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

the trial period was significantly lower in the 10-year group compared with the 5-year group (331 vs 397; p=0.01). Overall mortality was also significantly lower for the 10-year group (639 vs 722; p=0.01). The reductions in adverse breast cancer outcomes appeared to be relatively smaller earlier, with a recurrence rate ratio (RR) of 0.90 (95% CI, 0.79 to 1.02) during Years 5 to 9 and 0.75 (95% CI, 0.62 to 0.90) after Year 10, and breast cancer mortality RR of 0.97 (95% CI, 0.79 to 1.18) during Years 5 to 9 and 0.71 (95% CI, 0.58 to 0.88) after Year 10 [Davies C et al. *Lancet* 2012].

As the study of 10 years of tamoxifen compared with no tamoxifen has not yet been conducted, the authors combined data from the ATLAS trial and the EBCTCG meta-analysis (n=10,645), which compared 5 years of tamoxifen with no tamoxifen. The breast cancer death RR by period is shown in Table 1.

Table 1. Breast Cancer Death Rate Ratios: ER-Positive Disease by Period.

Tamoxifen	5 Years vs 0: EBCTCG Meta-Analysis (n=10,645)	10 Years vs 5: ATLAS Trial (n=6846)	10 Years vs 0: Estimated as a Product of RRs
Years 0–4	0.71‡ (0.62–0.80)	(1.0)	0.71‡ (0.62–0.81)
Years 5–9	0.66‡ (0.58–0.75)	0.97 (0.79–1.18)	0.64† (0.50–0.82)
Years 10+	0.73† (0.62–0.86)	0.71* (0.58–0.88)	0.52‡ (0.40–0.68)

*p=0.0016; †p=0.0001; ‡p<0.00001. ER=estrogen receptor; RR=rate ratio.

Endometrial cancer and pulmonary embolism mortality occurred in 0.2% of patients in the ATLAS trial and 0.2% of patients in the EBCTCG trial, indicating a total mortality of 0.4% with 10 years of tamoxifen compared with no tamoxifen. However, the reductions in breast cancer mortality by 9.1% in the EBCTCG meta-analysis and 2.8% in the ATLAS trial suggest an 11.9% total reduction with 10 years tamoxifen compared with no tamoxifen. Prof. Gray estimated the effects of 10 years of tamoxifen on 15-year mortality to have 30 times the benefits compared with not taking tamoxifen.

Combined data from ATLAS and the EBCTCG meta-analysis suggest that treatment with tamoxifen for 10 years decreases the rate of breast cancer mortality by approximately 33% in the first decade and 50% in the second decade after diagnosis. The authors proposed that, during Years 5 to 9, the smaller benefit from 10 years of tamoxifen compared with the later benefit from 5 years of tamoxifen was most likely due to the carryover effect of 5 years of tamoxifen.

Science Advisors' Statement

The findings of the ATLAS trial mirror the benefits of extended hormonal therapy in the National Cancer Institute of Canada Clinical Trials Group MA.17 [Goss PE et al. *J Clin Oncol* 2008] trial. The results of ATLAS should be discussed with patients receiving adjuvant tamoxifen therapy, and the benefits of extended tamoxifen therapy should be weighed against the small increased risk in side-effect morbidity.

CONFIRM Trial Final Analysis of Overall Survival: Fulvestrant 500 Versus 250 mg

Written by ***Toni Rizzo***

The Comparison of Fulvestrant 250 mg and 500 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing After Previous Endocrine Therapy [CONFIRM] trial compared treatment with 2 doses of fulvestrant (250 vs 500 mg) in postmenopausal women with locally advanced or metastatic estrogen receptor (ER)-positive breast cancer that had recurred or progressed after endocrine therapy. The primary analysis showed that progression-free survival (PFS) was significantly increased with fulvestrant 500 versus 250 mg [Di Leo A et al. *J Clin Oncol* 2010]. The final analysis of OS was presented by Angelo Di Leo, MD, Hospital of Prato, Prato, Italy.

In the CONFIRM trial, eligible patients were randomized to fulvestrant 250 mg (1 injection) plus placebo (1 injection; n=374) versus fulvestrant 500 mg (2 injections; n=362) on Days 0, 14, and 28, and every 28 days thereafter. The primary endpoint was PFS [Di Leo A et al. *J Clin Oncol* 2010]. The final analysis of OS was planned and conducted after 75% of the patients had died. After the primary analysis, patients receiving fulvestrant 250 mg were allowed to switch to 500 mg. The median age in both groups was 61 years and all patients were ER-positive. Eight (2.1%) of 374 patients in the fulvestrant 250-mg group switched to fulvestrant 500 mg.

At the first analysis, median PFS was 6.5 months with fulvestrant 500 mg versus 5.5 months with the 250-mg dose (HR, 0.80; 95% CI, 0.68 to 0.94; p=0.006). The first analysis of OS at 50% maturity showed that the median time to death was 25.1 months with fulvestrant 500 mg versus 22.8 months with fulvestrant 250 mg (HR, 0.84; 95% CI, 0.69 to 1.03; p=0.091) [Di Leo A et al. *J Clin Oncol* 2010].

The final analysis of OS at 75% maturity (full analysis set) demonstrated a median time to death of 26.4 months with fulvestrant 500 mg versus 22.3 months with 250 mg (HR,