by receptor status, DFS and OS were still similar between the 2- and 1-year groups. At the interim point of 4 years median follow-up, a transient DFS advantage was reported for patients with hormone receptor (HR)-negative breast cancer who received 2 years of trastuzumab compared with 1 year of treatment in patients with HR-negative breast cancer. However, this benefit was not sustained at 8 years median follow-up.

Although no differences in DFS and OS were observed between 2 years of trastuzumab and 1 year, secondary cardiac endpoints and other grade 3 or 4 adverse events were increased in the arm treated with trastuzumab for 2 years. Nonetheless, most cardiac endpoints were reversible and occurred during the treatment administration period.

Prof. Piccart-Gebhart said, "There is no evidence of long-term benefit of 2 years compared with 1 year trastuzumab when administered as sequential treatment following chemotherapy." She added that "transient DFS advantage for the 2-year arm in the hormone receptor-negative cohort [at 4 years follow-up] highlights the need for long-term follow-up in trials investigating different durations of adjuvant trastuzumab."

After disclosure of the first results in 2005, 885 of the 1698 patients (52.1%) crossed over to receive trastuzumab, which complicates long-term follow-up results. For the analysis of DFS and OS for 1 year trastuzumab versus observation at 8 years median follow-up, the HERA results show sustained statistically significant benefit for DFS and OS compared with observation in intention-to-treat analyses despite selective crossover. In addition, benefit was shown across HR-positive and HR-negative cohorts at 8 years median follow-up.

Prof. Piccart-Gebhart concluded, "One year of trastuzumab remains the standard of care as part of an adjuvant therapy for patients with HER2-positive early breast cancer."

Effectiveness of Letrozole Compared with Tamoxifen for Patients with Lobular Carcinoma in the BIG 1-98 Trial

Written by ***Toni Rizzo***

Invasive lobular carcinoma (ILC) is the second most common breast cancer histologic subtype, accounting for 10% to 15% of all breast cancers, with classic lobular carcinoma being the most common variant. Most classic ILCs are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative. Aromatase inhibitors and tamoxifen are established therapies used for the adjuvant treatment of estrogen receptor (ER)-positive breast cancer, but the relative benefits in invasive ductal carcinomas (IDCs) and ILCs has not been extensively studied. The authors previously presented data from a gene expression profiling study (n=174) that showed the majority of ILCs were low proliferative tumors (76%; luminal A), with a minority that had high proliferation markers (20%; luminal B) [Metzger O et al. SABCS 2011 (abstr P1-02-05)]. A previous analysis of the Letrozole or Tamoxifen in Treating Postmenopausal Women with Breast Cancer [BIG 1-98] trial (n=4922) demonstrated that letrozole resulted in improved disease-free survival (DFS) compared with tamoxifen in patients with tumors that had a higher Ki67 proliferative index [Viale G et al. *J Clin Oncol* 2008].

Otto Metzger Filho, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, presented an unplanned analysis of data from the BIG 1-98 trial comparing the outcomes of patients with IDC and ILC treated with adjuvant letrozole or tamoxifen. The analysis was also made to adjust for the distribution of luminal A and B subtypes, with a Ki67 of 14% used as a cutoff to separate the 2 subtypes. Among the patients analyzed, 2599 had IDCs (1436 [44%] luminal A and 1163 [36%] luminal B) and 324 had classic ILCs (237 [59%] luminal A and 87 [22%] luminal B) that were HR-positive and HER2-negative.

In patients with IDC, the 5-year DFS with letrozole compared with tamoxifen was 88% versus 84% (HR, 0.80; 95% CI, 0.68 to 0.94; no p value given). In patients with ILC, the 5-year DFS with letrozole compared with tamoxifen was 89% versus 75% (HR, 0.48; 95% CI, 0.31 to 0.74; interaction p=0.03). Multivariate analysis of DFS showed that letrozole was better compared with tamoxifen for treatment by histology (ductal/lobular; interaction p=0.006) and subtype (luminal A/ B; interaction p=0.01).

The 5-year overall survival (OS) rate in patients with IDC treated with letrozole compared with tamoxifen was 94% versus 92% (HR, 0.73; 95% CI, 0.60 to 0.89; no p value given). In patients with ILC, this comparison was 96% versus 86%, favoring letrozole (HR, 0.40; 95% CI, 0.23 to 0.69; interaction p=0.045). Multivariate analysis showed that OS was improved with letrozole compared with tamoxifen in patients with IDC (HR, 0.69; 95% CI, 0.57 to 0.85), and the relative benefit of letrozole was even greater in patients with ILC (HR, 0.39; 95% CI, 0.22 to 0.68; interaction p=0.035).

This analysis showed that letrozole is associated with statistically significant reductions in DFS and OS events for both IDC and ILC. In addition, the magnitude of benefit of adjuvant letrozole was higher among patients

with luminal B compared with luminal A tumors for both histologic subtypes, with patients with ILC deriving greater benefit from adjuvant letrozole compared with those with IDC. Dr. Metzger Filho suggested that clinicians might consider letrozole over tamoxifen for the upfront treatment of patients diagnosed with ILC. However, these results are retrospective in nature and need to be confirmed in other adjuvant aromatase inhibitor trials.

Neurocognitive Impact in Adjuvant Chemotherapy for Breast Cancer Linked to Fatigue: A Prospective Functional MRI Study

Written by Emma Hitt, PhD

Women diagnosed with and treated for breast cancer often experience problems with memory, concentration, and other cognitive abilities that affect their quality of life [Reuter-Lorenz PA, Cimprich B. *Breast Cancer Res Treat* 2013]. Although patients frequently attribute this to chemotherapy, cognitive complaints and deficits have been found before patients undergo any adjuvant treatment [Cimprich B et al. *J Clin Exp Neuropsychol* 2010]. Women treated for breast cancer often report fatigue, but an association between fatigue and neurocognitive function has not been systematically examined. Bernadine Cimprich, PhD, RN, University of Michigan, Ann Arbor, Michigan, USA, presented data from a prospective functional MRI (fMRI) study on the neurocognitive impact of breast cancer-linked fatigue.

Women enrolled in the study were patients with localized breast cancer stages I to IIIa. Twenty-eight patients received adjuvant chemotherapy (anthracycline-based regimen), 37 received radiotherapy alone without chemotherapy, and 32 age-matched healthy controls were enrolled. At 2 time points coinciding with pre- and 1-month postchemotherapy assessments, participants performed a verbal working memory task with varying levels of demand for cognitive control while undergoing fMRI scanning. Participants provided self-reports using the Attentional Function Index and the Functional Assessment of Cancer Therapy-Fatigue during these assessments.

Cognitive domains that may be affected in cancer patients include attention, working memory, processing speed, and executive function [Wefel JS, Schagen SB. *Curr Neurol Neurosci Rep* 2012]. Error rates on a verbal working memory task were significantly higher ($p<0.05$) before treatment in the chemotherapy and radiation groups compared with the healthy group.

In addition, fMRI scanning revealed that inferior frontal gyrus functioning differed between patients and controls over time ($F=3.88$, $p=0.05$). Left inferior frontal gyrus activation at the pretreatment evaluation was related to an increase in fatigue over time.

The group receiving chemotherapy had significantly higher fatigue levels both before and after treatment ($p<0.01$). However, higher levels of fatigue across all groups were associated with reduced cognitive function over time. In addition, preadjuvant treatment brain alterations during the working memory task were able to predict severity of post-treatment fatigue. Thus, fatigue and pretreatment neural vulnerability are contributors to cognitive problems in patients with breast cancer and may further compound any cognitive effects of chemotherapy.

Dr. Cimprich said, "'Chemo brain' is not an appropriate label for cancer-related cognitive dysfunction [and]... early interventions to reduce psychological distress may improve cognitive function over the course of treatment."

ATLAS: 10 Versus 5 Years of Adjuvant Tamoxifen in ER-Positive Disease

Written by Emma Hitt, PhD

Treatment with tamoxifen for 5 years has substantially reduced the risk of breast cancer recurrence and death throughout the first 15 years after diagnosis of estrogen receptor (ER)-positive early breast cancer [Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2011]. The Adjuvant Tamoxifen: Longer Against Shorter [ATLAS] trial compared the effects of continuing tamoxifen for a total of 10 years with stopping after the standard 5 years of treatment. Richard Gray, MSc, University of Oxford, Oxford, United Kingdom, presented data from the ATLAS trial on the effect of tamoxifen on 15-year survival [Davies C et al. *Lancet* 2012].

Women with ER-positive breast cancer (n=6846) who had received 5 years of adjuvant tamoxifen treatment were randomized to continue tamoxifen for another 5 years or to stop at Year 5 (control). Breast cancer recurrence, any other new primary cancer, compliance, hospital admissions, and cause of death were recorded during annual follow-up exams, with a median follow-up of 8 years.

Compliance to treatment was ~80%. During the trial, 617 women in the 10-year tamoxifen group experienced a recurrence compared with 711 women in the 5-year tamoxifen group ($p=0.002$). Breast cancer mortality during