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Translational and clinical research highlights from the 38th San Antonio Breast Cancer Symposium

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In November 1978, during Breast Cancer Awareness Week, the first annual San Antonio Breast Cancer Symposium (SABCS) was held as a part of an educational program conceived to reduce breast cancer death rate. Only 141 physicians attended the conference. Recently, the 38th edition of the SABCS welcomed >7000 attendees from all over the world. We will discuss a selection of the most significant advances presented at the 2015 SABCS, specifically focusing on those data that could have an impact on the clinical practice in the near future.

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Circulating tumor cells predict poor survival: a SUCCESSful project

High-risk breast cancer (BC) patients (node positive or T2–T4 or grade 3 or women ≤35 years or hormone receptor [HR] negative) were enrolled in the SUCCESS A trial [1]. This Phase III study randomized 3745 patients to adjuvant fluorouracil–epirubicin–cyclophosphamide followed by docetaxel or gemcitabine–docetaxel. In addition, patients were randomized to 2 versus 5 years of zoledronic acid. Circulating tumor cells (CTCs) measurements were available for 1103 patients. Multivariate analysis showed significant independent prognostic role for CTC status 2 years after chemotherapy on overall survival (OS; hazard ratio [HR]: 3.95; 95% CI: 2.13–7.32; $p < 0.001$) and disease-free survival (DFS; HR: 2.28; 95% CI: 1.48–3.50; $p < 0.001$), independently from hormone- and HER2-receptor status. In daily practice, CTC testing after curative BC treatment may be used as a surveillance marker to identify patients at higher risk for relapse who could benefit from an intensified follow-up program or secondary treatment intervention [2].

HER2-positive tumors: a long, heterogeneous story

After the introduction in clinical practice of the monoclonal antibody trastuzumab, the natural history of patients diagnosed with HER2-positive BC has dramatically changed. Over the last decade, new insights have been discovered on the HER2 pathway and new HER2-targeted drugs have been developed [3].

A whole-exome sequencing analysis, performed on 203 patients enrolled in the NeoALLTO trial [4], demonstrated that mutation of *PIK3CA* was the strongest predictor of response to HER2-targeted therapies (odds ratio for absence of pathological complete response [pCR]: 0.42; $p = 0.019$) [5]. Moreover, the study showed 33 pathways significantly associated with response; in the

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trastuzumab arm, 23 of the 33 pathways showed an association with response but none was independent of *PIK3CA* mutation. Considering that genes involved in the response to HER2-targeted drugs are mainly connected through the *PIK3CA* gene, and analysis of *PIK3CA* status in HER2-positive BC patients may be of great importance in daily practice.

Moving research from the laboratory to the clinic, other important results have been presented at the symposium.

The BCIRG-006 trial [6] evaluated three different adjuvant regimens in 3222 HER2-positive patients: four cycles of doxorubicin/cyclophosphamide followed by four cycles of docetaxel (AC-T) versus four cycles of doxorubicin/cyclophosphamide followed by four cycles of docetaxel and 1 year of trastuzumab (AC-TH) versus six cycles of docetaxel plus carboplatin and 1 year of trastuzumab (TCH). After a median follow-up of 10.3 years, 28% of risk of disease recurrence reduction was observed in the AC-TH arm (HR: 0.49; 95% CI: 0.37–0.65; $p < 0.001$) and 23% of reduction in the TCH arm (HR: 0.61; 95% CI: 0.47–0.79; $p = 0.002$), compared with AC-T arm [7]. Moreover, a significant OS benefit was also seen in both trastuzumab-containing arms compared with AC-T (risk of death reduction: 37% for AC-TH and 24% for TCH). To note, the anthracyclines/trastuzumab containing strategy showed a fivefold higher number of congestive heart failure cases compared with anthracyclines-free strategy (21 cases with AC-TH vs four cases with TCH). Considering that the TCH regimen showed to be a very active regimen, which essentially eliminates the cardiotoxicity issues, it may be considered as the first choice for patients with cardiac concerns.

In the Phase III TH3RESA trial [8], 602 patients with HER2-positive metastatic breast cancer who progressed after previous treatment with trastuzumab and lapatinib were randomized to receive HER2-targeted antibody–drug conjugate ado-trastuzumab emtansine (T-DM1) or treatment of physician's choice (TPC). After a median follow-up of 30.5 months, the median OS was 22.7 months in the 404 patients assigned to T-DM1 compared with 15.8 months in the 198 patients assigned to TPC (HR: 0.68; 95% CI: 0.54–0.85; $p = 0.0007$), regardless of patient's age, Hr-status, visceral involvement and number of prior therapeutic lines [9]. Moreover, the incidence of grade 3 or higher adverse events was 7.3% higher among patients assigned to TPC.

The efficacy of T-DM1 was also tested in the neoadjuvant setting for HER2-positive, Hr-positive BC in the WSG-ADAPT HER2+/Hr+ Phase II trial. Overall, 376 patients were randomized to 12 weeks of neoadjuvant therapy with: T-DM1 alone, T-DM1 with endocrine therapy (ET; according to menopausal status) or trastuzumab plus ET [10]. After surgery, standard TPC and completion of 1 year trastuzumab were recommended. The pCR rate was 40.5% with T-DM1, 45.8% with T-DM1/ET and 6.7% with trastuzumab/ET ($p < 0.001$ for difference between T-DM1 arms versus trastuzumab arm). Notably, the 15.8% of patients who harbored a *PIK3CA* mutation achieved a lower pCR rate (35.4% for wild-type and 17.6% for mutated).

These studies showed that T-DM1 has a key role in the treatment strategy of HER2-positive disease, in both early and metastatic setting.

Carboplatin for triple-negative breast cancer: an old drug with a new dress on

It has been demonstrated that up to 20% of triple-negative breast cancer (TNBC) patients harbor germline *BRCA* mutations and that *BRCA* mutations carriers may be more sensitive to platinum-based chemotherapy [11]. However, little is still known about the association between mutations and response to nonplatinum-based therapy.

A next-generation sequencing analysis was conducted on blood samples of TNBC patients exposed to fluorouracil–epirubicin–cyclophosphamide with or without bevacizumab enrolled in the neoadjuvant GeparQuinto study [12,13]. The analysis showed that patients harboring *BRCA1/2* mutations had a higher pCR rate compared with patients without mutations (50.0 vs 31.1%, respectively, $p = 0.002$), but no significant impact of pCR on DFS was detected in mutations carriers (HR: 0.48; 95% CI: 0.18–1.27; $p = 0.129$). These data suggest that TNBC patients with *BRCA* mutations may experience a better response when exposed to standard neoadjuvant treatment. However, the effect of pCR on prognosis is not demonstrated among the mutation carriers.

At the 2015 San Antonio Breast Cancer Symposium (SABCS), the updated survival analysis of two large neoadjuvant trials confirmed the beneficial effect of adding carboplatin to anthracycline/taxane-based chemotherapy in TNBC.

In the GeparSixto trial [14], patients were treated for 18 weeks with weekly paclitaxel plus

nonpegylated-liposomal doxorubicin. They were randomly assigned (1:1 ratio) to receive concomitant weekly carboplatin or not. In addition, the 315 women with TNBC received concurrently bevacizumab until surgery, and the 273 women with HER2-positive cancer received concurrently trastuzumab and lapatinib. After a median follow-up of 28 months, in the TNBC cohort, the addition of carboplatin lead to a 9.7% higher 3-year DFS rate (85.8% with carboplatin vs 76.1% without carboplatin; HR: 0.59; 95% CI: 0.33–0.96; $p = 0.035$); no effect of carboplatin was noticed in the HER2-positive cohort ($p = 0.372$) [15]. In contrast, the updated analysis of the CALGB (Alliance) 40603 trial [16] showed only a nonsignificant improvement in 3-year event-free survival (EFS) rate by the addition of carboplatin to 12 courses of weekly paclitaxel followed by doxorubicin/cyclophosphamide every 2 weeks for four cycles (76.5% with carboplatin vs 71.6% without carboplatin; HR: 0.84; 95% CI: 0.58–1.22; $p = 0.36$) [17]. However, the CALGB study was not powered to assess the impact of carboplatin on time-to-event end points.

To note, in both trials no differences in DFS/event-free survival were detected by the addition of bevacizumab.

The effect of carboplatin in neoadjuvant setting was also explored in the TNBC cohort of the WSG-ADAPT trial. Overall, 336 early-stage TNBC patients were randomized to 12 weeks of nab-paclitaxel/gemcitabine or nab-paclitaxel/carboplatin. Interim analysis, performed on 130 patients, showed a higher pCR rate in the platinum-based arm compared with platinum-free arm (49.2 vs 25.0%, respectively; $p = 0.006$) [18]. Interestingly, early response, defined as <500 BC cells and/or Ki-67 decrease $\geq 30\%$ in 3-week biopsy, was positively associated with pCR rate (44.4% in responders vs 19.5% in nonresponders; $p < 0.001$).

Taken together, these results support the development of neoadjuvant strategies designed to further assess the value of platinum-based regimens in early-stage TNBC in daily practice. However, a better characterization of TNBC, especially in terms of *BRCA* status, is mandatory for future research.

Which news for Hr-positive/HER2-negative BC patients?

The anti-PD-1 pembrolizumab has been tested in PD-L1-positive, Hr-positive/HER2-negative

with heavily pretreated metastatic breast cancer in the KEYNOTE-028 multicohort, Phase Ib study. Among the 25 patients enrolled, three patients achieved a partial response and four patients a stable disease, with a median time to response of 8.0 weeks and a median duration of stable disease of 16 weeks [19]. Only four patients experienced grade 3–4 adverse events, confirming the safety of pembrolizumab and endorsing the opportunity to further investigate this agent.

The ABCSG-18 trial randomized 3425 postmenopausal patients with Hr-positive BC receiving adjuvant aromatase inhibitors to the addition of the anti-RANK-ligand denosumab or placebo. Outcome results, presented at the 2015 SABCS after a median follow-up of 4 years, showed a significant impact of denosumab in terms of DFS (HR: 0.816; $p = 0.051$; DFS difference between the two arms was 4% at 2 years, 7% at 5 years and 10% at 7 years; $p = 0.0163$) [20]. Considering the previously reported dramatic reduction of bone-related events (HR for fracture: 0.5; $p < 0.0001$) [21], denosumab is going to gain an important role in the adjuvant setting.

Between 1977 and 1983, the Danish Breast Cancer Cooperative Group 77B (DBCG-77B) trial randomized 1146 Hr-positive high-risk premenopausal women (node positive or tumor >5 cm) to receive: oral cyclophosphamide, cyclophosphamide–methotrexate–fluorouracil, levamisole or observation alone [22]. The analysis of the 10-year DFS according to breast cancer subtypes presented at the 2015 SABCS showed that patients with luminal A BC did not benefit from chemotherapy (HR: 1.07; 95% CI: 0.53–2.14; $p = 0.86$), whereas patients with nonluminal A subtypes did (HR: 0.50; 95% CI: 0.38–0.66; $p < 0.001$). This heterogeneity was statistically significant ($p = 0.048$) [23]. These results further support the approach of avoiding adjuvant chemotherapy in patients with luminal A BC, even in presence of large tumors or nodal involvement.

Conclusion

The SABCS offered the unique opportunity to bring together the leading results from international studies. New and compelling data for the use of targeted therapies, as well as new insights on the use of traditional chemotherapy in both adjuvant and metastatic settings were presented and discussed, increasing the knowledge about BC and consequently improving every day clinical practice.

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