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REVIEW ARTICLE

Highlights of the 2015 San Antonio Breast Cancer Symposium

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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

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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