Developments in Adjuvant Therapy for Early-Stage Breast Cancer: Endocrine Therapy for Premenopausal Women and Small HER2-PositiveTumors

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Abstract

Development of targeted therapies against the estrogen receptor (ER) and human epidermal growth factor receptor 2-*neu* (HER2) have changed the landscape of treatment for women with early-stage breast cancer. For premenopausal women with ER-positive, early-stage breast cancer, the escalation of hormone therapy—either by the duration of therapy or the addition of ovarian suppression—has spurred debate as to the ideal adjuvant endocrine regimen. On the other hand, powerful therapies against HER2-positive early breast cancer have resulted in significant improvements in patient outcomes, and in patients with small HER-positive tumors the question of de-escalation of therapy has led to studies investigating less toxic regimens. Whether by escalation or de-escalation of therapy, individualizing patient therapy using evidence-based data and weighing the possible benefits of treatment versus treatment toxicity is crucial. Future studies focusing on specific populations and novel targeted therapies will lead to improved patient outcomes.

Key words: breast cancer, adjuvant endocrine therapy, premenopausal endocrine receptor-positive breast cancer, small HER2-positive breast cancer, adjuvant anti-HER2 therapy

Introduction

First reported in the 1970s, adjuvant chemotherapy for breast cancer can decrease the risk of distant metastasis and improve survival in patients initially diagnosed with early-stage disease.[1] While initial adjuvant studies included only the use of nontargeted cytotoxic chemotherapy, a deeper understanding of breast cancer biology has led to several agents designed to target specific molecular aberrancies.

Antiestrogen therapies were the first targeted therapies developed in any cancer; however, not all breast cancers responded to these treatments.[2] It was not until the development of a powerful predictive biomarker, the estrogen receptor (ER), that studies could be designed to test optimal treatment strategy in the adjuvant setting.[3]

Human epidermal growth factor receptor 2-*neu* (HER2), first described in the 1980s, is amplified or overexpressed in 25% to 30% of breast cancers, and its expression was found to predict inferior outcomes. Through translational science, a monoclonal antibody, trastuzumab, was developed to target HER2, and in studies it eventually showed significant clinical benefit when combined with chemotherapy, first in the metastatic setting, and then as adjuvant therapy for early-stage breast cancer.[4,5]

These significant breakthroughs in adjuvant therapy for specific subtypes of breast cancer have led to improvements in relapse rates; however, we are still learning how to balance optimal treatment with treatment-related toxicity.[6] This review will focus on advances in optimizing adjuvant endocrine therapy for women with early-stage, ER-positive breast cancer, and on research into developing less toxic regimens for women with small HER-positive breast cancer.

Optimizing Endocrine Therapy for Premenopausal Women

The selective ER modulator, tamoxifen, has long been a key therapy for women with ER-positive breast cancer. The standard of care for many years has been 5 years of adjuvant tamoxifen for women with early-stage, ER-positive breast cancer. Although aromatase inhibitor (AI) therapy improves recurrence rates in postmenopausal women compared with tamoxifen, these drugs are not effective when administered in premenopausal women; therefore, tamoxifen has remained the treatment of choice for premenopausal women.[7,8] An accurate assessment of menopausal status is key in determining the correct endocrine regimen for these patients, and involves menstrual history and evaluation of estradiol, luteinizing hormone, and follicle-stimulating hormone. The effects of 5 years of adjuvant tamoxifen are powerful: at 15 years, it decreases the risk of recurrence from 46.1% to 33.0% (log-rank 2p <.00001) and decreases breast cancer mortality from 32.7% to 23.6% (log-rank 2p <.00001).[3] Five studies have evaluated extended-tamoxifen regimens (**Table**), and while initially results were inconclusive, the larger Adjuvant Tamoxifen Treatment Offers More? (aTTom) and Adjuvant Tamoxifen: Lon-

TABLE. Extended Adjuvant Tamoxifen Therapy

Study	Number of Patients	Menopausal Status (pre-, peri-, post-)	Hormone Receptors	Lymph Node Status	Follow-up	Extended TAM Beneficial?	
						DFS and BC Mortality	OS
Scottish TAM Trial	169 control 173 TAM (indefinite)	85 pre- 257 post-	0-19[a] 75 >20[a] 132 Not done 135	N+: 78 N0: 240 Unknown: 25	15 Years	**No** (DFS; HR, 1.36; 95% CI, 0.95-1.95; *P* = .12); trend favoring control	**No** (OS; HR, 1.32; 95 % CI, 0.93-1.88; *P* = .12); trend favoring control
NSABP B-14	570 control 583 TAM	300 pre-/peri- 847 post-	ER/PR+	N0: all	12 years	**No**, worse (82% control vs 78% TAM DFS; *P* = .03)	**No** (94% control vs 91% TAM OS; *P* = .08)
ECOG (E4181+E5181)	93 control 100 TAM	107 pre- 87 post-	140 ER+ 53 ER-	N1: 118 >N2: 75	10 years	**Yes**, in ER+ (overall cohort, 73% control vs 85% TAM DFS; *P* = .1) (ER+ only, 67% control vs 84% TAM DFS; *P* = .014)	**No** (overall cohort, 89% control vs 86% TAM OS; *P* = .52) (ER+ only, 89% control vs 86% TAM OS; *P* = .52)
aTTom	6953 total 2755 ER+	NR	2755 ER+	NR	15 years	**Yes** (24% control vs 21% TAM BC mortality; *P* = .06 overall; RR, 0.88; 95% CI, 0.77-1.01; *P* = .05)	**No** (35% control vs 34% TAM overall mortality; *P* = .2; RR, 0.94; 95% CI, 0.86-1.03; *P* = .2)
ATLAS	12894 total 6846 ER+ 3418 control 3428 TAM	630 pre- 6079 post-	6846 ER+	N0: 3677 N1-3: 1831 ≥N4: 1070 Unknown: 268	15 years	**Yes** (12% control vs 10% TAM BC mortality; *P* = .01)	**Yes** (21% control vs 19% TAM overall mortality; *P* = .01)

[a]fmol mg-1 cytosol protein.
BC indicates breast cancer; DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; NR, not reported; OS, overall survival; RR, response rate; TAM, tamoxifen.

ger Against Shorter (ATLAS) studies concluded that extending therapy for a total of 10 years is beneficial.[9-12]

While we await the published and peer-reviewed aTTom data, it is important to understand certain limitations and considerations when interpreting the ATLAS trial. While statistically significant, the benefit of 5 additional years is modest, with recurrence improving by 3.7% and breast cancer mortality improving by 2.8% at 15 years. Of the analyzed cohort, nearly 90% of patients were postmenopausal, in whom tamoxifen is not a modern standard of care. How 10 years of tamoxifen compares with the 5 years of standard-of-care AI therapy in postmenopausal women is unknown. Additionally, the risk of pulmonary

embolism (PE) is higher with 10 years of tamoxifen compared with 5 years, although the risk decreased after cessation of therapy, and PE-related mortality was not different (event-rate ratio [ERR], 1.21; 95% CI, 0.48-3.04; *P* = .69). Both ATLAS and aTTom demonstrated an increased risk of endometrial cancer, a risk that persisted even after cessation of therapy. In addition, while endometrial cancer–related death was not different between arms in ATLAS (ERR, 1.49; 95% CI, 0.71-3.13; *P* = .29), aTTom did show an increased risk of endometrial-related death in the 10-year arm (ERR, 2.2; 95% CI, 1.09-3.09; *P* = .02), although the incidence was low (1.1% in the 10-year arm, 0.6% in the 5-year arm). For women who are pre- or perimenopausal who become menopausal during the first 5 years of tamoxifen therapy, extended therapy with an AI improves outcomes; however, how 5 additional years of endocrine therapy with an AI versus tamoxifen compares is not known.[13]

At the 2014 Annual American Society of Clinical Oncology (ASCO) meeting, the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) joint analysis was presented, and it demonstrated that the combination of exemestane plus ovarian suppression therapy (OST) compared with tamoxifen plus OST was associated with improved 5-year disease-free survival (DFS, 91.1% vs 87.3%, respectively; hazard ratio [HR], 0.72; 95% CI, 0.60-0.86; *P* = .0002).[14] These data unfortunately did not have a comparator arm without OST. It was not until the SOFT study was presented and published a few months later that we learned that adding OST to tamoxifen did not improve DFS at 5 years (*P* = .1). Secondary objectives investigating freedom from breast cancer rates demonstrated that the combination of the AI exemestane plus OST improved rates compared with 5 years of single-agent tamoxifen. Subset analysis of patients younger than 35 years, the majority of whom were treated with chemotherapy, suggested that compared with 5 years of tamoxifen, adding OST is associated with a decreased risk of relapse, particularly if OST is combined with exemestane rather than tamoxifen.[15] It is important to understand that this subset analysis was a small fraction of the overall cohort (350/3066 women), and median follow-up was relatively short (only 67 months), which limits the interpretation of these results. Furthermore, this study does not inform treatment after 5 years of adjuvant hormone therapy. Importantly, the addition of OST was associated with more side effects, including those associated with estrogen deprivation, particularly in terms of cardiovascular risk factors and bone health. The long-term effects on cardiovascular and bone health remain unknown.

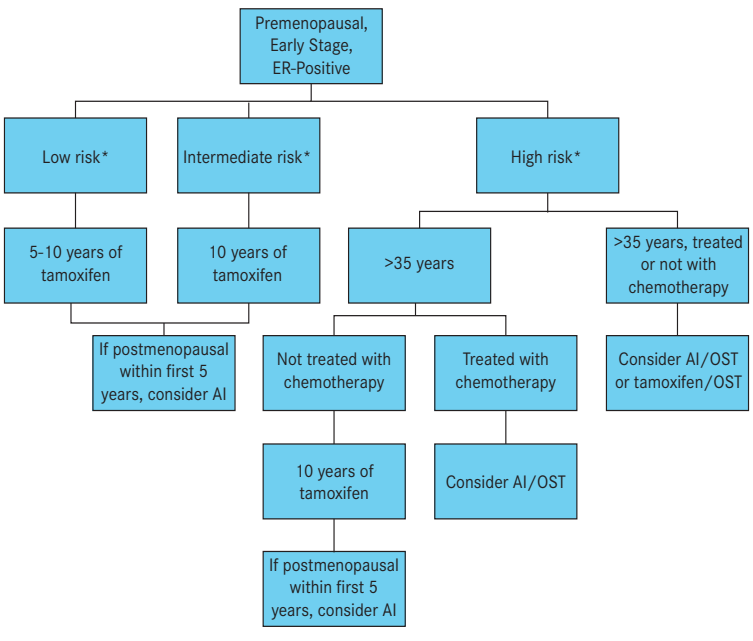
These data suggest that 5 years of tamoxifen alone may not be an optimal duration of therapy for most women; however, the decision to treat with 5 versus 10 years of adjuvant tamoxifen or to add OST must be individualized, and risks and benefits of therapy discussed with patients. A proposed algorithm is shown in the **Figure**.

Small HER2-Positive Breast Cancer

The adjuvant trastuzumab studies that demonstrated improved survival generally included larger and/or node-positive tumors, leaving the optimal treatment for smaller HER2-positive, node-negative tumors unclear.[16] While node-negative tumors smaller than 1 centimeter (T1a or T1b) have good outcomes irrespective of subtype without chemotherapy, HER2-positive tumors tend to have inferior outcomes compared with their HER2-negative counterparts.[17-21] While effective in higher-risk tumors, standard, adjuvant trastuzumab-based regimens have significant toxicity, and such aggressive therapy is likely not needed in all small HER2-positive breast cancers. Therefore, defining an optimal regimen for this clinical subset of tumors is critical from both efficacy and toxicity standpoints.

Data supporting the addition of trastuzumab to chemother-

FIGURE. Approach to Adjuvant Endocrine Therapy



*Consider chemotherapy.
AI indicates aromatase inhibitor; ER, estrogen receptor; OST, ovarian suppression therapy.

apy in small HER2-positive tumors was presented at the 2014 ASCO meeting. This patient-level meta-analysis included patients with HER2-positive tumors that were less than 2 centimeters, and included 5 randomized trials including the HERceptin Adjuvant (HERA), North Central Cancer Treatment Group (NCCTG) N9831, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, French Federation of Cancer Centers Sarcoma Group Protocole Adjuvant dans le Cancer du Sien (FNCLCC-PACS) 04, and Finland Herceptin (FinHER) trials. At 8 years of follow-up, the addition of trastuzumab in both in ER-positive and ER-negative cohorts was associated with improved recurrence rates (24.3% vs 17.3%, *P* <.001 in ER-positive; 33.4% vs 24%, *P* <.0001 in ER-negative) and overall survival (11.6% vs 7.8%, *P* = .005 in ER-positive; 21.2% vs 12.4%, *P* = .0001 in ER-negative).[22] Although many patients in this analysis had node-positive disease, these results support the importance of trastuzumab in small HER2-positive tumors. The question remains whether chemotherapy can be de-intensified, thereby reducing toxicity, without compromising outcomes.

A recent single-arm study investigated the combination of adjuvant paclitaxel with trastuzumab in HER2-positive tumors less than 3 centimeters with no lymph node macrometastasis. After a median follow-up of 4 years, the 3-year rate of survival, free from invasive disease, was 98.7% (95% CI, 97.6-99.8). This regimen was very well tolerated, with only 3.2% (95% CI, 1.7-5.4) of patients developing grade 3 neuropathy and 0.5% (95% CI, 0.1-1.8) with symptomatic congestive heart failure.[23] Although this study is limited by its single-arm design and short follow-up, it provides data demonstrating that patients treated with this regimen do very well. These data are not definitive, and providers should carefully weigh efficacy and toxicities of treatment when prescribing adjuvant therapy for patients with small HER2-positive breast cancer.

Future Directions

Optimizing adjuvant therapies for patients with early-stage breast cancer has resulted in improved outcomes and cure rates. While extended and intensified endocrine therapies may modestly decrease risk of recurrence, the risk persists for many patients.[24] Understanding endocrine resistance and other mechanisms of late recurrence, through drug and biomarker development, will be crucial in improving adjuvant treatment.

Newer anti-HER2 therapies are now being investigated in the adjuvant setting for patients with small HER2-positive breast cancer. The T-DM1 vs Paclitaxel/Trastuzumab for Breast (ATEMPT) trial (NCT01853748) is investigating ado-trastuzumab emtansine (T-DM1), a drug that demonstrates significant activity in the metastatic setting, in comparison with paclitaxel and trastuzumab.[25] The increasing investigation and use of targeted therapy in the adjuvant setting, which has a more limited toxicity profile than cytotoxic chemotherapy, will hopefully bring about more effective and less toxic therapies for patients. Additionally, patient population may be key in determining the need for the addition of chemotherapy to anti-HER2 therapy. The Evaluation of Trastuzumab Without Chemotherapy as a Postoperative Adjuvant Therapy in HER2 Positive Elderly Breast Cancer Patients (RESPECT) trial (NCT01104935) is investigating survival endpoints in elderly patients with early HER2-positive breast cancer treated with trastuzumab versus trastuzumab plus chemotherapy.

Conclusions

These newer studies presented here must be interpreted carefully, and treatment decisions must involve individual counseling of the pros and cons of therapy efficacy and toxicity based on available data. A continued understanding of tumor biology and mechanisms of resistance and recurrence will help researchers develop the next generation of adjuvant treatment regimens for patients with early-stage breast cancer.

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REFERENCES

1. Bonadonna G, Brusamolino E, Valagussa P,et l. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med.* 1976;294(8):405-410.

2. Jordan VC. Tamoxifen (ICI46,474) as a targeted therapy to treat and prevent breast cancer. *Br J Pharmacol.* 2006;147(suppl 1):S269-S276.

3. Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* 2011;378(9793):771-784.

4. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792.

5. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365(14):1273-1283.

6. Cossetti RJ, Tyldesley SK, Speers CH, et al. Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. *J Clin Oncol.* 2015;33(1):65-73.

7. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endo-

crine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol.* 2014;32(21):2255-2269.
8. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol.* 2010;28(3):509-518.
9. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *N Natl Cancer Inst.* 2001;93(6):456-462.
10. Fisher B, Dignam J, Bryant J, Wolmark N. 5 versus more than 5 years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst.* 2001;93(9):684-690.
11. Tormey DC, Gray R, Falkson HC; Eastern Cooperative Oncology Group. Postchemotherapy adjuvant tamoxifen therapy beyond 5 years in patients with lymph node-positive breast cancer. *J Natl Cancer Inst.* 1996;88(24):1828-1833.
12. Gray RG, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol.* 2013;31(suppl; abstr 5).
13. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97(17):1262-1271.
14. Pagani O, Regan M, Walley B, et al. Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): joint analysis of IBCSG TEXT and SOFT trials. *J Clin Oncol.* 2014;32(suppl 5s; abstr LBA1).
15. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2015;372(5):436-446.
16. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev.* 2012;4:CD006243.
17. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. *J Clin Oncol.* 2014;32(20):2142-2150.
18. Chavez-MacGregor M, Gonzalez-Angulo AM. HER2-neu positivity in patients with small and node-negative breast cancer (pT1a,b,N0,M0): a high risk group? *Clin Adv Hematol Oncol.* 2009;7(9):591-598.
19. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol.* 2009;27(34):5700-5706.
20. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol.* 2009;27(34):5693-5699.
21. Fehrenbacher L, Capra AM, Quesenberry CP, Jr, et al. Distant invasive breast cancer recurrence risk in human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: a cohort from an integrated health care delivery system. *J Clin Oncol.* 2014;32(20):2151-2158.
22. O'Sullivan CC, Bradbury I, De Azambuja E, et al. Efficacy of adjuvant trastuzumab (T) compared with no T for patients (pts) with HER2-positive breast cancer and tumors ≤ 2cm: a meta-analysis of the randomized trastuzumab trials. *J Clin Oncol.* 2014;32(suppl 5s; abstr 508).
23. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med.* 2015;372(2):134-141.
24. Brewster AM, Hortobagyi GN, Broglio KR, et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst.* 2008;100(16):1179-1183.
25. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.