Evidence-Based AET in Women Before and After Menopause

Written by Mary Mosley

The current evidence supports at least 5 years of tamoxifen (TAM) or extended adjuvant endocrine therapy (AET) with TAM that is transitioned to an aromatase inhibitor (AI) or 5 years of AI (for postmenopausal women only), stated Nancy E. Davidson, MD, University of Pittsburgh Cancer Institute and UPMC CancerCenter, Pittsburgh, Pennsylvania. A meta-analysis demonstrated the benefit of TAM for 5 years, and more recent data have shown the benefit of extending the duration to 10 years. However, the results of 4 ongoing trials with AIs are awaited to determine if there is benefit of a longer duration (>5 years) of AI treatment, and results from studies of molecular tests may help predict late recurrence and determine who should receive extended AET.

The Early Breast Cancer Trialists' Collaborative Group meta-analysis [*Lancet*. 2011] showed that in estrogen receptor (ER)-positive breast cancer (BC), the rate of recurrence was 33% with 5 years of TAM vs 46.2% without TAM at 15 years and the rate of BC mortality was 23.9% and 33.1%, respectively. The 15-year gain for recurrence was 13.0% (log-rank $P < .00001$) and for BC mortality, 9.1% (log-rank $P < .00001$).

The Adjuvant Tamoxifen, Longer Against Shorter trial [ATLAS; Davies C et al. *Lancet*. 2013] in nearly 7000 women with ER-positive BC showed that extending TAM to 10 years, compared with 5 years, was associated with a lower rate of recurrence (21.4% vs 25.1%, respectively; log-rank $P = .002$) and BC mortality (12.2% vs 15.0%, respectively; log-rank $P = .01$). The benefit in ATLAS was similar in all patient subsets. The rates of recurrence and BC mortality were also reduced with 10 vs 5 years of TAM in the Adjuvant Tamoxifen: To Offer More trial [aTTom; Gray RG et al. *J Clin Oncol*. 2013 (suppl; abstr 5)]. Recurrence was 28% vs 32%, respectively (log-rank $P = .003$), and BC mortality was 34% vs 35% (log-rank $P = .2$). The combined outcomes in ATLAS and aTTom showed a 15% reduction in mortality and improvement in overall survival (OS) at 15 years with extended AET (Table 1).

Extended AET with letrozole (LET) vs no LET for 5 years in women who had completed 5 years of TAM therapy improved disease-free survival (DFS), with an even greater benefit in the women who were premenopausal at diagnosis and became postmenopausal after TAM therapy [Goss PE et al. *Ann Oncol*. 2013].

Clinical factors that can guide the decision to extend AET include a higher stage of disease at diagnosis, the absence of or limited toxicity in a given patient, the absence of life-threatening comorbidities, younger age, and patient preference. In the emerging field of molecular biomarkers for late recurrence, a number of molecular tests are being tested and reported.

The Breast Cancer Index was shown to predict DFS in years 0 to 5 and ≥5 years in 2 different patient cohorts [Zhang Y et al. *Clin Cancer Res*. 2013]. The PAM50 Risk of Recurrence Score was shown to predict late recurrence in women who had been recurrence-free at 5 years after diagnosis, with a 50% lower risk of late recurrence in the women who were low risk based on the assay, compared with those who were at moderate or high risk [Sestak I et al. *J Clin Oncol*. 2014].

OPTIMAL TREATMENT IN PREMENOPAUSAL WOMEN

Ovarian function suppression (OFS) in women with BC prior to menopause has been evaluated in clinical studies. The SOFT study [Francis PA et al. *N Engl J Med*. 2014] in 3066 premenopausal women showed that there was no benefit of OFS + TAM vs TAM alone for the primary outcome of DFS at the 5.6-year follow-up (86.6% vs 84.7%; $P = .10$). Freedom from BC was greater with OFS + TAM (88.4%; HR, 0.81; $P = .09$) and exemestane (EXE) + OFS (90.9%; HR, 0.64) compared with TAM alone (86.4%). At 6 years, DFS was greater in women who did vs those who did not have chemotherapy. In the planned analysis of women aged <35 years, more were BC-free at 5 years in the OFS + TAM or EXE + OFS group vs TAM alone (78.9%, 83.4%, and 67.7%, respectively).

The ECOG E3193 study in 345 women with ER-positive BC and small node–negative tumors showed that DFS was similar at 9.9 years with OFS + TAM and TAM alone (89.7% vs 87.9%; log-rank

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Table 1. Breast Cancer Mortality and Overall Survival in the ATLAS and aTTOm Studies

	HR (95% CI)	
Years	Breast Cancer Mortality	Overall Survival
5-9	0.97 (0.84 to 1.15)	0.99 (0.89 to 1.10)
10+	0.75 (0.65 to 0.86)[a]	0.84 (0.77 to 0.93)[a]
All	0.85 (0.77 to 0.94)[a]	0.91 (0.84 to 0.97)[a]

ATLAS, Adjuvant Tamoxifen, Longer Against Shorter trial; aTTOm, Adjuvant Tamoxifen: To Offer More trial.

[a]$P < .05$ favoring 10 years.

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Source: Gray et al. ASCO. 2013.

Table 2. Outcomes in the Joint Analysis of the TEXT and SOFT Trials

	Exemestane + OFS vs Tamoxifen + OFS	
Outcome	HR (95% CI)	*P*
Disease-free survival	0.72 (0.60 to 0.85)	.0002
Breast cancer–free interval	0.66 (0.55 to 0.80)	< .0001
Distant disease–free interval	0.78 (0.62 to 0.97)	.02
Overall survival	1.14 (0.86 to 1.51)	.37

Median follow-up of 5.7 years.

OFS, ovarian function suppression.

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Source: Pagani O et al. *N Engl J Med*. 2014.

$P = .62$) [Tevaarwerk AJ et al. *J Clin Oncol*. 2014]. OS was also similar at 97.6% and 95.2%, respectively (log-rank $P = .67$). Dr Davidson noted that this trial was terminated early and that it was not sufficiently powered for these outcomes. However, the quality-of-life measures were worse in the women taking OFS vs those who did not, although this difference seemed to be mitigated over time, and she questioned whether this may be due to the women naturally moving toward menopause or adjusting to the changes.

Regarding the role of AIs in women treated with OFS, the joint analysis of the TEXT and SOFT trials showed that EXE + OFS vs OFS + TAM improved DFS, the BC-free interval, and the disease-free interval, although OS was similar with both treatments (Table 2) [Pagani O et al. *N Engl J Med*. 2014]. In ER-positive BC, the ABCSG12 trial showed that there was no difference in DFS at 94 months with anastrozole vs TAM (HR, 1.13; 95% CI, 0.88 to 1.45; $P = .33$), but OS was worse with anastrozole vs TAM (HR, 1.63; 95% CI, 1.05 to 1.45; $P = .03$) [Gnant M et al. *Ann Oncol*. 2014].

Based on these data, Dr Davidson states that there are now several evidence-based options available for AET in premenopausal women. These include TAM for 5 to 10 years, TAM for 5 years with a switch to an AI for 5 years, OFS + TAM, or OFS + AI. In her view, for patients at low risk, TAM alone for 5 to 10 years is sufficient. For women at higher risk—including those who have had chemotherapy, are aged < 35 years, or have multiple positive nodes—OFS + TAM or OFS + AI can be considered. The optimal duration of OFS-based therapy is uncertain, and long-term follow-up to determine the toxicity and benefit is needed.

Identification of Drivers of Metastasis in BC

Written by Lynne Lederman

Upon receiving the AACR Outstanding Investigator Award for Breast Cancer Research, Yibin Kang, PhD, Princeton University, Princeton, New Jersey, USA, discussed his research into the origin of metastatic traits in breast cancer (BC). Because the majority of patients with BC will develop metastatic disease, identification of the mechanisms of metastasis will provide new therapeutic targets.

Key questions include, what genes give metastatic tumor cells the ability to escape from the intrinsic constraints of the epithelium and initiate new tumors in a distinct microenvironment, and when does this occur? One level of research involves examining the natural heterogeneity of cells in tumors (intratumoral heterogeneity) to identify metastasis genes.

Another level involves looking at intertumoral heterogeneity, important because tumors of the same type from different patients behave differently. One hypothesis for this is the cell-of-origin model, in which tumors develop from different normal cells: aggressive tumors develop from stemlike cells, which become more metastatic after oncogenic events. Other tumors, derived from fully differentiated cells, are less likely to metastasize.

Another hypothesis, the oncogenic driver mutation model, suggests that poor-prognosis tumors result from oncogenic driver events during tumor initiation. Tumors may come from the same cell of origin but, through different oncogenic driver events, give rise to tumor cells that have little chance of metastasizing; another oncogenic driver event may lead to formation of highly aggressive metastatic tumors.

One amplicon associated with poor prognosis in breast cancer was identified by a computational biology in 8q22 [Hu G et al. *Cancer Cell*. 2009]. This small region contains about a dozen genes, half of which are highly differentially