EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

30TH ANNUAL SAN ANTONIO
BREAST CANCER SYMPOSIUM (SABCS)

CONTROVERSIES IN
ADJUVANT ENDOCRINE THERAPY
FOR BREAST CANCER

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CONTROVERSIES IN ADJUVANT ENDOCRINE THERAPY FOR BREAST CANCER

Most women with hormone-responsive early breast cancer receive adjuvant endocrine therapy, either with tamoxifen or an aromatase inhibitor (AI). These hormonal treatments are very effective for preventing recurrences but the choice of therapy, as well as its timing and duration, remain controversial.

A symposium at the 30th Annual San Antonio Breast Cancer Symposium (SABCS) addressed these and other issues regarding the use of adjuvant endocrine therapy. The international faculty reviewed studies of tamoxifen and AIs, including letrozole, anastrozole and exemestane. They debated whether all patients with early breast cancer should receive upfront AI therapy or whether they should receive tamoxifen before switching to an AI. Also at issue was whether adjuvant endocrine therapy should be extended beyond five years in high-risk patients.

Accomplishments and uncertainties of adjuvant endocrine therapy

Kathleen I. Pritchard (Sunnybrook Odette Cancer Centre, University of Toronto, ON, Canada) reviewed the wide array of endocrine therapy options for women with breast cancer.

**Endocrine therapy options**

Tamoxifen currently is the standard adjuvant endocrine therapy after chemotherapy for premenopausal women with breast cancer. Studies have shown that ovarian suppression plus tamoxifen is a reasonable alternative to therapy with cyclophosphamide, methotrexate and fluorouracil for selected premenopausal women. Questions still remain about the role of ovarian suppression after chemotherapy and whether sequential or concurrent therapy is best. Some questions may be answered by the ongoing SOFT (BIG 2-02, IBCSG 24-02) trial in the USA and Europe. The trial has randomised premenopausal oestrogen receptor (ER)-positive women with or without prior chemotherapy who are not amenorrhoeic to receive five years of tamoxifen, ovarian function suppression (OFS) plus five years of tamoxifen or OFS plus five years of exemestane. “In my view, there is no standard role for an AI in the premenopausal setting,” commented Dr. Pritchard.

Endocrine therapy options for postmenopausal women include tamoxifen and AIs. Long-term data show that significant reduction of recurrences with five years of tamoxifen therapy is sustained for up to 15 years. A similar effect of tamoxifen has been observed on mortality. AIs have also demonstrated efficacy in a number of trials.

The ATAC trial randomised over 9,000 women to tamoxifen, anastrozole or a combination of the two. The third arm was discontinued because the combination had no efficacy or tolerability benefit compared with tamoxifen alone. The efficacy summary showed that hazard ratios (HR) for disease-free survival (DFS), time to recurrence (TTR), occurrence of contralateral breast cancer, time to distant recurrence and time to breast-cancer death were better with anastrozole versus tamoxifen. Overall survival (OS) was only marginally improved with anastrozole. Adverse events (AEs) occurring more frequently with tamoxifen versus anastrozole were hot flushes (40.9% vs. 35.7%; p < 0.0001), vaginal bleeding (10.2% vs. 5.4%; p < 0.0001), vaginal discharge (13.2% vs. 3.5%; p < 0.0001), endometrial cancer (0.8% vs. 0.2%; p = 0.02), ischaemic cerebrovascular events (2.8% vs. 2.0%; p = 0.03) and venous thromboembolic events (4.5% vs. 2.8%; p = 0.0004). Anastrozole versus tamoxifen was associated with more joint symptoms (35.6% vs. 29.4%; p < 0.0001) and fractures (11.0% vs. 7.7%; p < 0.0001). An updated analysis of fracture rates over time showed less of a difference between the two treatment groups at 5–7 years than earlier in the trial.

The BIG 1-98 study randomised 8,028 patients to tamoxifen (Arm A) or letrozole (Arm B), with a third arm switching from tamoxifen to letrozole after two years (Arm C) and a fourth arm switching from letrozole to tamoxifen after two
years (Arm D). The initial analysis compared results from patients receiving tamoxifen in Arms A and C (n = 4,007) versus those receiving letrozole in Arms B and D (n = 4,003), but did not include data from after the switch in Arms C and D (Figure 1) [6]. The results for all end points were superior with letrozole versus tamoxifen: DFS (HR = 0.81), OS (HR = 0.86), systemic DFS (HR = 0.83), DFS without second non-breast cancers (HR = 0.79), time to distant recurrence (HR = 0.73) and TTR (HR = 0.72).

Analysis by ER/progesterone receptor (PgR) status showed that DFS was better with letrozole versus tamoxifen in all subgroups: ER+/PgR+ (n = 5,055; HR = 0.84), ER+/PgR– (n = 1,631; HR = 0.83) and ER+/PgR unknown (n = 1,154; HR = 0.72). The AE profile was similar to that observed with anastrozole in the ATAC trial. Hot flushes, night sweats, vaginal bleeding and thromboembolic events occurred more frequently with tamoxifen. Hypercholesterolaemia and bone fractures were more common with letrozole. The bone fracture rates were 5.8% with letrozole versus 4.1% with tamoxifen (overall response: 1.44; p = 0.0006).

The Intergroup Exemestane Study (IES) randomised 4,742 women to tamoxifen (n = 2,380) or exemestane (n = 2,362) for 2–3 years after an initial 2–3 years on tamoxifen [2,3]. The 37.6-month updated results showed better DFS (HR = 0.73; p = 0.0001), breast-cancer-free survival (HR = 0.70; p = 0.00005), time to contralateral breast cancer (HR = 0.50; p = 0.04) and OS (HR = 0.83; p = 0.08) with exemestane compared with tamoxifen. OS was significantly better in the ER+ subgroup. The AE profile was similar as observed for other AIs versus tamoxifen.

**Extended adjuvant endocrine therapy**

In the NCIC CTG MA.17 trial, patients who received 4.5–6 years of tamoxifen were randomised to letrozole (n = 2,575) or placebo (n = 2,582) within three months of ending tamoxifen therapy. The patients were stratified according to receptor, lymph-node and adjuvant chemotherapy status. Node-positive patients in the letrozole group had significantly better DFS (HR = 0.61; 95% confidence interval [CI]: 0.45–0.84), distant DFS (HR = 0.53; 95% CI: 0.36–0.78) and OS (HR = 0.61; 95% CI: 0.38–0.98) than those receiving placebo. Node-negative patients receiving letrozole had significantly better DFS but not distant DFS or OS. The overall DFS benefit in the letrozole group versus the placebo group increased with treatment duration, with 93% DFS with letrozole versus 87% DFS with placebo at four years [8].

The incidence rates of hypercholesterolaemia and cardiovascular (CV) events were similar in the letrozole and placebo groups. New CV ischaemic events occurred in 6.8% of letrozole patients versus 6.7% of placebo patients (p = 0.654). New osteoporosis occurred in 6.9% of letrozole patients versus 7.1% of placebo patients (p = 0.042). Bone fractures occurred in 5.9% of letrozole patients versus 5.5% of placebo patients (p = 0.548).

After a median follow-up of 30 months, 1,655 patients in the MA.17 placebo arm began letrozole therapy while 613 remained on placebo or no therapy. The women who started letrozole 1–3 years after completing tamoxifen had reduced risk of breast cancer recurrence (69%, p < 0.0001), distant breast-cancer recurrence (72%, p = 0.002), death (47%, p = 0.05) and contralateral breast cancer (77%, p = 0.012) versus placebo. Dr. Pritchard concluded there is a benefit to initiating letrozole for up to five years after tamoxifen is discontinued. The MA.17R trial is re-randomising MA.17 patients and randomising others with similar treatment histories to either letrozole or placebo for an additional five years.

**Optimising endocrine therapy in newly diagnosed early breast cancer**

Dr. Pritchard concluded that the current trials on adjuvant therapy described lead to more questions on initiation, sequence and duration of AI and tamoxifen therapy. One issue that has not been settled is whether newly diagnosed patients should be started on tamoxifen or an AI. Alan Coates (School of Public Health, University of Sydney, Sydney, Australia) argued that all patients should initially be treated with an AI, while Harold J. Burstein (Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA) contended that patients should start with tamoxifen, then switch to an AI.

**Upfront therapy with an AI**

Prof. Coates reviewed the evidence for initiating endocrine therapy in breast-cancer patients with an AI. The 2007 results of the BIG 1-98 trial compared five years of letrozole (n = 2,463) versus tamoxifen (n = 2,459) [8] (Figure 1). The BIG 1-98 and ATAC trials had similar results in time to relapse with an AI versus tamoxifen. In BIG 1-98, the five-year relapse rate was 13.4% for tamoxifen patients versus 10.2% for letrozole patients (absolute difference 3.2%) [8]. In ATAC, the absolute difference in recurrence rates between tamoxifen and anastrozole patients was 3.7%, favouring anastrozole [8]. In both trials, a real difference between the tamoxifen and AI arm is not seen until during the second year of therapy when the relapse curves begin to diverge significantly. Smoothed hazard curves for relapse in both trials show a large gap during the first two years of treatment (Figure 2). “This is a concern because of the patients allocated to upfront tamoxifen who relapse during that time,” said Prof. Coates. In BIG 1-98, sites of early relapse include distant metastases (3.3% tamoxifen vs. 2.3% letrozole) to soft tissue, bone and viscera [8].

Subgroup analyses in BIG 1-98 show that patients with ER ≥ 10% have the best DFS while those with ER absent have the worst DFS. By central review of ER/PgR, all subgroups except ER absent and not evaluable did better with letrozole than tamoxifen [8]. New evidence on the interaction between Ki-67 (cell proliferation marker and predictive of response
to endocrine therapy) and early treatment suggests that the adverse effect of high Ki-67 is worsened by early treatment with tamoxifen [9].

Prof. Coates concluded that switching to an AI after 2–3 years of tamoxifen is superior to continuing on tamoxifen. On average, five years of upfront AI therapy is better than five years of tamoxifen. However, patients who have made it through the first 2–3 years of tamoxifen have a lower risk of recurrence. Direct comparison of upfront and switching strategies awaits data from the BIG 1-98 and TEAM trials.

**Tamoxifen followed by an AI**

Dr. Burstein reviewed data from crossover and extended adjuvant endocrine therapy trials. Several studies have demonstrated the superiority of AI-based therapy over five years of tamoxifen: ATAC and BIG 1-98 compared initial treatment with an AI versus tamoxifen; MA.17 and NSABP B-33 evaluated extended AI therapy after five years of tamoxifen; IES, ITA and ARNO/ABC SG studied sequential AI therapy after 2–3 years of tamoxifen. However, there are no data comparing each of these strategies head-to-head.

Dr. Burstein summarised the data from these trials in clinical terms. Initial AI therapy offers small advantages over tamoxifen. Later introduction of an AI offers safety and efficacy for longer duration of therapy. Later introduction of an AI may also facilitate a survival difference. Finally, later introduction of an AI might offer advantages with respect to cost and side effects. Modelling scenarios of AI trials might help define an optimal treatment program. Current modelling scenarios suggest that differences between treatment strategies will be small [10,11].

Dr. Burstein concluded that it still remains unclear whether a sequential treatment program might prove superior to an ‘all-AI’ program. Differences in upfront trials are small and might reflect pharmacogenomic variation. Additionally, differences might be negated by sequential treatment. The duration of therapy may actually prove to be more critical than the agent used. Current data only support five years of AI therapy; however, sequential treatment could extend the treatment duration. “Sequential treatment is a more-than-reasonable option for patients and is endorsed by the NCCN and St. Gallen guidelines,” said Dr. Burstein.

**Extending adjuvant endocrine therapy beyond five years**

James N. Ingle (Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA) presented data supporting his position that patients with high-risk ER+ early breast cancer need more than five years of adjuvant endocrine therapy. The Oxford overview of recurrence risk shows that after five years of tamoxifen therapy, node-negative patients have an annual risk of recurrence of 2.0% compared to 4.4% for high-risk node-negative patients [12].

In the MA.17 trial, extended adjuvant therapy with letrozole significantly reduced the risk of recurrence in node-positive and node-negative patients compared with those receiving placebo [4]. Similar reductions in risk of recurrence were observed in the NSABP B-33 trial of exemestane versus placebo and the ABCSG 6a trial of anastrozole versus no endocrine therapy. A retrospective review of the MA.17 trial indicates the value of letrozole as delayed extended adjuvant therapy in women with high residual risk who completed tamoxifen several years ago [13]. In this analysis, adjusted hazard ratios for letrozole versus placebo were 0.37 for DFS (p < 0.0001; Figure 3), 0.38 for distant DFS (p = 0.004), 0.30 for OS (p < 0.0001) and 0.18 for contralateral breast cancer (p < 0.004). The ongoing ANZ 0501/LATER trial is prospectively studying delayed extended adjuvant therapy with letrozole versus placebo in postmenopausal women with endocrine-responsive breast cancer.

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Cumulative hazard analyses from the MA.17 delayed extended therapy trial [14] and the IES trial [15] suggest that at least out to four years, longer duration of letrozole is associated with greater benefit. Dr. Ingle concluded that patients with early breast cancer have a residual risk of
surgery. The study design calls for continued adjuvant therapy with an AI when possible and discretionary chemotherapy/radiotherapy.

Matthew J.C. Ellis (Department of Medicine, Medical Oncology Section, Washington University, St. Louis, MO, USA) discussed the issues with extended endocrine therapy, including who benefits, what are the risks and what are the costs. While randomised trials, including EBCTCG [16] and MA.17, support the benefits of adjuvant endocrine therapy for reducing the risk of recurrence and mortality, these therapies are not cytotoxic and only promote dormancy of the disease.

According to Dr. Ellis, patients with ER+ breast cancer after five years of tamoxifen therapy fall into four groups: those who never had metastatic disease; those whose metastatic disease is cured by five years of tamoxifen; those whose metastatic disease is not cured by tamoxifen but is suppressed by AIs; and those whose disease is endocrine-therapy-resistant and who ultimately develop fatal metastatic disease.

Multigene profiles to identify prognostic signatures can help to identify patient subgroups with high risk of recurrence and death. Gene-expression profiles also can be used to predict distant metastasis of node-negative primary breast cancer. Other methods for predicting outcomes for patients with ER+ breast cancer include clinical response, standard pathologic staging, biomarkers and Ki-67 analysis. Results from these analyses can be used to determine risk groups for prediction of relapse-free survival with different therapies (Figure 4).

Finally, AI response signatures can be developed with randomised trials of AIs powered to analyse outcomes based on these patient subgroups. Dr. Ellis and his colleagues are conducting the ongoing trial ACOSOG Z1031, of postmenopausal women with ER+ clinical stage 2 and 3 breast cancer in which patients are randomised to neoadjuvant exemestane, letrozole or anastrozole prior to

![Figure 4](https://example.com/figure4.png)

**PREDICTION OF RELAPSE BY RISK SCORE**

(A) Risk score

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<th>Pathology, biomarkers and response factors</th>
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<tr>
<td>No</td>
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<tr>
<td>Tumour size: T1/2</td>
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<tr>
<td>T3/4</td>
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<tr>
<td>Node status: No</td>
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<tr>
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<tr>
<td>Ln Ki-67 level: 0–1</td>
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<tr>
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Points weighting depends on the hazard ratio

![Figure 4](https://example.com/figure4.png)

**Prediction of relapse**

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Relapse

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<th>15 (21%)</th>
<th>31 (55%)</th>
<th>5 (100%)</th>
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References


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