Recap of SABCS 2014: Changes for Today and Hope for Tomorrow

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Overview

This CME activity features data from 4 presentations at the 2014 San Antonio Breast Cancer Symposium, chosen for their impact on current clinical practice or because they lay the groundwork for further investigations. Topics include the treatment of premenopausal breast cancer, early evaluation of immunotherapy in the treatment of triple negative breast cancer, outcomes from the ICE trial concerning the treatment of elderly patients with early-stage breast cancer, and the first presentation of a checkpoint inhibitor in breast cancer.

Target Audience

This activity is directed toward medical oncologists who treat patients with breast cancer. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

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

1. Review recent data on the treatment of breast cancer presented at national society meetings
2. Evaluate emerging breast cancer clinical data regarding new agents and evolving strategies

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The 2014 San Antonio Breast Cancer Symposium (SABCS) took place December 9-13 at the Henry B. Gonzalez Convention Center in San Antonio, Texas, with more than 7000 in attendance. Each year, this event draws leading researchers and clinicians from around the world for a presentation of the latest information geared to basic, translational, and clinical cancer research professionals.

Key developments reported at SABCS 2014 included practice-changing data for the treatment of premenopausal breast cancer, early evaluation of immunotherapy in the treatment of triple-negative breast cancer, outcomes from the ICE trial concerning the treatment of elderly patients with early-stage breast cancer, and the first presentation of a checkpoint inhibitor in breast cancer.

In this CME activity, we review a select group of abstracts from SABCS 2014, chosen for their impact on current clinical practice or because they lay the groundwork for further investigations, followed by expert commentary from Debu Tripathy, MD, chair, breast medical oncology at MD Anderson Cancer Center in Houston, Texas.

Updates in the Treatment of Premenopausal Breast Cancer

One of the most noteworthy and practice-changing presentations at SABCS 2014 was results of the large international Suppression of Ovarian Function Trial (SOFT). To date, tamoxifen has been the hormonal therapy of choice following surgery for premenopausal women with breast cancer. However, data from SOFT indicate that ovarian function suppression (OFS) combined with endocrine therapy may convey a significant advantage for a subset of women in this patient population.[1]

Beginning in November 2003 and extending to January 2011, 3047 premenopausal women with estrogen receptor (ER)+ and/or progesterone receptor (PR)+ breast cancer were randomized to 1 of 3 arms: 5 years of tamoxifen with or without OFS (via the GnRH agonist triptorelin, oophorectomy, or irradiation) or the aromatase inhibitor exemestane plus OFS. The trial was stratified by the use of prior chemotherapy: 47% of participants had received no prior chemotherapy while 53% received prior chemotherapy. All patients were premenopausal, which was confirmed by estradiol levels within 8 months of completion.[1]

The trial's primary objective was the comparison of tamoxifen alone versus tamoxifen plus OFS when tested at a 2-sided 0.05 level with median follow-up of at least 5 years; a secondary objective was to compare tamoxifen with exemestane plus OFS. The study's primary endpoint was disease-free survival (DFS), and secondary endpoints included breast cancer-free interval (BCFI), distant recurrence-free interval (DRFI), and overall survival (OS).[1]

After a median follow-up of 67 months, the 5-year rate of DFS was 86.6% in the tamoxifen plus OFS group versus 84.7% in the tamoxifen arm (hazard ratio [HR], 0.83; 95% CI, 0.66-1.04; $P = .10$). The primary analysis in the overall population was not statistically significant (HR, 0.78; 95% CI, 0.62-0.98; $P = .03$). OS data are not mature, but the 5-year rate of OS was 96.7% for tamoxifen plus OFS and 95.1% for tamoxifen (HR, 0.74; 95% CI, 0.51-1.09; $P = .13$).[1]

Among patients with no prior chemotherapy, BCFI was >95% with tamoxifen alone. There was a 4.5% absolute improvement in 5-year BCFI with tamoxifen plus OFS versus tamoxifen monotherapy in patients who remained premenopausal after chemotherapy. Five-year OS in the chemotherapy cohort was 94.5% for tamoxifen plus OFS and 90.9% for tamoxifen alone (HR, 0.64; 95% CI, 0.42-0.96).[1]

Grade 3 or higher toxicities were reported for 31% of patients in the tamoxifen plus OFS arm compared with 24% in the tamoxifen-only group. Menopausal symptoms, depression, osteoporosis, hypertension, and diabetes occurred more frequently with tamoxifen plus OFS.[1]

The researchers concluded that the addition of OFS to tamoxifen did not provide benefit in the overall premenopausal population after a median 67 months of follow-up. However, among the women who received adjuvant chemotherapy and remained premenopausal, as well in in women under 35 years (the majority of whom received chemotherapy), the addition of OFS reduced disease recurrence and enabled the use of aromatase inhibitor treatment, which further reduced recurrence in these higher risk cohorts.[1]

Targeting Triple Negative Breast Cancer

Triple-negative breast cancer (TNBC) is the umbrella term used to define breast cancers with the absence of ER, PR, and human epidermal growth factor receptor 2 (HER2) expression. TNBC has the poorest prognosis of all breast cancer subtypes.[2] One of the challenges inherent in treating TNBC is its heterogeneity: 6 distinct TNBC subtypes, each with its own biological composition, were recently identified in gene expression analyses, raising the question of how best to treat, or target, each particular subtype.[3]

Data from the Triple Negative Breast Cancer Trial (TNT) concerning the choice of chemotherapeutic agent in TNBC further informs therapeutic selection in *BRCA*-mutation positive metastatic TNBC. TNT was designed as a superiority trial to evaluate the use of the platinum agent carboplatin versus docetaxel in patients with metastatic or recurrent locally advanced TNBC or *BRCA1/2*-mutated breast cancer (N = 376). Eligible patients were

those with TNBC, or those known to have a *BRCA* mutation.[4]

Patients were randomized to carboplatin (target area under the concentration versus time curve at 6 mg/mL per minute) or docetaxel (100 mg/m^2) every 3 weeks for 6 cycles or until disease progression. The study's primary endpoint was objective response rate (ORR) defined as the proportion of patients with complete or partial response at cycle 3 or 6. Secondary endpoints included progression-free survival (PFS), ORR (crossover treatment), OS, and toxicity. A total of 188 patients were randomized to carboplatin (median age: 55.7 years), and 188 were randomized to docetaxel (median age: 54.9 years).[4]

In the randomized treatment population, the 2 treatment arms performed similarly, with an ORR of 31.4% for carboplatin and 35.6% for docetaxel (absolute difference –4.2%; 95% CI, –13.7 to 5.3; *P* = .44). Similarly, no difference in median PFS and OS was demonstrated. Median PFS was 3.1 months in the carboplatin arm (95% CI, 2.5-4.2) and 4.5 months in the docetaxel arm (95% CI, 4.1-5.2). Median OS was 12.4 months with carboplatin (95% CI, 10.4-15.3) compared with 12.3 months with docetaxel (95% CI, 10.5-13.6).[4]

A prespecified subgroup analysis revealed important differences among patients with *BRCA1/2* mutations. In this cohort (n = 43), ORR was 68.0% for carboplatin versus 33.3% for docetaxel (absolute difference, 34.7%; 95% CI, 6.3-63.1; *P* = .03).[4]

Although the trial provided no evidence of superior response in unselected TNBC, the investigators concluded results from TNT support *BRCA1/2* genotyping to inform therapeutic selection because carboplatin-treated patients with *BRCA1* or *BRCA2* mutations demonstrated improved response and PFS compared with docetaxel in the trial.

Immunotherapy for TNBC

The potential role of immunotherapy in the treatment of TNBC is an area of substantial clinical interest. The discovery of a TNBC subtype characterized by elevated expression of immune genes suggests that immune-based therapies may be of benefit to some patients with TNBC.[2] Preliminary findings presented at SABC 2014 from a phase 1b study of the anti-PD-1 agent pembrolizumab in TNBC—the first presentation of a checkpoint inhibitor in breast cancer—support further development of this compound in this setting of advanced TNBC.

The PD-1 receptor-ligand pathway can be used by tumors to evade immune surveillance, thereby allowing neoplastic growth.[5] Pembrolizumab is a humanized IgG4/kappa, high affinity anti-PD-1 antibody; when pembrolizumab is blocking the interaction of the inhibitory PD-1 receptor on T cells with its ligands PD-L1 and PD-L2 expressed on some tumor cells, the antibody prevents this method of tumor evasion from being effective.

Nanda and colleagues reported on their multicenter, nonrandomized trial of pembrolizumab administered intravenously at 10 mg/kg^2 every 2 weeks in patients with recurrent or metastatic PD-L1-positive TNBC.[5] The primary study objectives were to determine the safety, tolerability, and antitumor activity of pembrolizumab in this setting. Secondary objectives included assessments of PFS, OS, and duration of response.[5]

A total of 32 patients were enrolled in this ongoing study; the median age of patients was 51.9 years. The majority of patients had disease that had progressed on several lines of treatment used in the setting of advanced disease.[5]

Preliminary analysis of data collected in November 2014 indicates that 1 patient had a complete response, 14.8% of patients had a partial response, 25.9% of patients had stable disease, and 44.4% of patients had progressive disease.[5]

Overall, 56.3% (18/32) experienced an adverse event (AE) of any grade. Grade 3 AEs included anemia, headache, aseptic meningitis, and pyrexia (n = 1 each). One patient experienced a grade 4 AE of decreased blood fibrinogen. One fatality occurred due to disseminated intravascular coagulation with thrombocytopenia; this was the only treatment-related AE leading to drug discontinuation.[5] Further studies in TNBC are planned for pembrolizumab as well as other checkpoint inhibitors.

Treating Early Breast Cancer in Postmenopausal Women

Best practices for the treatment of elderly patients with early-stage breast cancer has been the subject of some debate. This has been complicated by the underrepresentation of elderly women in clinical trials, despite the fact that approximately 50% of newly diagnosed breast cancers occur in women older than 65 years.[6]

The prospective, multicenter, randomized phase 3 ICE study was designed to investigate if capecitabine added to the bisphosphonate ibandronate would lead to improved outcomes compared with ibandronate alone in elderly breast cancer patients with moderate- and high-risk primary breast cancer who were not considered candidates for standard chemotherapy.[6]

The controlled, open-label trial enrolled female patients 65 years or older with unilateral or bilateral breast cancer classified as either node-positive or high-risk node-negative (tumor size ≥2 cm, grade >I, and/or ER- and PR-negative) and who had a Charlson Comorbidity Index (CCI) of 2 or less. Patients received either ibandronate alone for 2 years (50 mg orally daily or 6 mg intravenously every 4 weeks) or the same ibandronate regimen together with capecitabine (2000 mg/m^2) on days 1 to 14 every 3 weeks for 6 cycles. Treatment was initiated within 6 months following axillary dissection. Patients with hormone-sensitive disease received an endocrine therapy according to guidelines. The primary objective was invasive DFS.[6]

The trial was held in Germany between June 2004 and August 2008; 1358 patients were randomized and treated (681 in the ibandronate arm and 677 in the ibandronate/capecitabine arm) and the median patient age was 71 years for both treatment groups.[6]

Results were similar among treatment arms: at 3 years, DFS was 85.4% in the capecitabine plus ibandronate arm versus 84.3% in the ibandronate arm.[6] At 5 years, 78.8% of patients in the capecitabine plus ibandronate arm were free of invasive disease, compared with 75% of patients in the ibandronate alone

arm. Grade 3/4 toxicities in the capecitabine group were 31% compared with 8.7% in the ibandronate group.[6] The investigators concluded that the ICE study failed to substantiate that adjuvant capecitabine improves invasive DFS in ibandronate-treated patients.

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Expert Commentary

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AJHO: Data from the oral abstract, *A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer*, were expected to have the potential to be practice changing. Did the data live up to expectations? What are the major implications of this study?

Dr Tripathy: The phase 1b study of pembrolizumab is important because it's the first study to test a new type of immunotherapy known as checkpoint blockade. It is blockade of the PD-1 or PD-L1 proteins, which are involved in suppressing the immune system and preventing autoimmunity. However, when you block these so-called checkpoint proteins, you can also enhance immunity against cancer. To date, most of the work in checkpoint blockade has been in melanoma and renal cell cancer; in fact, pembrolizumab is approved in melanoma. This was the first study that looked at checkpoint blockade in breast cancer.

There has been a lot of interest in TNBC because there are some signs that some cases of TNBC are immunogenic, as evidenced by the presence of lymphocyte infiltrates. TNBC is also a difficult disease to treat, with chemotherapy being the only option, so this was a logical setting for a phase 1b study.

I believe that the study did live up to its expectations. It wasn't as dramatic as we had hoped for, but about one-fifth of patients had a response. Keep in mind, we have never had a targeted therapy that has led to *any* responses in TNBC as a single agent, and many of the patients in this group had already undergone several lines of chemotherapy for advanced disease.

There are some general next steps for this approach to therapy. First, we need to better define the optimal group of patients for this type of therapy. In this study, the researchers selected patients who had more than 1% expression of PD-L1 in either the stromal cells or the tumor. The question is, should we be looking at other proteins to help us better identify patients who already have some baseline amount of immunity and thus might benefit more from this drug?

The other area that I think is even more important is treating patients at the right stage of disease. I think the time that immunotherapy works best is when the overall burden of disease in the body is lower, not in patients with bulky advanced disease, but perhaps in the adjuvant setting and in patients who have a very high risk of recurrence. These types of trials are already under consideration and being designed.

I think we are just beginning in this area and I look forward to more information about this exciting line of therapy. Whether it's going to ultimately live up to the expectations and actually prevent recurrences or have significant impacts on survival, of course, remains to be seen.

AJHO: Another important trial reported on at SABCS was the TNT trial (*The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or*

recurrent locally advanced triple negative or BRCA1/2 breast cancer [CRUK/07/012]). What particular implications do you think the findings from TNT might have both in the clinical setting and for future explorations?

Dr Tripathy: The TNT trial was another one focused on TNBC. There's been a lot of excitement about the use of platinum agents in TNBC because they seem to generate a better response than standard agents in the laboratory setting. TNBC can also have what is known as the BRCA phenotype: not only germ-line mutations in *BRCA*, but there may be some cancers with normal *BRCA* that still have defects on the BRCA pathway.

We've never formally tested whether or not a platinum agent is better than standard therapy, such as docetaxel, so that is exactly what this study did. The investigators compared carboplatin with docetaxel in patients with advanced TNBC. The study showed that both drugs were about equal in terms of response rates, but when investigators examined the subset of patients that actually did have *BRCA* mutations, they found that platinum appeared to be superior. That is what many would have expected, but it was very important to formally demonstrate that.

The other thing this trial did is ask the question, might there be patients who have normal *BRCA* genetics but who still have some abnormalities in the BRCA pathway who might also benefit from platinum agents? The investigators performed a homologous recombination deficiency (HRD) assay, and what they found is that there was no difference based on the HRD assay. The HRD assay is being developed for clinical use and it may identify a BRCA-like group of patients. This study did not support the notion that the HRD assay made a difference; however, we have to recognize that all the tumors tested were from the early-stage cancer and not from recurrence or metastasis.

I think that field is going to need some more work, but what we can say for now is that platinum agents do seem to have preferential activity in *BRCA*-positive cases. The next step is going to be to design trials specifically in that group of patients to see if we should be using those agents in the standard setting. The other important question that is also being asked in ongoing randomized trials is whether PARP inhibitors should be used for these patients. There's a large ongoing trial called the OlympiA study that is currently enrolling patients with TNBC who are also known to have *BRCA* mutations; eventually, all patients known to have *BRCA* mutations will be enrolled. The study will test the addition of the PARP inhibitor, olaparib, for 1 year following the completion of all standard therapy compared with placebo. This is going to be an important study not only for TNBC, but for all BRCA-related cancers.

AJHO: Let's discuss neoadjuvant therapy as a research platform for TNBC. Specifically, what makes it an important avenue for study?

Dr Tripathy: This is a very important area that will help us accelerate drug development. We know that the response to neoadjuvant therapy, especially for TNBC, is an important predictor of long-term survival. We've known for many years now that patients who have a complete pathologic response have a much better outcome—perhaps a recurrence risk of about 10%, whereas in patients who do not achieve a complete pathologic response to neoadjuvant therapy, the risk of recurrence may be as high as 40% or 50%, and even higher in some studies. By looking at the response rates and testing different drugs, we may get a much quicker way to test which drugs are likely to be successful in either advanced or early-stage breast cancer, so many investigators are now taking advantage of this design and taking patients who do not achieve a complete response to neoadjuvant therapy if they have TNBC and comparing the addition of one treatment or another.

Pembrolizumab is going to be tested in a study of that nature and so are PARP inhibitors, for example, in BRCA cancers. You can get an answer on complete pathologic response within 4 to 6 months of therapy as opposed to your typical metastatic trial, where it takes 2 to 3 years for the data to mature. So this gives us a better way to select what drugs should move forward into definitive testing, at a much more rapid pace.

AJHO: Results from the TEXT and SOFT trials, which were reported at the American Society of Clinical Oncology meeting, were considered practice changing by many, opening up the option of treating premenopausal women with hormone-sensitive breast cancer with a combination of ovarian function suppression and an aromatase inhibitor. How might the SOFT analysis that was presented at SABCS concerning only tamoxifen with or without ovarian function suppression further impact practice for treating oncologists?

Dr Tripathy: This is an important study because it's really the first large-scale study to look at ovarian ablation in addition to standard hormonal therapy. For premenopausal patients with ER+ cancers, for early-stage treatment the current standard is tamoxifen for 5 years. More recently, we've learned that for higher-risk patients, 10 years is perhaps better than 5 years.

There have been some studies in the past that looked at the addition of oophorectomy, but they have been relatively small and underpowered and haven't been that informative. They may have suggested that people under the age of 35 or 40 years might benefit. They've also shown that patients who do not achieve cessation of their menstrual periods have a worse outcome. In general, however, those studies never proved whether or not suppressing the ovaries adds any benefit.

Both the TEXT and SOFT trials were designed to ask 2 questions: 1) Is blockade of ovarian function using gonadotropin analogs helpful for premenopausal patients, and 2) If you do block ovarian function, is it better to use tamoxifen or an aromatase inhibitor?

Earlier, it had been shown that patients do benefit a little bit more from aromatase inhibitors than tamoxifen if the ovaries are suppressed, but the SOFT data presented at the San Antonio meeting showed that the effect of oophorectomy was not statistically significantly better than not blocking the ovaries. However, there are some important subset analyses that were presented. One is that for high-risk patients who are receiving chemotherapy in addition to hormonal therapy, there *did* seem

to be a clear benefit from ovarian blockade, particularly when an aromatase inhibitor was used. The other thing the data showed was that in women under the age of 35 years, there appeared to be a clear impact of ovarian ablation. Now, those patients had a higher chance of getting chemotherapy, so it's unclear if it's simply the fact that they were younger or that they were receiving chemotherapy and were in a higher risk category that conferred the additional benefit.

I would say the major conclusions of the study are that, at a high level, ovarian ablation does not seem to help the average patients, and certainly not the low-risk patients. In fact, the study showed that low-risk patients, stage I and even stage II, have an excellent overall outcome with tamoxifen alone: 95% or greater survival. For those patients, standard tamoxifen probably suffices. However, for your higher-risk patients, particularly those getting chemotherapy and, even more specifically, those who do not have cessation of their menstrual periods, one may consider ovarian ablation.

I do think that this is going to impact practice for those subsets, even though the results of the main trial were negative with respect to oophorectomy in the overall population. I would also say that, for high-risk patients, if you are going to use ovarian ablation, you might as well use an aromatase inhibitor.

AJHO: The potential for improved outcomes versus the risk of toxicity with immunotherapy drug combinations has been the subject of much debate. How do you navigate this divide in clinical practice? Are there practical strategies clinicians can employ to manage patients who may be at higher risk for immune-mediated adverse reactions?

Dr Tripathy: For now, this remains a research question in the area of breast cancer because none of these drugs are yet approved. But when we design clinical trials, we have to be very mindful of toxicities. Fortunately, the newer generation of immunomodulatory drugs, the PD-1 and PD-L1 inhibitors, seem to have fewer side effects than the last generation, such as the CTLA4 blockers like ipilimumab, which have a lot of side effects, including mostly skin and gastrointestinal toxicities. The PD-1 and PD-L1 inhibitors do have the same toxicities, but at a much lower rate. As we get more information on the benefit and efficacy of immunotherapy in breast cancer, as well as the short- and long-term toxicities, we'll be able to answer these questions more precisely.

AJHO: What were some key take-away messages from San Antonio—data with immediate impact on clinical practice, new hypotheses for future research, or anything else that stood out to you as the blockbuster finding or an unexpected result?

Dr Tripathy: I would say that the most practice-changing information came from the TEXT and SOFT trials. I wouldn't call these dramatic or unexpected findings, because we felt that oophorectomy probably does have a role, and what we've shown is that it has a very borderline role when you look at the overall population, but I do think it's going to change practice. That's the one practice-changing set of studies I would say emerged from San Antonio, specifically for the higher-risk patients, particularly those receiving chemotherapy and particularly those under the age of 35 years.

The other area that I would say was groundbreaking was immunotherapy. While the results were not dramatic, they did show for the first time that we can get a handle on TNBC with relatively safe immunotherapy. It's just the beginning. We have to understand more about immunotherapy. We have to design immunotherapy trials in the right patient populations, possibly in the adjuvant setting, where immunotherapy can actually have the potential to save lives. So this is just the beginning, but it's a very exciting beginning.

One thing we are learning as a community is that breast cancer is a collection of smaller entities that each have distinct biological characteristics. So the importance of us linking tissue-based research to drug-based research is critical. We have to be treating the right target population. We have to be aware of the science and we have to make sure that we gather tissue and continue to develop a robust platform for analysis, at the genomic level, at the protein level, and at the epigenetic level. There's really a revolution in science going on, but it's going to be challenging because instead of now just treating breast cancer as 1 group or even the subtypes like triple-negative, we're realizing that there are even subtypes within these subtypes. So you're going to see much more about this in the future, and it's a challenge because now we're dealing with smaller numbers of patients and we have statistical challenges that make it more difficult to interpret these studies. We have to be creative in how we design trials going forward; you will see this in the trials that are reported in the future. They're going to be smaller, but they're going to be much more biologically focused.