, and that has many of us concerned about the use of pCR rate in this setting.

Moderator: *What evidence is available that allows us to use tumor subtype as a predictor of recurrence in patients who receive neoadjuvant treatment strategies?*

Dr Brufsky: There are now a lot of studies among the 4 major tumor subtypes: luminal A, which is strongly ER-positive, slow-growing; luminal B, which is ER-positive, faster-growing; triple-negative; and HER2-like. It turns out that the luminal As have the lowest pCR rate. Luminal B is kind of in the middle, with a lower response rate. Triple-negatives have the highest pCR rate, as does the HER2 subtype when given trastuzumab. So luminal subtype does actually predict quite nicely the eventual pCR rate, with luminal A having the worst and triple-negatives and HER2 types having the best.

Moderator: *How does the use of pCR as a clinical endpoint relate to completed and ongoing neoadjuvant clinical trials in the context of solving problems related to drug development in this area?*

Dr Brufsky: pCR is now a clinical endpoint for drug development in the United States. In terms of FDA approval, if you have a good phase II or even a good phase III clinical trial comparing drug X plus standard of care versus standard of care, if drug X increases the pCR rate, there's a decent chance it will be approved. That's how pertuzumab, for example, was approved for neoadjuvant therapy by the FDA, even though we don't yet have any adjuvant data with pertuzumab. So I think that for now it is a very important endpoint. It's probably the most important endpoint right now in neoadjuvant clinical trials, at least until we finally sort out whether it truly is a predictor in the entire database. I think the NeoALTTO data have kind of thrown us for a loop a little bit, but I still think there's enough evidence that this is a decent surrogate endpoint, and I think we'll continue to use it for the time being.

Moderator: *Are there other predictors of recurrence in patients who receive treatment in the neoadjuvant setting for their breast cancer?*

Dr Brufsky: There are lots of other ones. But probably the biggest predictor of disease recurrence, other than pCR rate, at least that I use and I think a lot of people use, is really the amount of disease that's left—in particular, the number of remaining lymph nodes. If a number of lymph nodes are left after neoadjuvant therapy, I think that's a good predictor of a not-so-good outcome. Other predictors are the degree of ER/PR positivity, the tumor subtype, and the amount of disease that's left over after neoadjuvant therapy. The rule of thumb that we always use, and I believe others still use, is that whatever disease is left probably relates to your prognosis. So, if you go from a stage 3 to a stage 1, you're more likely to be a stage 1. I think if you go from a stage 3 to a stage 2, you're likely to be a stage 2. I don't know how true that is, but there are data that go back and forth on that, depending on when you use those data or when the paper was published. But it goes either way.

Moderator: *What are remaining areas of clinical controversy in the setting of neoadjuvant treatment, and which of these are currently being addressed by either ongoing or planned clinical trials?*

Dr Brufsky: Two big ones are whether pCR really predicts for DFS, and whether pCR predicts OS. A number of follow-ups of existing trials are trying to answer those questions. I think the other big question is what we do if someone has disease that's left over after neoadjuvant therapy. There are a number of trials within the HER2-positive setting. For example, there's a trial called KATHERINE, which studies patients with HER2-positive, early-stage breast cancer who are given neoadjuvant therapy. For maybe 50% of patients who don't have a pCR, there's a trial of a T-DM1 [ado-trastuzumab emtansine] versus regular trastuzumab for a year. There are a number of trials like that. If a patient has ER-positive breast cancer and residual disease, there's a trial of palbociclib called PENELOPE that's actually just about to start. So there are all sorts of trials out there trying to test these hypotheses. We know that doing additional chemotherapy with residual disease after upfront chemotherapy, regardless of the chemotherapy given, doesn't seem to add much. I think that's the overall thought right now with this. So the biggest area of clinical controversy right now is really what to do with those people who have residual disease after neoadjuvant therapy.

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