



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 27th San Antonio Breast Cancer Symposium (SABCS), December 8–11, 2004 and at the 46th Annual Meeting of the American Society of Hematology (ASH), December 4–7, 2004. Leading Canadian experts offer commentary and clinical interpretations.

Presentations from the 27th Annual San Antonio Breast Cancer Symposium

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Aromatase inhibitors in early breast cancer

ATAC ('ARIMIDEX', TAMOXIFEN, ALONE OR IN COMBINATION) COMPLETED TREATMENT ANALYSIS: ANASTROZOLE DEMONSTRATES SUPERIOR EFFICACY AND TOLERABILITY COMPARED WITH TAMOXIFEN.

Investigators: A. Howell et al.

The 'Arimidex', tamoxifen, alone or in combination (ATAC) trial evaluated the efficacy and safety of initial adjuvant treatment for 5 years with anastrozole and tamoxifen, both alone and in combination, in 9366 postmenopausal women with early breast cancer. The combination arm was discontinued early because it showed similar efficacy compared to treatment with tamoxifen alone. At this report of 68 months median followup, results continue to demonstrate superior efficacy of anastrozole vs tamoxifen, especially in patients with hormone receptor-positive (HR+) tumours, in measures of disease-free survival (DFS), time to recurrence and incidence of contralateral breast cancer (Table 1). The differences in benefit have increased over time. Overall,

TABLE 1. Hazard ratios for benefit of 5 years of therapy with anastrozole vs tamoxifen in 6186 postmenopausal women with early breast cancer

	All patients	HR+ patients
Disease-free survival	0.87 (P = 0.01)	0.83 (P = 0.005)
Time to recurrence	0.79 (P = 0.0005)	0.74 (P = 0.0002)
Contralateral breast cancer	0.58 (P = 0.01)	0.47 (P = 0.001)

women with HR+ tumours receiving anastrozole have a 3.3% absolute improvement in DFS compared to those receiving tamoxifen (hazard ratio [HR] 0.83, 95% CI 0.73–0.94, P = 0.005). There is still no difference in overall survival (OS), however, between the 2 groups (HR 0.97,

P = 0.7). Anastrozole has continued to show better safety and tolerability than tamoxifen, with significantly fewer withdrawals due to adverse events. Tamoxifen was associated with fewer fractures (7.7% with tamoxifen vs 11% with anastrozole, P < 0.0001) and less arthralgia than anastrozole.

BENEFITS OF SWITCHING POSTMENOPAUSAL WOMEN WITH HORMONE-SENSITIVE EARLY BREAST CANCER TO ANASTROZOLE AFTER 2 YEARS ADJUVANT TAMOXIFEN: COMBINED RESULTS FROM 3,123 WOMEN ENROLLED IN THE ABCSG TRIAL 8 AND THE ARNO 95 TRIAL.

Investigators: R. Jakesz et al.

This presentation combined results from 2 similar trials in postmenopausal women with HR+ early breast cancer randomized to 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrozole. A total of 3224 women were enrolled: 2262 from the Austrian

Breast Cancer Study Group (ABCSG) Trial 8 and 962 from the Arimidex-Nolvadex (ARNO) 95 trial. No adjuvant chemotherapy was given. At median followup of 28 months, the 3-year estimated event-free survival (EFS) was 95.8% for women who switched to anas-

trozole compared to 92.7% for those remaining on tamoxifen (HR 0.60, $P = 0.0009$). OS was the same for both groups but there was a significant difference in distant recurrence-free survival in favour of women who switched to anastrozole (HR 0.61, $P = 0.0067$).

THE INTERGROUP EXEMESTANE STUDY: A RANDOMIZED TRIAL IN POSTMENOPAUSAL PATIENTS WITH EARLY BREAST CANCER WHO REMAIN DISEASE-FREE AFTER TWO TO THREE YEARS OF TAMOXIFEN-UPDATED SURVIVAL ANALYSIS.

Investigators: R.C. Coombes et al.

The Intergroup Exemestane Study (IES) randomized 4742 postmenopausal women with early-stage breast cancer who were disease-free after 2–3 years of tamoxifen to switch to 2–3 years of exemestane or continue on tamoxifen for a total of 5 years adjuvant hormonal therapy. At median followup of 37.4 months, patients who switched to

exemestane had a 27% relative improvement in DFS (HR 0.73, 95% CI 0.62–0.86, $P = 0.0001$) and a reduction in incidence of contralateral breast cancer (HR 0.46, $P = 0.04$). The difference in OS was not statistically significant (HR 0.83, $P = 0.08$). Women taking exemestane experienced fewer thromboembolic and gynecologic events

but had more joint symptoms. There was a nonsignificant trend for increased osteoporosis in those switching to exemestane compared to those remaining on tamoxifen (8.3% vs 6.9%, respectively) and a small increased rate of myocardial infarction in the exemestane group (0.9% vs 0.4% if remaining on tamoxifen, $P = 0.02$).

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital and Assistant Professor, University of Manitoba, Winnipeg, MB.

Evidence for efficacy of aromatase inhibitors (AIs) in the adjuvant setting continues to accumulate. These 3 pivotal studies presented at the 2004 SABCs reinforce the concept that AIs reduce breast cancer recurrences in postmenopausal women with HR+ tumours. Of the 3 AIs studied in these trials, only anastrozole is currently approved by Health Canada for use in early-stage breast cancer. The ASCO Technology Assessment Panel¹ recently updated its guidelines and recommended adjuvant treatment with an AI as initial therapy or after prior treatment with tamoxifen. Invariably as data emerge, more questions arise.

Still to resolve

First and foremost, which strategy is best: upfront AI, tamoxifen followed by an AI at 2–3 years or tamoxifen followed by an AI at 5 years? Results of the Breast International Group (BIG) 1-98 adjuvant trial are awaited with interest. This multinational, Phase 3 trial randomized more than 8000 postmenopausal women to 5 years of tamoxifen, 5 years of letrozole, 2 years of letrozole followed by 3 years of tamoxifen, or 2 years of tamoxifen followed by 3 years


of letrozole. Until the results on switching are available from this trial it remains unknown which strategy is best. Meanwhile, Punglia and colleagues have developed a Markov model to simulate the clinical outcomes of hypothetical cohorts of postmenopausal women with HR+ invasive breast cancer.² Risk estimates were derived from results of the updated randomized clinical trials as well as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Oxford Overview data. The modelling estimates suggest that sequential adjuvant therapy with tamoxifen followed by an AI after 2.5 years yields improved 10-year DFS, compared to either drug alone or late crossover treatment. In contrast to this result, however, xenograft models using MCF-7 breast tumour cells suggest that initial AI is the superior strategy.³

A second question is whether certain subsets of patients might derive differential benefit from an AI compared to tamoxifen. Retrospective analysis of the ATAC efficacy data based on estrogen receptor (ER) and progesterone receptor (PR) status suggests that tamoxifen's efficacy is reduced in ER+ and PR– tumours: it showed HR 0.43

for time to recurrence for anastrozole vs tamoxifen if the tumour was ER+ and PR-, compared to HR 0.84 if it was ER+ and PR+.⁴ A similar trend was noted in the ABCSG/ARNO trials but not in the IES study. Several clinical trials, primarily of neoadjuvant treatment, have also shown that AIs are more effective than tamoxifen in tumours that overexpress HER2. In fact, the lack of a progesterone receptor may be a surrogate for increased signalling by HER2 and other growth factors, because one of the downstream effects of growth-factor signalling is a block in the transcription of the PR gene, resulting in a tumour that is ER+ and PR-.⁵ Undoubtedly, the future lies in the development of tailored therapy whereby biomarkers will predict responses to one treatment vs another — such studies are eagerly anticipated.

Questions also arise regarding the long-term toxicity of AIs. Thus far, short-term toxicities appear acceptable and more favourable overall than those of tamoxifen. Further followup of women in the current trials will hopefully address this concern; mature results from bone and lipid subprotocols included in many of these studies are awaited. The optimal duration of AI therapy is also unknown. NSABP researchers are proposing a trial to compare 5 years of letrozole vs placebo in women completing 5 years of adjuvant endocrine therapy that may have included an AI, and NCIC is planning a similar trial in women who received 5 years of adjuvant letrozole in the NCIC MA17 trial. Whether one AI is superior to another in terms of efficacy and safety remains to be seen: the current NCIC MA27 is comparing upfront adjuvant anastrozole to the steroidal AI exemestane. Importantly, no overall survival benefit has yet been conferred by the use of an AI instead of tamoxifen. Several adjuvant trials of tamoxifen vs placebo have shown, however, that DFS was a surrogate for eventual overall survival.⁶

Current recommendations

Until more data emerge, upfront AI or AI after tamoxifen are both acceptable therapies for postmenopausal women with early HR+ breast cancer. Patients whose tumours are ER+, PR+ and HER2- could be treated with tamoxifen, while others may do better with an initial AI. Any woman taking an AI should have regular bone mineral density monitoring and receive appropriate therapy for osteopenia and/or osteoporosis. Tamoxifen remains the standard endocrine treatment for premenopausal women; AIs in combination with ovarian suppression in this group are the subject of ongoing clinical trials. The decision for specific treatment needs to be individualized and ultimately depends on the patient's preference once she has been fully informed of the potential benefits and side effects. 

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Breast cancer chemotherapy

FIVE YEARS ANALYSIS OF THE PACS 01 TRIAL: 6 CYCLES OF FEC100 VS 3 CYCLES OF FEC100 FOLLOWED BY 3 CYCLES OF DOCETAXEL (D) FOR THE ADJUVANT TREATMENT OF NODE POSITIVE BREAST CANCER.

Investigators: H. Roché et al.

This trial evaluated the effect of adding docetaxel to FEC100 (5-fluorouracil 500 mg/m² + epirubicin 100 mg/m² + cyclophosphamide 500 mg/m²) in initial chemotherapy treatment of women with localized, resectable, node-positive, non-metastatic, unilateral breast cancer. The 1999 trial subjects were randomized to receive either 6 cycles of FEC100 or 3 cycles of FEC100 followed by 3 cycles

of docetaxel 100 mg/m² on Day 1, q 3 weeks. Other treatment included radiotherapy if surgery was conservative and tamoxifen for HR+ tumours. At a median of 60 months followup, patients in the group receiving docetaxel had significant improvement in DFS (73.2% vs 78.3%, P = 0.04). OS was also superior in the docetaxel arm (90.7% vs 86.7%, P = 0.05). Toxicity, including febrile

neutropenia, nail changes and edema were more common in the FEC100-docetaxel group, while more suboptimal cardiac ejection fractions were reported in the FEC100-only group. No toxic deaths were reported. The authors concluded that substituting docetaxel for FEC100 in the last 3 cycles of treatment improves outcomes in this group of patients.

A RANDOMIZED, MULTICENTER PHASE III TRIAL COMPARING REGIMENS OF DOXORUBICIN + CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL OR DOXORUBICIN + PACLITAXEL FOLLOWED BY WEEKLY PACLITAXEL AS ADJUVANT THERAPY FOR PATIENTS WITH HIGH RISK BREAST CANCER.

Investigators: D. Loesch et al.

This study compared DFS of patients with Stage 1–3 high-risk breast cancer given 2 regimens containing doxorubicin and paclitaxel. The 1830 subjects were randomized to receive either AC–T (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² q 3

weeks for 4 cycles, followed by paclitaxel 175 mg/m² q 3 weeks for 4 cycles) or AT–T (doxorubicin 50 mg/m² + paclitaxel 200 mg/m² q 3 weeks for 4 cycles, then paclitaxel 80 mg/m² weekly for 12 more weeks). At 3 years followup, patients in the AT–T group had better

DFS (88.4% vs 84.6%, P = 0.05) and OS (94.6% vs 91.8%, P = 0.005) compared to those taking AC–T. Grade 3–4 toxicities were similar in both groups, except for more neuropathy in those receiving AT–T. Rates of arthralgia, neutropenia and cardiotoxicity were the same.

CONCURRENT (CAFT) VERSUS SEQUENTIAL (CAF-T) CHEMOHORMONAL THERAPY (CYCLOPHOSPHAMIDE, DOXORUBICIN, 5-FLUOROURACIL, TAMOXIFEN) VERSUS T ALONE FOR POSTMENOPAUSAL, NODE-POSITIVE, ESTROGEN (ER) AND/OR PROGESTERONE (PGR) RECEPTOR-POSITIVE BREAST CANCER: MATURE OUTCOMES AND NEW BIOLOGIC CORRELATES ON PHASE III INTERGROUP TRIAL 0100 (SWOG-8814).

Investigators: K. Albain et al.

This update of the SWOG-8814 (INT-0100) presented 10-year survival data and results of multivariate analysis of biomarkers, in an effort to determine which breast cancer patients can be expected to benefit from chemotherapy added to hormonal therapy, as well as optimal timing of treatments. Subjects were 1477 postmenopausal women with node-positive, HR+ disease, who were treated following surgery with either tamoxifen alone, chemohormonal therapy with CAF (cyclophosphamide 100 mg/m² PO x 14 days; doxorubicin 30 mg/m² IV and 5-fluorouracil 500 mg/m² IV, on Day 1 and Day 8 every 29 days for 6 cycles) with **concurrent** tamoxifen (20 mg/day PO for 5 years beginning on CAF Day 1) or CAF with **sequential** tamoxifen (20 mg/day for 5 years starting after the 6th cycle of CAF). Results showed

TABLE 2. Percent of patients surviving at 10-year followup of SWOG 8814/INT-0100

	Tamoxifen only	CAF with concurrent tamoxifen	CAF with sequential tamoxifen
Disease-free survival	48%	53%	60%
Overall survival	60%	62%	68%

a survival benefit from chemotherapy (Table 2). Overall, the adjusted hazard ratio (HR) for benefit of CAF with tamoxifen — concurrently or sequentially — alone was 1.31 for DFS (P = 0.001) and 1.21 for OS (P = 0.02).

Analysis of biomarkers showed worse prognosis for patients with HER2+ tumours (P = 0.005), high mitotic grade (P = 0.0002) and p53 positivity (P = 0.022) and favourable prognosis for women with tumours

that were both HER2– and PR+ (P = 0.003). Tumour factors predictive of CAF chemotherapy benefit included low or intermediate ER score (≤ 6), (HR 1.44), HER2 positivity, (HR 1.54), nuclear grade 3 (HR 1.48) and p53 positivity (HR 1.56). Groups showing no benefit from the chemotherapy were those with both HER2– tumours and 1–3 positive nodes, those with high ER scores (7–8) and those with nuclear grade 1–2.

COMMENTARY: Susan Dent, MD, FRCPC, Medical Oncologist, The Ottawa Hospital Regional Cancer Centre and Assistant Professor of Medicine, University of Ottawa.

The treatment of early-stage breast cancer has evolved over the years from the traditional CMF regimen (cyclophosphamide 600 mg/m² IV on Day 1; methotrexate 40 mg/m² IV on Day 1; and 5-fluorouracil 600 mg/m²

IV on Day 1, repeated at 21-day intervals for at least 8 courses), popularized by Bonadonna, to anthracycline regimens for women with node-positive and high-risk, node-negative breast cancer. The results of NSABP-B28

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and CALGB 9344 established a benefit of adding 4 cycles of paclitaxel to 4 cycles of doxorubicin + cyclophosphamide (AC) chemotherapy in treatment of women with early-stage breast cancer. BCIRG 001 combined docetaxel and AC (TAC) and demonstrated an improvement in DFS of 75% vs 68% ($P = 0.001$) in women with node-positive disease over a regimen of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC).

Evolving role of taxanes


PACS 01 was designed to determine whether 3 cycles of FEC100 chemotherapy followed by 3 cycles of docetaxel improved DFS compared to the standard 6 cycles of FEC100 in women with operable, node-positive breast cancer. The improved DFS and OS shown by this study, presented at the recent SABCS by Henri Roché, adds further support to the important role of taxanes in the treatment of women with early-stage breast cancer. Several questions have been raised by the adjuvant taxane studies. Which taxane should we be using in women with early-stage breast cancer: paclitaxel or docetaxel? Should taxanes be administered concurrently or sequentially with an anthracycline? How many cycles of a taxane are optimal alone or in combination? Several large ongoing studies may help to address these questions. NSABP-B30 randomizes women with node-positive breast cancer to AC x 4 followed by docetaxel x 4 vs AT x 4 vs TAC x 4. PACS 04, which has completed accrual, randomized women with node-positive breast cancer to FEC100 x 6 vs epirubicin + docetaxel x 6. Other studies are investigating the role of taxanes in non-anthracycline combinations. Results are awaited from a study conducted by US Oncology of docetaxel + cyclophosphamide x 4 vs AC x 4. These trials will help to further define how taxanes can be optimally used in women with early-stage disease.

The study presented by David Loesch and colleagues was designed to determine whether administering paclitaxel concurrently with adriamycin, followed by weekly paclitaxel, improved DFS compared to AC followed by q 3-weekly taxol. Patients with Stage 1–3 breast cancer were randomized to receive AC x 4 followed by paclitaxel x 4 (AC–T) vs AT x 4 followed by weekly paclitaxel x 12 (AT–T). This first analysis at 3 years suggests an improvement in DFS in the patients receiving AT–T compared to AC–T (88.4% vs 84.6%, $P = 0.05$) and improvement in OS (94.6% AT–T vs 91.8%, $P = 0.005$), although statistical significance was not reached. The omission of cyclophosphamide in the AT–T arm had no impact on DFS and OS. Sensory neuropathy was more pronounced in patients who received weekly paclitaxel (AT–T). The tendency towards improved efficacy shown by this study when paclitaxel was administered weekly following AT must be weighed against the requirement for more frequent chemotherapy visits and the risk of detrimental impact on quality of life posed by increased sensory neuropathy. Longer followup is needed to determine whether the trends seen in this study will become statistically significant.

Chemotherapy in lower-risk breast cancer

SWOG-8814 (INT-0100) was a large, randomized study designed to determine whether adding chemotherapy (CAF) to hormonal therapy (tamoxifen) would improve DFS and OS in postmenopausal women with early-stage, node-positive breast cancer. The updated 10-year analysis presented by Kathy Albain continues to demonstrate the benefit of chemotherapy added to hormonal therapy in this population, with a HR of 1.31 ($P = 0.001$) for DFS favouring CAF + tamoxifen vs tamoxifen alone. Further, DFS was superior when tamoxifen was administered following chemotherapy vs concurrently (HR 1.20, $P = 0.03$). OS was also superior in women receiving CAF + tamoxifen vs tamoxifen alone (HR 1.21, $P = 0.02$) although the timing of tamoxifen was not significant (HR 1.12) for OS. This long-term followup data adds further strength to the established benefit of chemotherapy in postmenopausal women with node-positive breast cancer.

The benefit derived from systemic chemotherapy in early-stage breast cancer is dependent on the risk of disease recurrence: the higher the risk the greater the potential benefit from systemic therapy. The INT-0100 study analyzed several biomarkers retrospectively and compared them to clinical outcome. Patients with HER2 positivity, p53 positivity; nuclear grade 3 and low or intermediate ER score experienced more benefit from CAF chemotherapy. Negative predictors of DFS included more than 4 positive lymph nodes, p53 positivity and progesterone receptor negativity. Patients with high estrogen receptor positivity did not benefit significantly from CAF chemotherapy; there was no added benefit of CAF over tamoxifen alone in women with 1–3 positive nodes and HER2– tumours. Similarly, a retrospective analysis of 3 randomized CALGB chemotherapy trials (CALGB 8541, 9344 and 9741) presented by Berry concluded that patients with node-positive, ER– tumours have benefitted more significantly from advances in systemic therapy over the last 20 years compared to those individuals with ER+ tumours.¹

This study highlights the need for further prospective studies to identify factors that will predict which individuals will experience the greatest benefit from chemotherapy. A 70-gene prognostic signature has been developed² to do this and is currently undergoing external validation. 

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