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Perspectives from the American Society of Clinical Oncology 2014 Conference: breast cancer highlights

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50th annual American Society for Clinical Oncology Meeting, Chicago, IL, USA, 30 May–4 June 2014

The meeting included basic science and translational and clinical research in all specialties of hematology and oncology. From the multitude of abstracts presented, we will review the highlights regarding four abstracts discussing breast cancer.

The 50th annual American Society for Clinical Oncology meeting was held from 30 May to 4 June 2014 in Chicago, IL, USA. From the multitude of abstracts presented, we will review the highlights regarding four abstracts discussing breast cancer. One of the highlights and most controversial results was from the highly anticipated ALTTO trial [1]. ALTTO is a randomized Phase III trial comparing adjuvant anti-HER2 therapy concurrent with or after the completion of chemotherapy for early-stage HER2⁺ breast cancer. The trial enrolled 8381 women at 946 medical centers in 44 countries. The treatment arms compared 1 year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T). The primary end point was disease-free survival (DFS). The event rate was lower than the anticipated 850 event target, with 555 DFS events for the L + T arm versus the T arm at 4.5 years of median follow-up, with patients doing better than anticipated. In fact, 4-year DFS rates of approximately 86% and overall survival (OS) rates of approximately 90% were observed. The trial did not meet its primary end points of showing that either dual blockade or sequential use of T followed by L significantly improved DFS. There was no significant difference in the 4-year DFS for L + T (88%) versus T (86%; hazard ratio: 0.84; 97.5% CI: 0.7–1.02). Nor did it meet its primary end point, as DFS for the T→L arm was 87% versus 86% for the T arm (hazard ratio: 0.93; 97.5% CI: 0.76–1.13). This is in stark contrast to the NeoALTTO trial in the neoadjuvant setting where L + T resulted in a doubling in pathologic complete response (pCR) compared with T alone. With this difference comes an even larger concern regarding the significance of pCR and its relationship with long-term patient outcomes in HER2⁺ disease. Equally as important is the conclusion that the pCRs of neoadjuvant trials may not be so easily translated into the adjuvant setting.

The addition of bevacizumab (BV) to chemotherapy in the metastatic breast cancer setting has shown improvements in progression-free survival, but not OS, in several studies. Data evaluating BV in the adjuvant setting were reported by Miller *et al.* in the context of the Phase III E5103 study that enrolled 4994 patients with HER2⁺ breast cancer [2]. Patients were assigned in a 1:2:2 fashion

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to one of three arms: standard therapy with doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel and placebo (arm A); AC followed by paclitaxel with BV throughout chemotherapy (arm B); and the same as arm B followed by ten additional cycles of BV after the completion of chemotherapy during radiation and endocrine therapy if appropriate (arm C). Patients had a median age of 52 years with 64% ER⁺ and 27% lymph node-negative disease. In terms of receiving therapy, BV exposure was less than anticipated, with only 76% of patients in arm B and 45% of patients in arm C completing all planned BV therapy. Chemotherapy-associated adverse events included grade 4 neutropenia in approximately 20% and grade 3 or worse neuropathy in approximately 8% of patients across all arms. The primary end point was invasive DFS (IDFS), with the study meeting its predetermined power requirement with 430 IDFS events. At a median follow-up of 47.5 months, IDFS for arm A was 77% (95% CI: 70.9–81.2%), arm B was 76% (95% CI: 71.5–79.8%) and arm C was 80% (95% CI: 77–82.5%). The conclusion was that BV when added to AC→paclitaxel in the adjuvant setting in HER2⁺ patients provides no improvement in IDFS or OS and is more toxic, with increased adverse events.

Pagani *et al.* presented data regarding the hormonal therapy of premenopausal women with breast cancer [3]. The current standard of care of premenopausal women with ER⁺ breast cancer is to receive endocrine therapy with tamoxifen. Despite the benefit of aromatase inhibitors (AIs) in postmenopausal women, the question remains as to whether ovarian suppression and AIs would be superior to tamoxifen with or without ovarian suppression in premenopausal women. Both the SOFT and TEXT trials looked to address the question of tamoxifen versus AI for women who undergo ovarian suppression, and through an international collaboration, their data were analyzed together due to lower-than-expected DFS event rates for each study. Taken together, the trials enrolled 4690 women with early-stage ER⁺ breast cancer with or without axillary node involvement. Neoadjuvant and adjuvant chemotherapy was permitted. 57.4% of patients received chemotherapy either after randomization in TEXT (34.3% of all patients) or before randomization in SOFT (23.2%). Patients were randomly assigned to

exemestane 25 mg daily (an AI) and ovarian suppression (EX-OS), tamoxifen 20 mg daily and ovarian suppression (TX-OS) or tamoxifen alone (only in the SOFT trial). Ovarian suppression was achieved with the use of the gonadotropin-releasing hormone agonist triptorelin, oophorectomy or ovarian irradiation. The primary end point was DFS and secondary end points included breast cancer-free interval, distant recurrence-free interval and OS. DFS for EX-OS was 91.1% and for TX-OS was 87.3% (hazard ratio for recurrence, second invasive cancer or death: 0.72; 95% CI: 0.60–0.85; $p < 0.001$). The current analysis reveals a 4% absolute improvement in breast cancer freedom with EX-OS compared with TX-OS. There was no difference in OS with the conclusion that the OS analysis is too soon at 68 months of follow-up. This study provides a reasonable alternative with exemestane and ovarian suppression, but best practice will not be established until comparison of tamoxifen alone is included (data are expected from the SOFT trial in December 2014).

The world of genomics is exploding throughout all cancer types. For HER2⁺ breast cancer, a novel predictive gene panel was presented by Perez *et al.* [4]. In order to better understand why certain patients develop tumor relapse after treatment with trastuzumab, an analysis of the North Central Cancer Treatment Group (NCCTG) N9831 adjuvant trastuzumab trial was conducted. Among the 1282 patients enrolled in the N9831 trial, whole-genome analysis technology was used in order to identify genes as well as key biological networks and pathways that are associated with relapse-free survival (RFS). For the trastuzumab-containing arms of the trial, six biological pathways (510 genes) associated with RFS were identified. Further analysis showed that 87 genes were prognostic for RFS for the patients in the trial arms receiving trastuzumab. This was further narrowed down to 14 genes that showed a significant difference in RFS when comparing the trastuzumab-containing arms with the chemotherapy-alone arm. This 14-gene panel was tested and validated repeatedly with the same predictive results. This integration of biology, genomics and clinical data provides a powerful predictive model for the benefit of trastuzumab. Additional validation of this work could have implications for patient care in the future.

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