Genes & Diseases (2016) 3, 110–113

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REVIEW ARTICLE

Highlights of the 2015 San Antonio Breast Cancer Symposium

Mark Keaton [a], Debu Tripathy [b], Joyce O'Shaughnessy [c], Shou-Ching Tang [a,d,*]

[a] *Georgia Regents University Cancer Center, 1411 Laney Walker Blvd., Augusta, GA 30912, USA*
[b] *The University of Texas MD Anderson Cancer Center, 1515 Holcombe, Unit 1354, Houston, TX 77030, USA*
[c] *Baylor University Medical Center, Texas Oncology, US Oncology, 3410 Worth St Suite 400, Dallas, TX 75246, USA*
[d] *Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Received 7 March 2016; accepted 14 March 2016
Available online 25 March 2016

KEYWORDS
San Antonio Breast Cancer highlights;
Breast cancer prognosis;
Diagnosis and treatment;
Biomarkers;
Immunotherapy and targeted therapies

Abstract This manuscript provides a comprehensive review and highlights of the 2015 San Antonio Breast Cancer Symposium by the leading breast cancer specialists and investigators in the field.

Breast cancer is the most common malignancy and the cause of cancer mortality affecting women worldwide. Each year, a multi-disciplinary group of researchers and clinicians around the world gather in San Antonio, Texas, USA to share the latest development in research and clinical treatment of breast cancer. The recent symposium held in December 2015 was another exciting mix of translational research and clinical presentations that further advances the field of breast cancer understanding and management. In this article we will review selected abstracts that we feel will have future impact on breast cancer research and clinical practice. We will initially cover those presentations that impact our understanding of breast cancer biology and

* Corresponding author. Georgia Regents University Cancer Center, 1120 15th Street, AN-2017, Augusta, GA 30912, USA. Tel.: +1 706 721 0548; fax: +1 706 721 0360.
E-mail address: stang@gru.edu (S.-C. Tang).
Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2016.03.002

then cover the clinical presentations that have the potential to influence and alter clinical practice.

Several of the presentations assessed the impact and role of tumor infiltrating lymphocytes (TILs) and expands our understanding of this interesting pathologic finding. A recent meta-analysis has shown that high levels of FOXP3+ TILs are associated with improved recurrence-free survival (RFS) and overall survival (OS) of patients with triple negative breast cancer (TNBC). Just the opposite effect was seen in the hormone receptor positive patient with increased TILs being associated with a worse RFS and OS.[1] In the HER2+ subset increase in TILs has been associated with an increase in pathologic complete response rate (pCR) in the neoadjuvant chemotherapy (NAC) combined with anti-HER2 directed therapy. And this has correlated with an improved RFS and OS.[2] Efforts to standardize TIL's have recently been published and validated.[3,4]

Dr. Molinero presented retrospective analyses of molecular markers of the tumor immune and stromal microenvironment from the BEATRICE study. This was an adjuvant study in TNBC that compared chemotherapy to chemotherapy with bevacizumab. This study was negative for any benefit of bevacizumab but provided a large tumor repository to perform additional testing. They showed that gene signatures that correlated with increased TILs and especially increased CD 8 effector T cells showed an improved invasive disease free survival (IDFS) and OS. They also demonstrated that increased stromal cell gene expression was associated with a negative effect on IDFS and OS. Dr. Loi presented pooled data from several randomized clinical trials of TNBC patients (991 patients) treated with anthracycline based adjuvant chemotherapy and showed that increasing TILs were associated with an improved IDFS and OS. They also demonstrated that there was a continuous association such that every increase in TILs by 10% was associated with a 12% reduction of risk of recurrence in patients.

Dr. Desmedt group look at the expression of TILs in a large cohort of patients with invasive lobular carcinoma. Unlike the HER2+ and TNBC subgroups the increased expression of TILs was associated with a worsening prognosis. However the overall expression of TILs in this group of patients was fairly low (median 5%) and only 15% of patients had TILs greater than 10%. Increased TILs when present was associated with classical poor prognostic pathologic markers such as node positivity, high tumor grade and increased tumor size. This supports the idea that the ER+ group of tumors for the most part is less immunogenic than the more aggressive subtypes of breast cancer.

Several of the oral presentations examined preclinical as well as clinical data on mutations of the gene coding for the estrogen receptor alpha (ESR1). ESR1 mutations are uncommon in primary breast cancer however with endocrine therapy activating mutations of the ESR1 occur and lead to ligand-independent ER activation and endocrine resistance.[5] More recently cell free DNA (cfDNA) from the plasma has allowed for a non-invasive method to detect the development of these mutations.[6,7] Using cfDNA of plasma samples from the BOLERO-2 study showed a high incidence (29%) of the two most common mutations of the ESR1 (Y537S, D538G). Both mutations were associated with a shorter OS. Also they showed a beneficial effect of everolimus in patients with the wild type (WT) ESR1 and the D538G mutation but not the Y537S mutation. Another presentation by Dr. Gellert using paired primary and metastatic tumor specimens showed that estrogen deprivation with an aromatase inhibitor produced an increase in ESR1 mutations with the incidence in the primary tumor being very low as previously reported.

The last area in the diagnostic arena that was looked at was circulating tumor cells (CTCs). This was an update of the previously reported SUCCESS, a study that showed the number of CTCs both before and after adjuvant chemotherapy in a large prospective trial of patients with primary breast cancer was an independent prognostic marker.[8] All patients received an anthracycline and taxane based adjuvant chemotherapy protocol and hormonal therapy for endocrine responsive tumors. There were randomizations to gemcitabine and duration and schedule of zoledronate as part of the protocol. Dr. Janni presented the data on the analysis of CTCs that was assessed 2 years after study entry. They found that 18.2% of patients had at least 1 persistent CTCs and this correlated independently for RFS and OS. They suggested that this may allow at some point the introduction of possible delayed treatment options that could alter the poorer prognosis for this group of patients.

Several oral presentations revolved around adjuvant treatment. Dr. Nielsen presented a look back at an older Danish study, DBCG77B which randomized patients to no chemotherapy, classical CMF or oral cyclophosphamide. The study overall was positive for the chemotherapy arms vs the control arm. All patients were either node positive or had T3 primaries. They went back and using a panel of immunohistochemical stains, defined a subgroup of patients as luminal A. They showed that this group despite being higher risk derived no benefit from adjuvant chemotherapy. Additionally patients with the luminal A subtype even in the control arm had a better prognosis than the other defined groups. This is concordant with several other retrospective analyses of other randomized trials (NSABP 20, IBCSG 8 and 9). This also agrees with the recent publication of the non-randomized arm of TAILORx that showed patients with low recurrence score risk did well despite no chemotherapy. The rate of freedom from recurrence of breast cancer at a distant site was 99.3% at 5 years of follow-up. One would assume most of these patients are luminal A subtype.[9] Currently, there is no randomized trial to address the question if we can safely omit adjuvant chemotherapy in high risk patients with early breast cancer who have the luminal A histology.

One of the potentially practice changing studies was presented by Dr. Gnant and was the survival analyses of ABCSG-18. This was a placebo double blind study that randomized 3425 patients who were postmenopausal and ER positive that were being treated with an aromatase inhibitor to denosumab 60 mg SQ every 6 months or placebo. This study has previously been shown to reduce the fracture rate by 50%.[10] There was a 4% absolute reduction in recurrence in the treated arm vs the control, just outside the level of statistical significance. This is very similar to the benefit seen with bisphosphonates in the EBCTCG meta-analyses where a 3% absolute difference was seen with the use of bisphosphonates.[10] So this may give us another

option to use a bone modifying agent to reduce fracture risk and recurrence risk in postmenopausal patients, especially those who have high risk early breast cancer. Also denosumab can be used in patients with chronic kidney disease where one would not wish to use the other agents.

The 10-year update by Dr. Slamon of BCIRG-006 continued to show a similar benefit of the TCH (docetaxol, carboplatin, and trastuzumab) compared to that of AC-TH (Adriamycin/cyclophosphamide with docetaxel and trastuzumab), in all patients as well as the high risk subsets (node positive or those with 4 or more positive nodes). There continues to be a fewer secondary leukemias and congestive heart failure in the non-anthracycline containing arm as initially reported.

In the area of immunotherapy there were several presentations evaluating a number of the checkpoint inhibitors in metastatic breast cancer. Dr. Dirix presented the Phase 1b data on Avelumab, an investigational anti-PD-L1 inhibitor in 168 patients with metastatic breast cancer. The activity was low with only 1 CR and 7 PR with a response rate of 4.7%. The activity was higher in the TNBC patients with a RR of 8.6%. They observed higher activity in the patients, with increased PD-L1 staining of tumor-associated immune cells. Dr. Rugo then presented the data from the KEYNOTE-028 study testing the anti PD-1 antibody pembrolizumab given on an every 2 week schedule. In the 25 patients in the breast cancer cohort that had positive staining for anti-PD-L1 there was a RR of 12% and clinical benefit rate of 20%. Thus we see there appears to be modest activity of these checkpoint inhibitors in patients with metastatic breast cancer, especially those who have triple negative breast cancer. However some of the responses were durable and ongoing. There is the potential to combine these agents with other biologics and chemotherapy that may increase the activity of this class of agents. Additional biomarkers continue to need to be explored to help determine the most appropriate patients for these new agents.

There were two randomized studies that assessed the addition of carboplatin in the neoadjuvant setting. The GeparSixto trial tested the addition of carboplatin weekly (initially AUC of 2 reduced to 1.5) to a novel induction regiment of weekly paclitaxel, weekly non-pegylated liposomal doxorubicin and every 3 week bevacizumab for 18 weeks in patients with TNBC and HER2-positive early breast cancer. In the HER2-positive patient there was no benefit in pCR rates but in the TNBC patients there was a marked increase in pCR from 36.9% to 53.2%. This effect was translated into a statistically significant improvement of 3 year DFS in the TNBC group independent of BRCA status. The other study CALGB 40603 was a 2×2 randomization of bevacizumab and carboplatin to a neoadjuvant induction of weekly paclitaxel for 12 weeks followed by dose-dense doxorubicin and cyclophosphamide for 4 cycles in TNBC patients with Stage II—III disease. Carboplatin was dosed every 3 weeks at an AUC of 6. As has been seen previously, pCR correlated with an improved 3-year EFS and OS. This study failed to demonstrate any EFS or OS benefit to bevacizumab or carboplatin although the investigators did state the study was underpowered to firmly answer this question. It is not clear why the outcomes were better with GeparSixto unless there may be some advantage to giving carboplatin weekly. However, the absence of an alkylator in the chemotherapy backbone of this study could have explained the benefit of platinum. There are not enough data to be conclusive at this time. Are there times that addition of carboplatin can be considered for neoadjuvant treatment in TNBC outside a clinical trial? Possibly for a patient who is young with advanced stage disease who needs a rapid local control of their disease. There is significant increase in myelosuppression with the addition of carboplatin to our traditional AC/T induction treatment, and this has been shown to attenuate the delivered dose intensity of paclitaxel. Additional ongoing clinical trials of neoadjuvant and adjuvant platinum salts will hopefully answer this question. Finally the WSG-ADAPT TN randomized phase II trial was presented that compared a 12 week induction protocol of carboplatin AUC 2 D1 and D8 every 21 days for 4 cycles with either gemcitabine 1000 mg/M2 D1 and D8 or nab-paclitaxel 125 mg/M2 D1 and D8 in patients with TNBC. The pCR rate with the nab-paclitaxel/carboplatin was 45.9% without the use on an anthracycline in just 4 cycles which is impressive. No DFS or OS in this study was available at this time.

One interesting study presented was the CREATE-X study which was a large phase III study of adjuvant capecitabine in HER2-negative breast cancer in patients who had residual invasive disease after neoadjuvant chemotherapy. Patients were randomized to initially 6 and later 8 cycles of capecitabine 2500 mg/M2/day for 14 out of 21 days after neoadjuvant chemotherapy with an anthracycline and taxane or TC with a non-pCR. Eighty percent of the patients received sequential A—T type therapy. All ER positive patients had endocrine therapy as well. The 5 year DFS improved from 67.7% to 74.1% and OS improved from 83.9% to 89.2%, both statistically significant. The most prominent hazard ratio (HR) was seen in the TNBC subgroup. Other studies have shown positive effects of adjuvant capecitabine added to standard chemotherapy in the TNBC subgroups, although it was given in different doses with other agents. The USON 01062 saw a benefit in OS in the TNBC subgroup[11] and similar effect was seen in the TNBC subgroup of FinXX.[12]

In the area of management of DCIS updated information was presented on NSABP B-35. This study compared anastrozole to tamoxifen in postmenopausal patient with ER or PR positive DCIS treated with lumpectomy and radiotherapy. Overall the breast cancer-free (BCFI) interval was improved with anastrozole over tamoxifen from 89.2% to 93.5%. The bulk of this improvement was seen in patients under the age of 60. This presentation looked in detail at the patient reported outcomes and showed a definite difference in side effects between the two treatments. Vasomotor symptoms appeared worse with tamoxifen while musculoskeletal symptoms were worse with anastrozole. Vaginal symptoms were worse with anastrozole while bladder control problems were increased in patients on tamoxifen. There was no difference in sexuality functioning scores, cognitive issues or weight control problems between the two drugs. However, vasomotor symptoms, weight problems and vaginal symptoms were worse in the patients under 60 years of age. With the information on the toxicity profile of the agents the BCFI patients and their physicians can now make personalized decisions about which of these two effective agents to select in this setting.

Dr. Jack Cuzick also presented the data from IBIS-II DCIS which randomized 2980 postmenopausal patients with DCIS to anastrozole or tamoxifen for 5 years. There was a trend favoring anastrozole in reduction of breast cancer recurrence but it was not statistically significant with 7.2 years of median follow-up. Compliance to both agents was equivalent with 2/3 of patients completing 5 years of therapy. Toxicity profile was as anticipated with a noted exception being a significant increase in carpel tunnel seen in the patients on anastrozole and decrease in endometrial, ovarian and skin cancers seen with anastrozole.

Dr. Taylor for the EBCTCG presented an analysis of the long term effects of radiotherapy in relationship to the development of lung cancer and ischemic heart disease. They showed the doses today to the heart and lung are significantly less than the averages in the trials and even less in the more modern radiotherapy trials. Using data from the trials and assigning a value of excess risk per Gy they showed that with current breast treatment protocols the increase in lung cancer in nonsmokers is minimal but even with current techniques there is a marked increase of risk in smokers, going from 9.4% to 13.8% by age 80 when radiation is given at age 50. Minimal increase of the risk of heart disease is seen in non-smokers (1.8%—2.0%) and slightly more in smokers (8.0%—8.6%). The take home message is that patients who are smokers and have breast cancer who are going to require radiation therapy should be strongly encouraged to enter a smoking cessation program since the risk is very much delayed and therefore could be avoided. These data can provide further information to help reinforce that plan.

Finally the MANTICORE study was presented that looked at the utility of using either a beta-blocker or an ACE inhibitor to reduce the risk of cardiotoxicity in patients with early stage HER2 positive breast cancer receiving trastuzumab-based chemotherapy. This was a 3-arm study that was double blinded and placebo controlled. The primary endpoint was change in indexed left ventricular end-diastolic volume by cardiac MRI following 17 cycles of trastuzumab with secondary outcome being change in left ventricular ejection fraction (LVEF) by the same technique. Both interventional arms had a marked reduction in dose interruptions of trastuzumab compared to the placebo and a significant less decline in LVEF. The study was stopped prematurely since further accrual was not felt to likely change the results. Both interventions had minimal toxicity compared to placebo. Over 3/4 of the patients were treated with TCH with the rest having an anthracycline regimen followed by taxane and trastuzumab.

This year's meeting may not have reported any major breakthroughs, but did provide updates to influence clinical practice and further increased our understanding of breast cancer and also helped reduce the toxicities of our treatments. The use of bone-protecting agents in patients on adjuvant AI's was further consolidated and the use of AI's in DCIS was further solidified. When treating a patient with adjuvant trastuzumab you would probably look for an excuse to prescribe either a beta-blocker or ACE inhibitor to reduce the risk of cardiotoxicity. Finally the Create-X trial does provide us with an option to use post-op capecitabine in patients with residual disease after neo-adjuvant AC/Taxane. We anxiously await the results of other studies that are ongoing, which will help answer some of the questions raised by this year's presentations.

Conflicts of interest

All authors have none to declare.

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