Final Results of AMAROS Trial

Written by Mary Beth Nierengarten

For breast cancer patients with a positive sentinel node biopsy (SNB), treatment with axillary radiotherapy (AxRT) provides excellent locoregional control that is comparable to axillary lymph node dissection (ALND) but with significantly less lymphedema.

This is the conclusion of the final analysis of the Comparison of Complete Axillary Lymph Node Dissection With Axillary Radiation Therapy in Treating Women With Invasive Breast Cancer trial [AMAROS; NCT00014612; Rutgers EJ et al. *J Clin Oncol* 2013 (suppl; abstr LBA1001)] by lead investigator Emiel J. T. Rutgers, MD, Netherlands Cancer Institute, Amsterdam, The Netherlands.

The Phase 3 AMAROS trial was designed to demonstrate the noninferiority of AxRT compared with ALND on 5-year axillary recurrence rate in patients with cT1-2N0 primary breast cancer. Between 2001 and 2010, 4806 patients were enrolled in the trial and, after SNB-positive identification, 1425 were randomized to ALND (n=744) or AxRT (n=681), forming an intention-to-treat (ITT) sample. Patients of any age were eligible for study enrollment, along with those with invasive breast cancer of 0.5 to 5.0 cm and clinical N0 disease and had undergone either breast-conserving surgery or mastectomy. Patients were excluded from the study if they had multicentric disease, neoadjuvant systemic treatment, previous axillary treatment, or prior malignancy.

In patients treated with AxRT, treatment started <12 weeks after SNB, was delivered to levels I, II, III, and the medial supraclavicular node area, at a dose of 25x2 Gy or equivalent.

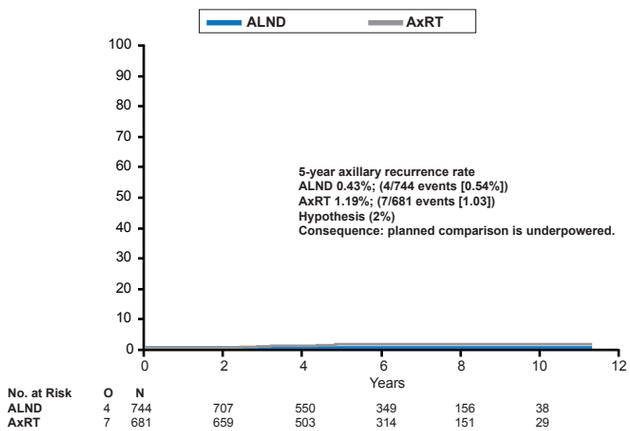
Baseline characteristics were comparable between the two treatment arms regarding age, characteristics of the tumor (size, grade, and type), as well as use of systemic chemotherapy. In both arms, ~82% of the patients underwent breast-conserving surgery and ~17% underwent mastectomy.

Based on an ITT analysis, the study found that at a median follow-up of 6.1 years the 5-year axillary recurrence rate was 0.54% (4/744 events) for the patients in the ALND arm and 1.03% (7/681 events) in the AxRT arm after a positive SNB (Figure 1). According to Prof. Rutgers, this axillary recurrence rate was far less than anticipated which resulted in the study being underpowered for the planned noninferiority comparison.

The study also looked at secondary endpoints of overall survival (OS) and disease-free survival (DFS), as well as safety (ie, lymphedema, shoulder function, and quality of life). No significant differences were found in the ITT group between ALND and AxRT in OS (92.9% vs 92.1%, respectively; HR, 1.17; 95% CI, 0.85 to 1.62; p=0.34), nor in DFS (HR, 1.17; 95% CI, 0.93 to 1.51; p=0.18).

However, the study did find significant differences in the incidence of lymphedema with patients treated with AxRT at half the risk of lymphedema compared with ALND. At 1 year, lymphedema-related symptoms were observed in 40.0% of ALND patients and 21.7% of AxRT patients (p<0.0001) and at 5 years in 28.0% and 13.6% of patients, respectively (p<0.0001; Figure 2).

Figure 1. Axillary Recurrence Rate



ALND=axillary lymph node dissection; AxRT=axillary radiotherapy.

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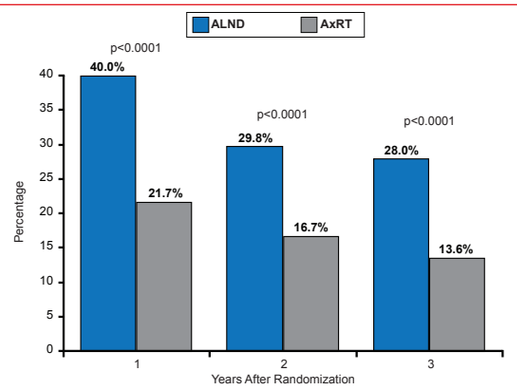
The other measures of safety were comparable between the two arms, with a nonsignificant trend toward more impairment in early shoulder movement after AxRT. No differences in quality of life were found, except for a trend in reduced swelling with AxRT and improved movement with ALND.

Figure 2. Lymphedema: Clinical Observation and/or Treatment



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Based on these results, Prof. Rutgers concluded that AxRT can be considered standard treatment for patients with a positive SNB, offering considerably less lymphedema and comparable locoregional breast cancer control with ALND.

Results From the LOGiC Trial

Written by Mary Beth Nierengarten

The addition of lapatinib (L) to capecitabine plus oxaliplatin (Cape/Ox) does not improve overall survival (OS) in patients with locally advanced or metastatic gastric, esophageal, or gastroesophageal junction cancer whose tumors have amplification of the HER2 gene, although an improvement in survival was seen in patients of Asian descent and those aged <60 years.

Results were presented from the Lapatinib Optimization Study in ErbB2 (HER2) Positive Gastric Cancer [LOGiC; NCT00680901; *J Clin Oncol* 2013 (suppl; abstr LBA4001)] by J. Randolph Hecht, MD, University of California, Los Angeles, Los Angeles, California, USA, which compared Cape/Ox alone or in combination with lapatinib (Cape/Ox/L) as first-line treatment for patients with advanced or metastatic HER2 -positive upper gastrointestinal tract cancers.

The Phase 3 trial included 545 patients enrolled between June 2008 and January 2012 from 186 centers in 22 countries. Eligible patients included those with locally advanced or metastatic histologically confirmed adenocarcinoma of the stomach, esophagus, or gastroesophageal junction; measurable or evaluable disease according to RECIST; HER2-positive disease, ≥18 years of age; ECOG PS <2, and no prior palliative chemotherapy.

HER2-positive disease was confirmed in a central laboratory in 487 of the 545 patients by fluorescence *in situ* hybridization. These patients were used as the primary efficacy population (PEP) to evaluate the primary outcome of OS.

Of these 487 patients, 249 were randomized to Cape/Ox/L (oxaliplatin 130 mg/m^2 Day 1, capecitabine 850 mg/m^2 BID Days 1 to 14, and lapatinib 1250 mg QD Days 1 to 21) and 238 to Cape/Ox plus placebo (Cape/Ox/P).

Based on this PEP, the study found no difference in OS between the two treatments with a median OS of 12.2 months and 10.5 months for Cape/Ox/L and Cape/Ox/P, respectively (HR, 0.91; 95% CI, 0.73 to 1.12; p=0.3492).

Under prespecified subgroup analyses, however, significant improvements in OS were seen in Asian patients compared with populations in the rest of the world (ROW) and those aged <60 years. Asian patients had an improvement in median OS from 10.9 months with Cape/Ox/P to 16.5 months with Cape/Ox/L (HR, 0.68; 95% CI, 0.48 to 0.96). The median OS in ROW populations improved from 9.1 for Cape/Ox/P to 10.0 months for Cape/Ox/L (HR, 1.04; 95% CI, 0.79 to 1.37).

Patients aged <60 years also had significantly improved OS compared with those aged ≥60 years, with an improvement in median OS from 9.0 months with Cape/Ox/P to 12.9 months with Cape/Ox/L (HR, 0.69; 95% CI, 0.51 to 0.94). In patients aged ≥60 years, the median OS was 10.9 months with Cape/Ox/P and 11.3 months with Cape/Ox/L (HR, 1.08; 95% CI, 0.81 to 1.45). .

Secondary outcomes of the study showed a progression-free survival of 6 months and 5.4 months for Cape/Ox/L and Cape/Ox/P, respectively, as well as overall response rates of 53% and 40%, respectively, with a median duration of response of 7.3 months and 5.6 months, respectively.

Toxicity was comparable between the two treatment arms, except that Cape/Ox/L was associated with increased overall diarrhea (58%) compared with Cape/Ox/P (29%), Grade 3 diarrhea (12% vs 3%), and skin rash (21% vs 7%).

Based on these results, no improvement in OS was seen with the addition of lapatinib to Cape/Ox except for in Asian patients and those aged <60 years; however, the addition of lapatinib did confer some improvement in progression-free survival and overall response rates.

Sequential Therapy Fails to Extend DFS in Gastric Cancer

Written by Emma Hitt, PhD

There was no significant difference in 3-year disease-free survival (DFS) in sequential treatment of paclitaxel (PAC) and the oral fluoropyrimidine tegafur-uracil (UFT) or paclitaxel and another fluoropyrimidine, S-1, in serosa-invading gastric cancer. Kazuhiro Yoshida, MD, PhD, Gifu University School of Medicine, Gifu, Japan, presented data from the Adjuvant Paclitaxel Followed by Oral Fluorinated Pyrimidines for Locally Advanced Gastric Cancer trial [SAMIT; Yoshida K et al. *J Clin Oncol* 2013 (suppl; abstr LBA4002)].

In Japan, the standard adjuvant chemotherapy for the treatment of gastric cancer was UFT [Oba K et al. *J Chemother* 2006], until results of the ACTS-GC trial resulted in the replacement of UFT by S-1 [Sakuramoto S et al. *N Engl J Med* 2007]. However, Prof. Yoshida pointed out that UFT and S-1 have not been evaluated head-to-head in a clinical trial. In addition, PAC has demonstrated efficacy in advanced gastric cancer. The hypothesis of the SAMIT trial was to demonstrate the superiority of PAC followed by UFT or S-1 compared with no PAC use and the noninferiority of UFT to S-1.

In the multicenter, Phase 3 trial, 1495 patients with serosa-invading gastric cancer were randomized with a 2x2 factorial design to receive 267 mg/m^2 of daily UFT alone Q4W for 12 cycles, 80 mg/m^2 of daily S-1 alone for