Guideline Summary

American Society of Clinical Oncology Clinical Practice Guideline Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer

By Harold J. Burstein, MD, PhD, Jennifer J. Griggs, MD, MPH, Ann A. Prestrud, MPH, and Sarah Temin, MSPH

Dana-Farber Cancer Institute, Boston, MA; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; American Society of Clinical Oncology, Alexandria, VA

Introduction

Journal of Clinical Oncology recently published the ASCO clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer.[1] ASCO initially published its first technology assessment of the use of aromatase inhibitors (AIs) in the adjuvant setting in 2002; it was last updated in 2004. ASCO's Update Committee on Aromatase Inhibitors reconvened in May 2009 to update this guideline.

In its current update, the Committee considered various adjuvant endocrine strategies, including tamoxifen, AIs, or both in sequence; the appropriate duration of AI therapy; the long-term adverse effects of AI therapy; identification of subpopulations that might derive selective benefit from various treatment strategies; efficacy of AIs among women who are premenopausal; and similarities and differences among commercially available third-generation AIs. In ASCO's systematic review of the literature, the primary outcomes of interest were disease-free survival, overall survival, and time to contralateral breast cancer. Secondary outcomes included adverse events and quality of life.

Note: The guideline refers to three strategies used in clinical trials (Table 1):

Primary: patients who have not had prior endocrine (tamoxifen or AI) therapy.

Sequential: patients who have completed 2 to 3 years of tamoxifen or an AI.

Extended: patients who have completed 5 years of adjuvant tamoxifen.

Clinical Questions and Recommendations

1a. What Adjuvant Endocrine Treatments Should Be Offered to Postmenopausal Women With Hormone Receptor–Positive Breast Cancer?

Recommendation 1a. The Update Committee recommends, on the basis of data from randomized controlled trials, that most postmenopausal women consider taking an AI during the course of adjuvant treatment to lower recurrence risk, either as primary therapy or after 2 to 3 years of tamoxifen, strategies that have yielded equivalent outcomes in prospective studies. Duration of AI therapy should not exceed 5 years.

Comment. In absolute terms, the reduction in risk of recurrence associated with AI-based therapy compared with tamoxifen is modest, typically amounting to less than 5% through multiple years of follow-up. However, studies consistently report improvements in disease-free survival. Inclusion of an AI is recommended because locoregional recurrence, contralateral breast cancer, and earlier distant metastatic recurrence are clinically important to patients.

1b. What Is the Appropriate Duration of Adjuvant Endocrine Therapy?

Recommendation 1b. Therapy with an AI should not extend beyond 5 years in either the primary or extended adjuvant settings, outside of the clinical trials setting. In the sequential setting, the Update Committee recommends, on the basis of available evidence from randomized controlled trials, that patients receive an AI after 2 or 3 years of tamoxifen, for a total of 5 years of adjuvant endocrine therapy. The Update Committee recommends that patients who are initially treated with an AI but discontinue treatment before 5 years have elapsed consider taking tamoxifen, for a total of 5 years of adjuvant endocrine therapy.

Comment. Data from randomized controlled trials demonstrate that women who receive primary AI therapy should be treated for a total of 5 years. Women who initially receive tamoxifen and switch to an AI should also receive at least 5 total years of endocrine therapy; no available data evaluate durations of AI therapy in excess of 5 years among patients receiving sequential therapy. Women who receive extended adjuvant therapy should receive 8 to 10 years of total endocrine treatment, 5 years of tamoxifen followed by 3 to 5 years of an AI. The recommended limit on AI treatment is 5 years total, across all strategies.

1c. If Tamoxifen Is Administered First, How Long Should It Be Continued Before the Switch to an AI?

Recommendation 1c. The Update Committee recommends that, on the basis of available evidence from randomized con-

Table 1. Comparison of Adjuvant Endocrine Treatment Strategies

Treatment Scenario	Options	Recommended Duration of Tamoxifen	Recommended Duration of AI	Recommended Total Duration of Endocrine Therapy
If patient is commencing adjuvant endocrine therapy (patient may have just finished surgery or chemotherapy) (P/S)	AI monotherapy Tamoxifen → AI	N/A 2-3 years	5 years 2-3 years	5 years 5 years
If patient is in middle of tamoxifen (S)	Tamoxifen → AI	2-3 years	2-3 years	5 years
If patient is in middle of AI (S)	AI → Tamoxifen	2-3 years (administer second)	2-3 years (administer first)	5 years
If patient is finishing 5 years of tamoxifen (E)	Tamoxifen → AI	5 years	3-5 years	8-10 years
If patient is pre- or perimenopausal	Tamoxifen	5 years	NR	5 years

Abbreviations: AI, aromatase inhibitor; N/A, not applicable; P, primary; S, sequential; E, extended; NR, not recommended.

trolled trials, patients who initially receive tamoxifen as adjuvant therapy may be offered an AI after 2 to 3 years (sequential) or after 5 years (extended) of therapy. The time to switch from an AI to tamoxifen (or the converse) that maximally improves outcomes is not known from available direct evidence. The recommendation to switch at 2 to 3 years is based on data from sequential trials that used this strategy. Switching at 5 years is also a strategy supported by the extended adjuvant randomized trials.

Comment. Data comparing switching at 2 to 3 or 5 years are not available. In most of the clinical trials, participants switched to an AI after 2 or 3 years of tamoxifen. Findings suggest that incorporating an AI into the adjuvant treatment regimen during the first 5 years yields clinical improvements compared with 5 years of tamoxifen monotherapy, justifying consideration of a switch between years 2 and 3.

For postmenopausal women who complete 5 years of tamoxifen, extended therapy with an AI for 3 to 5 years is recommended. For a woman who is newly diagnosed or one who has taken tamoxifen for 2 to 5 years, the best time to switch drugs is currently unknown. Consequently, the Update Committee recommends considering a switch from tamoxifen to an AI after 2 or 3 years of tamoxifen therapy, on the basis of existing data. Clinicians and patients may reasonably opt to consider extended therapy after reviewing individualized considerations.

2. Are There Specific Patient Populations That Derive Differing Degrees of Benefit From an AI Compared With Tamoxifen?

Recommendation 2. Direct evidence from randomized trials does not identify a specific marker or clinical subset that predicted which adjuvant treatment strategy—tamoxifen, AI monotherapy, or sequential therapy—would maximally improve outcomes for a given patient. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The Update Committee recommends against using CYP2D6 genotype to select adjuvant endocrine therapy. The Committee encouraged caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine; see Table 11 in the full guideline for a complete list of inhibitors) and tamoxifen because of the known drug-drug interactions.

Comment. The adjuvant endocrine therapy recommendations in this update are for all women, irrespective of any specific clinical subset or prognostic marker. AI therapy has not been evaluated in men, thus the continued recommendation that men with breast cancer receive adjuvant tamoxifen.

Data suggest that variability in tamoxifen metabolism affects the likelihood of cancer recurrence in patients treated with tamoxifen. Factors that contribute to this variability include concurrent use of other drugs that inhibit the CYP2D6 isoenzyme and pharmacogenetic variation (polymorphisms) in CYP2D6 alleles. It is not yet known whether these variations account for differences in outcomes among patients treated with tamoxifen.

Available data on CYP2D6 pharmacogenetics are insufficient to recommend testing as a tool to determine an adjuvant endocrine strategy. Patients who clearly benefit from known CYP2D6 inhibitors might consider avoiding tamoxifen because of potential pharmacologic interactions. Conversely, patients who receive tamoxifen may prefer to avoid concurrent use of known CYP2D6 inhibitors if suitable alternatives are available.

3. What Are the Toxicities and Risks of Adjuvant Endocrine Therapy?

Recommendation 3. The Update Committee recommends that clinicians consider adverse effect profiles, patient preferences, and pre-existing conditions when recommending an adjuvant endocrine strategy for postmenopausal women. Clinicians should discuss adverse effect profiles when presenting available treatment options to patients. The Update Committee suggests that clinicians consider recommending that patients change treatment if adverse effects are intolerable or patients are persistently noncompliant with therapy.

Comment. Accumulated experience with and data on AIs have delineated the adverse effect profile for this drug class. These agents are generally well tolerated but are associated with specific toxicities, including effects on bone, cardiovascular, and gynecologic health (Table 2). Tables in the full guideline provide a compilation of adverse effects noted in the systematic review.

AIs and tamoxifen have distinct adverse effect profiles that are relevant to individualizing therapy for patients. Neither has

Table 2. Common or Serious Adverse Events Comparison

Adverse Event	Tamoxifen	AI
Hypercholesterolemia		√
Hypertension (HT) and CVD		Yes (hypertension slight and < 1% difference in serious CVD incidence)
VTE	√	
Loss of BMD		√
Bone fracture		√
Osteoporosis		√
Musculoskeletal/ arthralgia		√
Gynecologic	√ (uterine cancer, benign endometrial pathology, hysterectomy, vaginal discharge)	
Hot flashes	√	
Endometrial cancer*	√	

NOTE: Check marks indicate higher risk of the adverse effect.
Abbreviations: AI, aromatase inhibitor; BMD, bone mineral density; CVD, cardiovascular disease; VTE, venous thromboembolic event.
* Low incidence.

been found to be less toxic or better tolerated than the other. Importantly, late effects of AI therapy remain to be fully characterized.

No direct data indicate that changing drug agents or classes alleviates treatment-related symptoms. However, on the basis of limited clinical experience, the Update Committee favored switching drugs if needed to promote compliance with therapy among patients whose treatment-related symptoms are intolerable.

4. Are AIs Effective Adjuvant Therapy for Women Who Are Premenopausal at the Time of Diagnosis?

Recommendation 4. The Update Committee recommends that women who are pre- or perimenopausal at the time of breast cancer diagnosis be treated with 5 years of tamoxifen. In addition, the Update Committee recommends that clinicians use caution in evaluating the menopausal status of patients who were pre- or perimenopausal at diagnosis. Unequivocal determination of menopausal status may be challenging to prove. Even among women who have not experienced menses for > 1 year, laboratory testing is inadequate as patients may recover ovarian function. This particularly applies to those patients who experience chemotherapy- or tamoxifen-induced amenorrhea.

Comment. AIs are contraindicated in women who are premenopausal. All the trials, except for one, excluded women who were premenopausal.

At present, no data suggest that an AI-based therapy is superior to tamoxifen-based therapy in women who are premenopausal and are treated with ovarian suppression. Because of tamoxifen equivalence with AI therapy in that setting and the occasional failure to achieve menopausal status with ovarian-suppression treatments, the Update Committee strongly recommends tamoxifen as primary adjuvant endocrine therapy for all women who are pre- or perimenopausal and women with treatment-induced amenorrhea.

No prospective data are available to guide therapy for women who are pre- or perimenopausal at the time of initial diagnosis and then become unequivocally postmenopausal during tamoxifen treatment. The Committee suggests it is appropriate to consider sequential or extended adjuvant endocrine therapy with AIs for such patients.

5. Can the Third-Generation AIs Be Used Interchangeably?

Recommendation 5. In the absence of direct comparisons, the Update Committee interprets available data as suggesting that benefits of AI therapy represent a "class effect." Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date. In the clinical opinion of the Committee (rather than direct evidence from randomized trials), postmenopausal patients who are intolerant of one AI but are still candidates for adjuvant endocrine therapy may be advised to consider tamoxifen or a different AI.

Comment. No data from head-to-head comparisons between the AIs are available. However, data from randomized, prospective trials for the three commercially available third-generation AIs for each of the adjuvant treatment strategies (primary, sequential, extended) have been published. The Update Committee suggests that the AIs are qualitatively similar in efficacy and tolerability.

Toxicity reports have not suggested obvious clinical advantages of one AI over another with respect to compliance, constitutional or menopausal symptoms, bone health, cardiovascular disease, or quality of life.

Additional Information

Limitations

The Update Committee noted the following limitations among the clinical trials identified by the systematic review: timing of randomization—patient populations in sequential, extended, and primary therapy trials may differ from one another; short follow-up time (the longest median follow-up data available is 8 years but is shorter for most studies); median time to event yet to be achieved; modest number of events, particularly within subgroup analyses; and different definitions of study end points.

Patient-Doctor Communication

Rates of nonpersistence (early discontinuation of medications) in women who start tamoxifen are as high as 30% at 3 years after filling a first prescription. Other data indicate that persistence is no better with AIs. Patient beliefs about the benefits and risks of medications are associated with improved adherence and persistence; thus, discussing and addressing such beliefs is warranted. Information support for patients about anticipated adverse effects and their management may improve persistence rates.

Clinicians should discuss realistic, quantitative risks of cancer recurrence and death, as well as benefits from cancer therapy, as part of the adjuvant treatment decision-making process. Clinicians should alert patients to common adverse effects of therapy and serially inquire about treatment-related toxicities, adherence with therapy, and factors that may affect adherence and persistence. A Decision Aid that accompanies this guideline may assist in this discussion.

Health Disparities

Representation of people of color in clinical trials of adjuvant endocrine therapy is low. Only small samples of people of color were included in persistence studies, largely preventing an examination of correlates and mechanisms of optimal therapy in ethnic minorities.

Methods

The literature search for this update was facilitated through the systematic review by Cancer Care Ontario that examined available literature through May 2007. The ASCO Update Committee reviewed that and additional searches of MEDLINE, preMEDLINE, the Cochrane Collaboration Library, and ASCO and San Antonio Breast Cancer Symposium abstracts and conducted a systematic review of the literature published between May 2007 and February 2009.

Additional Resources

Journal of Clinical Oncology published a full-text abridged version of this guideline on July 12, 2010. The full-text unabridged version is available at www.asco.org/guidelines/endocrinebreast, along with a slide set and other resources. Patient information is available at www.cancer.net/whattoknow.

Authors

The ASCO Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women with Hormone Receptor–Positive Breast Cancer was developed and written by Harold J. Burstein, Ann A. Prestrud, Jerry Seidenfeld, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Jennifer Malin, Eleftherios P. Mamounas, Diana Rowden, Alexander J. Solky, MaryFran R. Sowers, Vered Stearns, Mark R. Somerfield, Eric P. Winer, Jennifer J. Griggs.

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Author Contributions

Conception and design: Harold J. Burstein, Jennifer J. Griggs, Sarah Temin

Administrative support : Sarah Temin

Collection and assembly of data: Harold J. Burstein, Jennifer J. Griggs, Ann A. Prestrud

Data analysis and interpretation: Harold J. Burstein, Jennifer J. Griggs

Manuscript writing: Harold J. Burstein, Jennifer J. Griggs, Ann A. Prestrud, Sarah Temin

Final approval of manuscript: Harold J. Burstein, Jennifer J. Griggs, Ann A. Prestrud, Sarah Temin

Corresponding author: Sarah Temin, MSPH, American Society of Clinical Oncology, 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: sarah.temin@asco.org.

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Reference

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