The UK START Trials: 10-Year Follow-Up Results

Written by Toni Rizzo

The international standard for radiotherapy after primary surgery for early breast cancer has been a total dose of 50 Gy administered in 25 small daily fractions over 5 weeks. However, the randomized UK Standardisation of Breast Radiotherapy [START] trials indicate that a lower total dose delivered in fewer larger fractions is likely to be safe and effective [START Trialists' Group. *Lancet* 2008; *Lancet Oncol* 2008]. The 5-year results of the START B trial suggested that 40 Gy in 15 fractions is as safe as and noninferior in terms of tumor control to 50 Gy in 25 fractions [START Trialists' Group. *Lancet* 2008]. John Yarnold, MBBS, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom, presented the 10-year follow-up results of the UK START trials, which tested 13- and 15-fraction regimens in women with completely excised early breast cancer (T1-3, N0-1, M0). The START trials were coordinated by the Clinical Trials and Statistics Unit at The Institute of Cancer Research and funded by Cancer Research UK, the UK Medical Research Council, and the UK Department of Health.

In Trial A, 2236 patients were randomized to receive 50 Gy in 25 fractions (n=749), 39.0 Gy in 13 fractions (n=737), or 41.6 Gy in 13 fractions (n=750), all given for 5 weeks [START Trialists' Group. *Lancet Oncol* 2008]. In Trial B, 2215 patients were randomized to 50 Gy in 25 fractions for 5 weeks (n=1105) or 40 Gy in 15 fractions for 3 weeks (n=1110) [START Trialists' Group. *Lancet* 2008]. The primary endpoint was local-regional relapse. Secondary endpoints included effects on normal tissue, disease-free survival, and overall survival. The median follow-up was 9.3 years for Trial A and 9.9 years for Trial B.

In Trial A, the 10-year rate of patients with local-regional relapse was 7.4% (95% CI, 5.5 to 10.0) after 50 Gy, 6.3% (95% CI, 4.7 to 8.5) after 41.6 Gy, and 8.8% (95% CI, 6.7 to 11.4) after 39 Gy. The hazard ratio (HR) for 41.6 versus 50 Gy was 0.91 (95% CI, 0.59 to 1.38) and for 39 versus 50 Gy was 1.18 (95% CI, 0.79 to 1.76). In Trial B, the percentage of patients with a local-regional relapse was 5.5% (95% CI, 4.2 to 7.2) after 50 Gy and 4.3% (95% CI, 3.2 to 5.9) after 40 Gy. The HR for 40 vs 50 Gy was 0.77 (95% CI, 0.51 to 1.16).

Trial A results showed similar rates of moderate/marked adverse effects on conserved breast tissue with 41.6 versus 50 Gy (HR, 0.94; 95% CI, 0.79 to 1.11) and suggested lower rates with 39 versus 50 Gy (HR, 0.80; 95% CI, 0.67 to 0.96). In Trial B the rates were lower with 40 versus 50 Gy (HR, 0.77; 95% CI, 0.66 to 0.89).

The UK START 10-year results indicate that patients can be safely and effectively treated with a lower total dose with fewer fractions than the historical standard of 50 Gy per 25 fractions. No detrimental effects of hypofractionation were identified in patient subgroups, including age <50 or >50 years, type of primary surgery, axillary node status, tumor grade, whether a tumor-bed boost was given, and treatment with adjuvant chemotherapy. These results support the use of 40 Gy in 15 fractions as the UK standard for patients with early invasive breast cancer after breast-conserving surgery or mastectomy, as recommended in the *NICE Clinical Guidelines, No. 80* [National Institute for Health and Clinical Excellence 2009] and supported by the advice given in the American Society for Radiation Oncology guidelines for fractionation in whole-breast irradiation (for patients not receiving a tumor-bed boost) [Smith BD et al. *Int J Radiat Oncol Biol Phys* 2010].

HERA TRIAL: 2 Years Versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in Women with HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up

Written by Emma Hitt, PhD

In 2005, data from 3 large randomized trials demonstrated that 1 year of trastuzumab treatment provided a statistically significant disease-free survival (DFS) benefit compared with no trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer [Piccart-Gebhart MJ et al. *N Engl J Med* 2005]. One of these studies, the Trastuzumab in Treating Women with Primary Breast Cancer [HERceptin Adjuvant (HERA); NCT00045032] trial, continued trastuzumab therapy to assess whether 2 years of treatment was superior to 1 year. Martine J. Piccart-Gebhart, MD, PhD, Jules Bordet Institute, Brussels, Belgium, provided an update of the HERA trial after 8 years of median follow-up.

Women with locally determined and centrally confirmed early HER2-positive invasive breast cancer who had undergone surgery and neoadjuvant chemotherapy with or without radiation therapy were recruited globally except in the United States (n=5102). Patients were randomized to observation, 1 year of trastuzumab every 3 weeks, or 2 years of trastuzumab every 3 weeks. Patients in the observation arm were given the option of crossing over after the release of first results in 2005.

No significant difference was found in DFS or overall survival (OS) between the 2- and 1-year trastuzumab arms at 8 years median follow-up. When patients were stratified

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