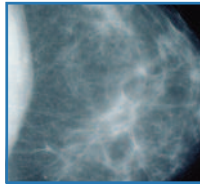


Update

IN GYNECOLOGIC ONCOLOGY



Current Issues in Breast Cancer for the Gynecologist

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Hereditary Breast and Ovarian Cancer Screening

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The current recommendations for the screening of women at risk for hereditary breast cancer are based on lower-level evidence, but despite the absence of data from randomized controlled trials, there is uniform consensus that these recommendations are appropriate.

Due to the early age of onset seen in hereditary breast cancer, screening should be initiated considerably earlier than standard recommendations. Training in breast self-examination (BSE) with regular monthly practice should begin at age 18, and semiannual clinical breast examinations should begin by age 25. Patients should begin having annual mammograms and breast MRI screening at age 25 or on an individualized timetable based on the earliest age of cancer onset in family members, typically 5–10 years earlier than the earliest age of first diagnosis of breast cancer in the family.

The sensitivity of mammography for detecting breast cancer in BRCA mutation carriers appears to be lower than in other high-risk women owing to higher breast density or differences in morphologic features. In an analysis of women with deleterious BRCA mutations followed at MSKCC who opted for breast cancer screening, one half of the incident breast cancers diagnosed over a 2-year period in women were not detected by annual mammography. Most of these interval cancers were detected by BSE [1].

Women with BRCA mutations may be more susceptible to radiation-induced carcinogenesis because of the role of BRCA proteins in DNA repair. The institution of frequent mammography at a young age has raised concerns about a possible increase in the risk of developing breast cancer in these women, although the available data are conflicting.

In young women (particularly those with dense breasts) with an inherited risk of breast cancer, surveillance with screening MRI may be especially advantageous. Retrospective and prospective studies have found MRI to be more sensitive but less specific than mammography for the detection of invasive cancers in high-risk women.

In these studies, screening MRI detected up to twice as many invasive tumors as did mammography; however, it was also associated with a higher false-positive rate, leading to additional examinations and unneeded biopsies. In addition, it is not yet known if the enhanced detection rates afforded by the more expensive MRI studies have an influence on survival in populations of high-risk women.

It is important to emphasize that MRI is a useful supplement to, but not a replacement for, mammography. In a United Kingdom prospective cohort study of 639 women aged 35–49 with a strong family history of breast cancer or a high likelihood of BRCA1, BRCA2, or p53 mutations, MRI was more sensitive than mammography (77% vs. 40%), but less specific (81% vs.

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Update on Adjuvant Hormone Therapy

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Introduction

Recently, a highly publicized study reported a sharp decline in the annual age-adjusted incidence of breast cancer among women in the United States, particularly among women 50–69 years of age with hormone receptor-positive disease. This trend was ascribed primarily to the response to early reports of the Women's Health Initiative, wherein the deleterious effects of hormone replacement therapy (HRT) were reported and resulted in a subsequent decline in post-menopausal HRT prescriptions. Because the majority of breast cancers are hormone receptor-positive, hormone therapies remain a cornerstone of adjuvant therapy for these patients.

Hormone Therapy Overview

Hormone therapies commonly used in the management of early-stage breast cancer include medications that induce ovarian suppression such as goserelin acetate, selective estrogen receptor modulators such as tamoxifen, and aromatase inhibitors (AIs). Tamoxifen competitively binds to estrogen receptors in breast and other tissue targets. However, it also exerts partial agonist activity in estrogen-responsive sites. Contemporary third-generation AIs are classified as either steroidal or non-steroidal. AIs block estrogen synthesis by inhibiting aromatase, the enzyme responsible for the peripheral conversion of androstenedione and testosterone to estrone and estradiol. The steroidal AI exemestane exerts its effects by irreversibly inhibiting aromatase, while the non-steroidal AIs anastrozole and letrozole bind reversibly to aromatase. However, AIs are inadequate for overcoming the quantity of ovarian-generated estrogen in premenopausal women and may potentiate ovarian follicular stimulation in this population. Thus, the use of AIs, outside of a clinical trial, is restricted to post-menopausal women.

Adjuvant Hormone Therapy

Pre- or Peri-Menopausal

Adjuvant hormone therapy for

pre- or peri-menopausal women with hormone receptor-positive breast cancer consists of tamoxifen or ovarian suppression [1]. The efficacy of tamoxifen or an AI in combination with medical or surgical ovarian suppression is uncertain. The Suppression of Ovarian Function Trial (SOFT) is currently randomizing pre-menopausal women with early-stage, hormone receptor-positive breast cancer to tamoxifen, tamoxifen with ovarian suppression, or an AI (exemestane) with ovarian suppression. Currently, the recommended duration of tamoxifen therapy is 5 years and is associated with a 41% reduction in the relative risk of recurrence and a 34% reduction in mortality for hormone receptor-positive women [1]. However, the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, a multicenter, international study has randomized 11,500 women completing approximately 5 years of tamoxifen to a further 5 years of tamoxifen or cessation of therapy. In a recent report, a trend toward recurrence and breast cancer-specific mortality ben-

efit was reported for the 10-year tamoxifen cohort [2].

Post-Menopausal

Tamoxifen was the cornerstone of hormone therapy for post-menopausal women with early-stage, hormone receptor-positive disease until the recent reporting of several adjuvant AI trials. Adjuvant AIs have been compared with conventional tamoxifen in a number of study designs including sequential strategies after 2–3 years of tamoxifen, upfront strategies, and extended strategies beyond 5 years of tamoxifen (Figure 1). Although each of these strategies has demonstrated significant benefits, the superiority of any given strategy has not yet been determined (Table 1). NCIC MA.17, which randomized women completing 5 years of tamoxifen to 5 years of letrozole or placebo, demonstrated significant disease-free survival benefits, and in the node-positive population, overall survival benefits with extended letrozole therapy [3]. In a study of exemestane after 2–3 years of tamoxifen

among 4742 estrogen receptor-positive postmenopausal women, the “early switch” was associated with a 24% reduction in the risk of recurrence [4]. In the Arimidex, Tamoxifen Alone or in Combination (ATAC) study, more than 9000 post-menopausal women with hormone receptor-positive or unknown breast cancer were randomized to tamoxifen alone, anastrozole alone, or the combination of tamoxifen and anastrozole for 5 years. After 100 months of follow-up, an absolute 2.8% recurrence benefit after 5 years in favor of the anastrozole-alone arm compared with the tamoxifen-alone arm was reported [5]. However, this absolute difference increased to 4.8% after 9 years, making ATAC the first adjuvant AI study to demonstrate a significant

long-term carry-over effect after completion of therapy. No overall survival advantage has yet been observed.

Common AI-related toxicities are listed in Table 2. In a recent report by the ATAC investigators, the risk of fracture was significantly increased with anastrozole compared with tamoxifen during the 5 years of treatment; however, fracture rates subsequently declined and appeared to converge in years 5 through 10 [5].

One putative approach to preventing AI-induced declines in bone mineral density (BMD) is

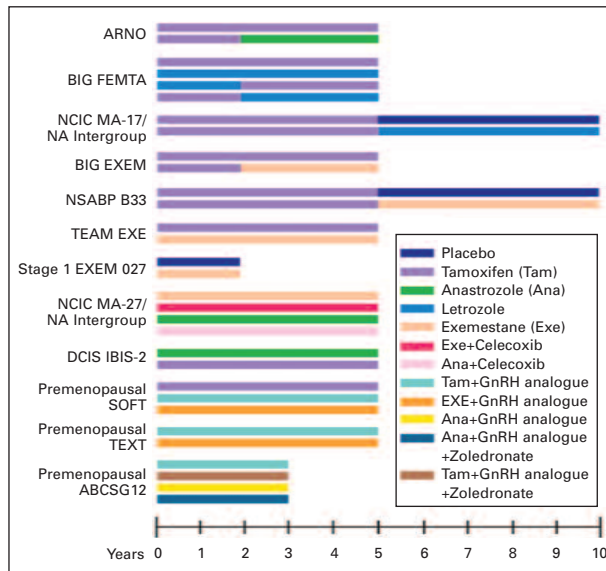


Figure 1. Selected adjuvant aromatase inhibitor trials among women with early-stage, hormone receptor-positive breast cancer

Strategy	RCT	Pts	Update	Median F/U (mo)	AI	Efficacy (HR, P)	
						DFS/EFS	OS
Up-front	ATAC ⁶	6241	SABCS 2007	100	ANA	0.85 (.003)	0.97 (.7)
“Early” Switch	BIG 1-98	4922	JCO 2007	51	LET	0.82 (.07)	0.91 (>.05)
	ITA	448	Ann Oncol 2006	64	ANA	0.57 (.005)	0.56 (.1)
	IES5	4742	Lancet 2007	56	EXE	0.76 (.0001)	0.85 (.08)
	ABCSG/ARNO	3224	Lancet 2005	28	ANA	0.60 (.0009)	NR
“Extended” Switch	NCIC MA.17 ⁴	5157	JNCI 2005	30	LET	0.58 (.001)	0.82 (.3)
	ABCSG 6a	856	ASCO 2005	60	ANA	0.64 (.047)	NR
	NSABP B-33	1598	SABCS 2006	30	EXE	0.68 (.07)	1.20 (.64)

Table 1. Selected adjuvant aromatase inhibitor (AI) trial results for post-menopausal women with early-stage, hormone receptor-positive breast cancer
 RCT, randomized controlled trial; HR, hazard ratio; DFS, disease-free survival; EFS, event-free survival; OS, overall survival

Adjuvant Chemotherapy for Breast Cancer

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The most important prognostic factor in survival or recurrence after potentially curative surgery for breast cancer is the number of involved axillary lymph nodes. Systemic chemotherapy remains a critical component in the eradication of occult micrometastatic disease in the adjuvant setting. The 2000 Early Breast Cancer Trialists' Collaborative Group overview of polychemotherapy in breast cancer demonstrated that anthracycline-based regimens are superior to non-anthracycline-based therapies in terms of disease-free survival (DFS) and overall survival (OS) [1].

There are several adjuvant chemotherapy regimens that are commonly used in the United States. These include doxorubicin + cyclophosphamide (AC), AC followed by paclitaxel (AC → P), AC followed by docetaxel (AC → D), docetaxel + AC (TAC), 5-fluorouracil + doxorubicin + cyclophosphamide (FAC/CAF), 5-fluorouracil + epirubicin + cyclophosphamide (FEC/CEF), and FEC → P or FEC → D. Since anthracycline-based regimens overall are superior to non-anthracycline-based therapies, cyclophosphamide + methotrexate + 5-fluorouracil (CMF) has generally been reserved for node-negative breast cancer treatment [1].

The taxanes, paclitaxel and docetaxel, were well established in metastatic breast cancer and lack cross-resistance with anthracyclines, and were therefore quickly deemed worthwhile for evaluation in the adjuvant setting. A large meta-analysis showed that the addition of a taxane to an anthracycline-based regimen improves DFS and OS in high-risk patients regardless of age, menopausal status, number of nodes involved, hormone-receptor status,

and type of taxane [2]. There are several effective anthracycline-taxane combinations traditionally studied in patients with node-positive disease. The regimen TAC is superior to an old standard FAC. The popular treatment AC → P has replaced AC. Furthermore, AC → P given every 2 weeks (dose-dense) has shown superiority over the every-third-week schedule, demonstrated in CALGB 9741 [3]. ECOG 1199 compared 4 schedules of a taxane after AC (every 3 weeks or weekly P versus every 3 weeks or weekly D). This study demonstrated the superiority of weekly paclitaxel, and docetaxel every third week. Thus, AC → weekly P and AC → D are also available options. In Europe, both FEC → D and FEC → P have replaced FEC [2]. Thus, it is the addition of a taxane to an anthracycline (AC → P, AC → D, TAC, FEC → P, FEC → D), rather than an anthracycline-based treatment alone, that has demonstrated improved outcomes. Although these regimens were studied

chemotherapy and/or hormonal therapy in risk reduction. Furthermore, genomic analysis has been introduced in combination with conventional assessments to identify patients for specific treatments. As we develop more sophisticated ways to characterize tumors by using techniques such as gene-array analysis, we are reminded that breast cancer is a heterogeneous disease.

A prospective trial, TailorRx, uses the OncoType Dx® score to determine treatment decisions in patients with small, hormone receptor-positive tumors. Patients with recurrence scores < 11 do not receive chemotherapy, those at intermediate risk are randomized to receive or not receive chemotherapy, and those with recurrence scores > 25 receive chemotherapy (Figure 1). All patients receive hormonal therapy. With the availability of targeted agents, trastuzumab has now demonstrated a clear benefit when combined with chemotherapy in the adjuvant treatment of patients with high-risk, HER2-positive breast cancer. With the ongoing implementation of well-designed clinical trials incorporating new therapeutic agents in a rational way, we hope to continue to see a trend toward improved DFS and OS in patients presenting with early-stage breast cancer. ■

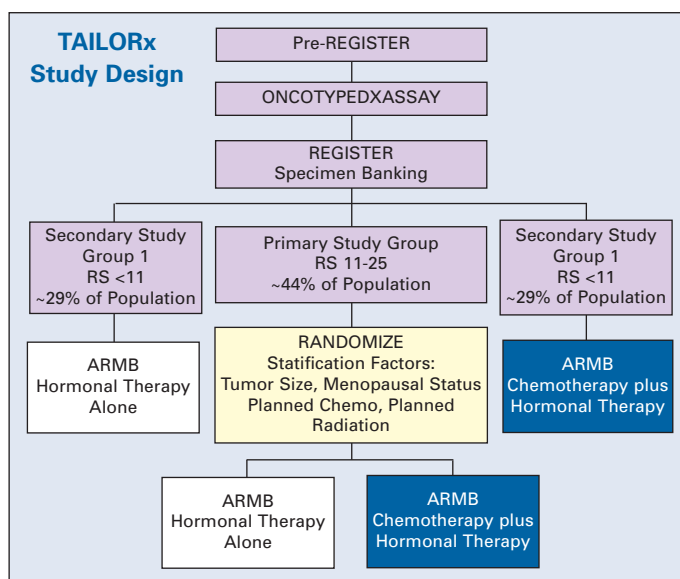


Figure 1. TAILORx trial for node-negative patients

in node-positive patients, they are certainly appropriate to use in treating high-risk, node-negative patients (i.e., triple-negative disease).

Chemotherapy is not for all patients, however, especially those in the node-negative group. The “Adjuvant! Online” program developed by Ravdin et al [4] is used to estimate the patient’s risk of recurrence based on age, co-morbidities, tumor size and grade, hormone-receptor status, and nodal status, and to estimate the contribution of

combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;26:44-53.

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STAFF NOTES

- The Gynecology Disease Management Team would like to congratulate **Douglas A. Levine, MD**, for his recent receipt of an NCI contract for work to be done in association with the ovarian cancer portion of The Cancer Genome Atlas Project.
- The Gynecology Disease Management Team would like to congratulate **Karin Shih, MD**, on being awarded the ACOG/Ortho Women's Health Academic Training Fellowship.

- The Gynecology Disease Management would like to congratulate Pelvic Reconstruction Fellow **Heather Einstein, MD**, on being awarded the Society of Gynecologic Oncologists President's Award for her study, **Decrease in Perioperative Venous Thromboembolism with Use of Dual Prophylaxis in Patients with Gynecologic Cancer**. This award is given to the best all-around clinical abstract, paper, and/or presentation at the SGO Annual Meeting.

93%) for detecting breast cancer. When both modalities were used, sensitivity increased to 94% at the expense of a lower specificity of 77% [2].

The 2007 guidelines from the American Cancer Society and the National Comprehensive Cancer Network (NCCN) recommend annual breast MRI screening in addition to mammography for women with a lifetime risk of breast cancer greater than approximately 20–25%, including those with a strong family

history of breast or ovarian cancer. The recommendation covered women with BRCA mutations, a first-degree relative of a BRCA carrier (untested), Li-Fraumeni syndrome or first-degree relative with that condition, and Cowden syndrome [3, 4]. ■

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Update on Adjuvant Hormone Therapy

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bisphosphonate co-administration. The Z-FAST study, for example, randomized 602 post-menopausal women with early-stage breast cancer on adjuvant letrozole to upfront or delayed zoledronic acid (ZA) [6]. Women in the delayed arm received ZA only, with a marked decline in BMD or a symptomatic or asymptomatic fracture at annual follow-up. Significant BMD improvements were observed in both study arms. At 36 months, however, there was no difference in symptomatic or asymptomatic fracture rates between the two arms. Although the absence of a significant difference may reflect the study's modest sample size, this finding supports the strategy of delaying bone-targeted therapies until symptoms arise. This is particularly relevant given the small but potentially devastating risk of osteonecrosis of the jaw with bisphosphonate administration.

Conclusions

Tamoxifen remains an important component of adjuvant treatment for pre-/perimenopausal women with hormone receptor-positive breast cancer. In the post-menopausal population, multiple large randomized clinical trials have consistently demonstrated significant benefits with adjuvant AIs. However, the optimal strategy for incorporating AIs into the

Tamoxifen	Aromatase inhibitors
Hot flashes	Hot flashes
Vaginal bleeding	Vaginal dryness
Vaginal discharge	Arthralgias/myalgias
Endometrial cancer	Arthritis
Ischemic cerebrovascular events	Bone mineral density declines/fractures
Venous thromboembolic events	Diarrhea

Table 2. Common adverse effects of tamoxifen versus aromatase inhibitors

adjuvant treatment paradigm has not yet been determined and will continue to evolve. ■

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