Evolving Management Strategies for Triple-Negative Breast Cancer

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Overview
This activity is designed to inform physicians about the latest treatment advances and data in the management of triple-negative breast cancer (TNBC), including approved and investigational treatment strategies.

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

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- Discuss how biomarkers are being used to select treatment regimens that may be particularly effective in certain subgroups of patients with advanced TNBC
- Summarize phase I clinical trial outcomes reported with immunotherapy agents that are under investigation in advanced TNBC
- Describe recent research efforts that have sought to optimize neoadjuvant treatment of patients with early-stage TNBC

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Breast cancer is the most common cancer among women in the United States.[1] Of the approximately 232,000 cases expected in 2015, triple-negative breast cancers (TNBCs) will comprise 10% to 20% (23,000 to 46,000) of diagnoses.[1,2] Unfortunately, this subtype of breast cancer, which is negative for estrogen, progesterone, and HER2 receptors, is more aggressive and carries a worse prognosis than other subtypes. A main reason for its poor prognosis is that unlike ER/PR-positive and HER2–positive breast cancer, TNBC has no biological target for therapy that has been clinically validated, leaving chemotherapy as the only approved treatment option.[2-3]

In light of the poor prognosis of TNBCs, recent research has focused on identifying biomarkers to help select patients for optimal treatment regimens. For example, many clinical trials are comparing outcomes of chemotherapy in subgroups of patients with *BRCA1/2* wild-type and *BRCA1/2*–mutated metastatic TNBCs. As one example, the Triple Negative Breast Cancer trial (TNT trial) identified significant differences in objective response rates (ORRs) with first-line carboplatin or docetaxel among women with a known *BRCA1/2* mutation compared to the all-comer population.[4] Whereas first-line docetaxel and carboplatin elicited similar response rates in the total patient population, more than twice the number of women with *BRCA1/2*–mutated TNBC responded to carboplatin than docetaxel (68% vs 33%, respectively; $P = 0.03$) presumably reflecting greater sensitivity to DNA-damaging platinum due to loss of BRCA-mediated double strand DNA repair function.[4]

First-line taxanes still have a place in unselected patients with TNBC, however. This point is evidenced by outcomes from the phase III CALGB 40502 trial, which enrolled 799 patients with chemotherapy-naïve advanced breast cancer, including a subset of patients with TNBC. In the total population, which was concurrently treated with bevacizumab, paclitaxel achieved a similar progression-free survival (PFS) to nab-paclitaxel (11 vs 9.3 months, respectively [hazard ratio (HR) 1.20; $P = 0.054$]). By comparison, ixabepilone was inferior to weekly paclitaxel (7.4 vs 11 months, respectively [HR 1.59; $P < .001$]) with all taxoids given weekly.[5]

Early clinical trials of novel immunotherapy approaches are investigating checkpoint inhibitors pembrolizumab (PD-1 antibody) and atezolizumab (PD-L1 antibody) in patients with metastatic TNBCs that express tumor or stromal PD-L1. In a phase Ib trial of 32 women with heavily pretreated TNBC, pembrolizumab elicited partial responses in 16.1% of patients and stable disease in 9.7% of patients.[6] Five patients experienced drug-related serious adverse events, including grade 3 anemia, headache, aseptic meningitis, or pyrexia, and disseminated intravascular coagulation with thrombocytopenia and decreased blood fibrinogen.[6] The encouraging activity associated with targeting the PD-L1/PD-1 pathway was confirmed in a phase I trial of atezolizumab (N = 27), which elicited a 24% unconfirmed ORR.[7] Grade 3 to 5 drug-related AEs occurred in 11% of patients and included grade 3 adrenal insufficiency, neutropenia, nausea, vomiting, and decreased white blood cell levels, as well as grade 5 fatal pulmonary hypertension.[7] These preliminary findings have led to the initiation of larger clinical trials, which will help define the potential role of immunotherapy in advanced TNBC.

Another potentially predictive biomarker for advanced TNBCs is the androgen receptor (AR). In the largest study of an AR antagonist in TNBC (N = 75 evaluable patients), first- or second-line enzalutamide, in combination with an endocrine therapy, achieved a median PFS of 32 weeks.[8] In addition, an unexpected outcome of this phase II trial was that 47% of participants had an androgen-associated gene signature that was associated therapeutic response. This finding suggests that the AR may have a larger role in TNBC pathophysiology than previously thought and may be worth investigating in this setting.[8]

In early-stage TNBC, several clinical trials have also sought to identify optimal treatment regimens in the neoadjuvant setting. In particular, two large randomized phase II studies, Gepar-Sixto (N = 595) and CALGB 40603 (N = 454), found that compared with an anthracycline- and taxane-containing regimen alone, adding carboplatin to these regimens improved the pathologic complete response (pCR) rate.[9,10] As expected, however, these gains in efficacy came at the expense of additional toxicities, including neutropenia, thrombocytopenia, anemia, and diarrhea and resulted in less delivered paclitaxel.[9,10] Therefore, additional studies are warranted to determine whether these findings will translate to an overall survival and improved risk-to-benefit ratio for women with early TNBCs.

Also in early-stage TNBC, ongoing clinical trials are evaluating whether to administer adjuvant therapy to patients with TNBC who have residual disease after neoadjuvant therapy, and prior to surgery or to add platinum agents to standard anthracycline/taxane adjuvant therapy. Although the standard of care is to not typically administer post-operative chemotherapy, one drug that is being evaluated in this setting is olaparib in patients with *BRCA* mutations.[11] Thus, clinical trial participation may be a viable option for some of these patients in whom adjuvant therapy may be warranted.

Moderator: Do you test all of your TNBC patients for *BRCA* mutations? Are there other genomic or molecular methods that can help clinicians to personalize therapy for patients with TNBC?

Dr. Traina: In terms of clinical genetic testing for germline hereditary *BRCA* mutations, the NCCN (National Comprehensive Cancer Network) Guidelines actually have a lower threshold for genetic testing when a patient has TNBC. So they recommend genetic testing for patients 60 years and younger with TNBC. Therefore, I send any woman under the age of 60 who is diagnosed with TNBC for a clinical genetic consultation and *BRCA* testing, regardless of family history. That point is important because it has implications for the patient, as well as her family members, for identifying a heredity predisposition to breast cancer. But we'll also talk in a bit about how testing for germline hereditary *BRCA1/2* mutations has implications

for making treatment choices about conventional cytotoxic chemotherapy and/or participation in clinical trials investigating agents that might work better in folks who have *BRCA*-associated TNBC.

Moderator: What is your preferred frontline approach for patients with *BRCA*-mutated triple-negative metastatic breast cancer and is there specific data that support that approach or approaches?
Dr. Traina: There have been a couple of trials reported over the past year or two that help to guide the decision for the first-line treatment of women with metastatic TNBC. For someone who carries a *BRCA* mutation, the TNT trial that Andy Tutt (Andrew Tutt, MB, ChB, PhD, MRCP, FRCR, of Kings College and Institute of Cancer Research, London) reported about a year ago gives us the most guidance from a prospective randomized trial. That study had almost 400 women with either TNBC or known *BRCA* mutations, but only about 10% of participants had a known *BRCA* mutation. Women were randomized to either first-line carboplatin or first-line docetaxel, and what they found was for all-comer TNBC, response rates and PFS were comparable whether patients received docetaxel or carboplatin. But when they looked at the subset of women with *BRCA*-associated TNBC, granted a small subset, response rates with carboplatin were significantly higher than docetaxel. The difference was 68% versus 33% and the same held for median PFS. If you were *BRCA*-positive and you got carboplatin, median progression-free survival was over 6 months, but if you were *BRCA* mutation positive and you had docetaxel, it was closer to 4 months, a 4-to-5 month range. Therefore, we finally have randomized prospective data that tells us that for patients with *BRCA*-associated TNBC, first-line platinum chemotherapy appeared to be a bit better than a first-line taxane.

Now, outside of having a *BRCA*-associated TNBC, a first-line taxane such as weekly paclitaxel still appears to be a preferred regimen. And we have data from the CALGB trial that Hope Rugo published where weekly paclitaxel was compared to ixabepilone or nab-paclitaxel and, really, the weekly paclitaxel regimen came out on top. Nab-paclitaxel is not inferior. Ixabepilone actually appeared to be a bit worse, and weekly paclitaxel was very well tolerated. And that lack of difference held true in the subset of women that had TNBC. So, I think in short, the TNT trial told us that a first-line platinum chemotherapy appeared a bit better than docetaxel in *BRCA*-associated TNBC, but in all-comer TNBC, first-line treatment with a taxane is still very appropriate therapy.

Moderator: How about emerging immuno-oncology agents and clinical trials? Specifically, which of these agents are being evaluated in triple negative breast cancer and in what settings?
Dr. Traina: Good question. The idea of immuno-oncology is really a hot topic right now, and the idea is that disrupting the interaction between PD-1 and PD-L1 between tumor and T cell helps to unleash the body's own immune system in recognizing the tumor as foreign and attacking it. And so there are two agents in the past year that I think are furthest along in development in breast cancer to note. One is pembrolizumab and the other is atezolizumab. Both of these compounds have been studied in stage I clinical trials. Rita Nanda presented the pembrolizumab data at the San Antonio Breast Cancer Symposium last year, and what was remarkable was that in a phase 1 trial, an anti-PD-1 antibody elicited response rates as high as 20% and prolonged stable disease in as many as 25% of patients with TNBC who were PD-L1-positive in either tumor or stroma. This was a tiny phase 1 trial, with a total of 30-something patients who were heavily pretreated. And to see a well-tolerated regimen with a response rate of about 20% is encouraging. These findings were somewhat confirmed in at AACR earlier this year with the other immuno-oncology agent, atezolizumab. A phase 1 trial reported in *Breast* showed that atezolizumab elicited response rates of about 20% in a heavily pretreated population.

Given the encouraging findings in phase 1 trials of pembrolizumab and atezolizumab, these two compounds are both moving forward in larger phase 2 studies that are accruing right now, some of which are focused solely on women with TNBC. The thought is that triple-negative tumors, which have high turnover and a higher mutational load, may be more easily identifiable by the immune system because of their high mutation rates. For example, several trials are looking at pembrolizumab with or without chemotherapy. Essentially, that's one of the big research questions: Should immuno-oncology agents be given as monotherapy or will giving them with a partner chemotherapy, like eribulin, kill more cells and release more antigen and help rev up the immune system a bit more? There is currently a large randomized trial that's comparing pembrolizumab to treatment of physician's choice, including either eribulin, capecitabine, or gemcitabine. There are also some trials looking at pembrolizumab in combination with other targeted therapies that will inhibit molecules that suppress the immune response. Similar trials are underway with atezolizumab. For example, there's a study in TNBC of nab-paclitaxel with or without atezolizumab. So immuno-oncology is a rich area of investigation and a lot of answers are still remaining about whether these agents should be used as monotherapy or in combination with chemotherapy. There are even some trials examining radiation therapy with pembrolizumab or with other checkpoint inhibitors. So a lot going on in this field.

Moderator: How about earlier stage or locally advanced triple-negative breast cancer? What are the current treatment standards here?
Dr. Traina: Starting with the adjuvant setting of early-stage TNBC, I think one important point to raise is that NCCN Guidelines recognize that even small triple-negative tumors have a higher risk of recurrence. So they lowered the bar on even considering adjuvant chemotherapy for tumors that are as small as 5 mm node-negative cancers. So that's one important point for the readership to know, that the threshold to even think about adjuvant chemotherapy includes even the teeny, tiny stage I TNBC. The next important point is that because these are higher risk tumors, we often are utilizing anthracycline and taxane-based adjuvant regimens for even the stage I cancers.

Where there's variability in clinicians' treatment patterns and new

data is in the neoadjuvant setting. Two large randomized phase 2 studies have supported the use of carboplatin in addition to anthracycline and taxane-containing regimens for women with triple negative breast cancer. Now, those trials were Gepar-Sixto and the CALGB 40603 (Alliance) study that Bill Sikov published. Both trials had a primary endpoint of pCR, so right now, all we can say from those two studies is that when platinum chemotherapy was added to an anthracycline and taxane-containing regimen, you had a higher likelihood of pCR. Outcomes from both trials consistently looked like platinum chemotherapy helped raise that pCR rate to about 60%, and, in the absence of platinum, the pCR rate was around 30% to 40%.

When interpreting these data, I think we have to be cautious in recognizing there is zero survival data that support adding platinum chemotherapy to an early-stage triple negative regimen. We have no survival data from the neoadjuvant trials, and we lack any adjuvant data for the addition of platinum. There's really a question about pCR rate serving as a surrogate for survival. We just do not know what magnitude of a difference we need in pCR from these neoadjuvant trials to show any difference in survival in the long run. And if you look at the GeparSixto and CALGB 40603 data in terms of toxicity, the arms that received platinum, in addition to anthracycline and taxane, had much greater rates of adverse events, requirements for dose reductions, and treatment delays. So I think we need to just balance, recognizing that platinum can improve pCR rates; but we have to be cautious in recognizing we do not have long-term survival data to inform decisions about the addition of carboplatin to an adjuvant regimen.

Moderator: How do you manage patients who receive neoadjuvant therapy, but still have residual disease at the time of surgery?

Dr. Traina: This is a very challenging and frustrating situation to be in. It's disconcerting when a patient has gone through excellent conventional cytotoxic therapy, goes on to surgery, and and has residual disease. The standard of care today would suggest that if you've given all of your best drugs in the regimen up-front pre-operatively, there's no data to support administering additional chemotherapy in the adjuvant setting. And it's quite possible that if there was residual disease, that that cancer may be somewhat resistant to cytotoxic therapy. So the standard of care would not support additional chemotherapy, but I think it's an excellent opportunity to explore clinical trials. For example, I can think of one ongoing study that is investigating adjuvant olaparib, a PARP inhibitor, in patients with *BRCA* mutations who have not achieved a pCR with neoadjuvant therapy by the time of surgery. So although the standard of care is to not administer additional chemotherapy, I would encourage folks to look for clinical trials in their area in the post-neoadjuvant setting.

Moderator: Looking into the near future, how do you see the field of TNBC management evolving in the context of emerging treatment options and prognostic and/or predictive tools we can use to personalize care in these patients?

Dr. Traina: Good question. I guess the first step is recognizing the heterogeneity of TNBC. It is not all the same and we've seen that already with recognizing differences in *BRCA*-associated TNBC versus other non-*BRCA*-mutated TNBC. At ASCO earlier this year, our group actually presented data on targeting the subtype of TNBC that is driven by the AR. And I had the pleasure of presenting our data from a large phase 2 study that used an AR antagonist, enzalutamide, to treat AR-positive TNBC. In this trial, we saw a long medical progression-free survival of 40 weeks or so in the setting of having AR-positive disease treated in the first or second-line setting with an endocrine therapy. So, I think a reason to remain optimistic and a take-home message is recognizing heterogeneity and looking toward biomarker development to subtype TNBC to help guide treatment choices.

Many of these targeted therapies are being developed with companion biomarkers, and I think having these biomarkers will be critical in knowing how to choose the best treatment for our patients. Chemotherapy will still remain an important component, but we have immunotherapy; anti-androgen therapy; DNA damaging agents; and PARP inhibition, which is still being actively evaluated. So I think recognizing heterogeneity in TNBC and identifying biomarkers to guide treatment decisions are some of the biggest take-home points. In addition, the field has also begun to move toward tumor genomic profiling to see whether we can identify particular driver mutations that might even help guide clinical trial choice.

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