

Adjuvant Endocrine Therapy Trials in Postmenopausal Patients

Tamoxifen has been the predominant form of adjuvant endocrine therapy utilized in clinical practice since the first International Breast Cancer Overview was presented at the 1985 NIH Consensus Conference. Successive overviews and a number of individual trials have demonstrated that greater benefit was observed with increasing duration of therapy up to five years. Early results from the ATAC trial demonstrated that, in postmenopausal women with primary invasive breast cancer, the third-generation aromatase inhibitor, anastrozole, conferred an advantage over tamoxifen. This historic study is the largest clinical trial conducted in breast cancer treatment and randomized over 9,000 women to either tamoxifen, anastrozole or a combination of both agents. Clinicians and researchers are now struggling with the clinical implications of this study. Several adjuvant endocrine therapy trials are currently examining the related issues of duration of tamoxifen treatment, sequencing tamoxifen with aromatase inhibitors, and the use of the other third-generation aromatase inhibitors.

DURATION OF TAMOXIFEN THERAPY

Breast cancer is a disease with at least a 20-year natural history. An important research question is, "Would 10 years of tamoxifen be better than five years for providing protection against recurrence in the second decade after diagnosis?" There are almost as many breast cancer deaths in the second decade after diagnosis as in the first. We've really got to think on a long-term scale. When we do that, the idea that 10 years might be better than five years actually becomes quite interesting. We've got virtually no information on that second decade. The idea that there might be some serious adverse effect on breast cancer from continuing tamoxifen beyond five years, has disappeared. That, in retrospect, was just a chance fluctuation, a "zig" in one trial, which has been counterbalanced by "zags" elsewhere. Now it's just averaged out. So, I don't think there's any reason to fear that longer treatment — for example, 10 years of treatment — is going to be any worse in terms of having an adverse affect on breast cancer itself. But whether it's going to actually have any worthwhile benefit in that second decade, is still unanswered.

—Richard Peto, FRS

POTENTIAL DIFFERENCES BETWEEN AROMATASE INHIBITORS (A.I.s) IN THE ADJUVANT SETTING

I do not know if this is a class effect of aromatase inhibitors. I can only speak for anastrozole in the ATAC trial. There are subtle differences in the pharmacology and pharmacokinetics of the two nonsteroidal aromatase inhibitors (anastrozole and letrozole), and even more with the steroidal aromatase inhibitor, exemestane. These differences could lead to different results. Although I suspect that they will have similar efficacy, I don't think we can assume they will have the same adverse events.

—Michael Baum, ChM, FRCS

A very important question that needs to be addressed is the interchangeability of the available aromatase inhibitors — anastrozole, letrozole and exemestane — in the adjuvant setting. Right now, there is only data with anastrozole. The other two agents are available for use by physicians, but there is no safety and efficacy data for them in the adjuvant setting. I have reservations about saying that this is a class effect, and switching to another aromatase inhibitor for which we do not have any adjuvant data.

—Aman Buzdar, MD

The degree of aromatase inhibition is slightly different between the agents. There have been claims that letrozole reduces estrogen levels fractionally more than the other aromatase inhibitors. While this difference may or may not translate into an efficacy benefit, there are two sides to every sword — it also may translate into a worse side-effect profile. My personal view is that the differences we will see between the aromatase inhibitors in the adjuvant setting will most likely be in terms of their side-effect profiles rather than efficacy.

—John F Robertson, MD, FRCP

SEQUENCING A.I.s AFTER TAMOXIFEN

For women already receiving tamoxifen, I would leave them on tamoxifen. It is a very safe and effective drug with decades of proven experience. For women finishing their course of tamoxifen, I encourage physicians to think about enrolling women in those trials studying the effects of sequencing treatments, such as tamoxifen followed by an aromatase inhibitor.

—Harold Burstein, MD, PhD

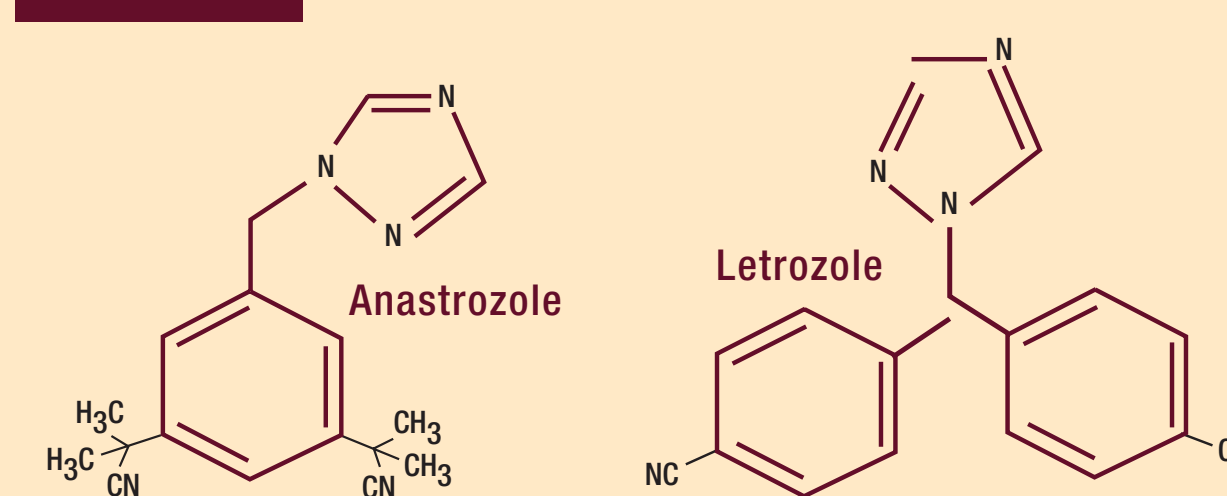
ONGOING PHASE III RANDOMIZED ADJUVANT TRIALS COMPARING AROMATASE INHIBITORS TO TAMOXIFEN

Protocol ID	Eligibility	Randomization Arms
CRC-TU-TEAM/ EU-20149	Any N; primary tumor > 3cm or grade III & > 1 cm, MO	ARM 1 Tamoxifen x 5 years ARM 2 Exemestane x 5 years
IBCSG-1-98/ EU-99022	pT1, pT2, pT3; pN0, pN1, pN2; MO	ARM 1 Tamoxifen x 5 years ARM 2 Letrozole x 5 years ARM 3 Tamoxifen x 2 years ↓ Letrozole x 3 years ARM 4 Letrozole x 2 years ↓ Tamoxifen x 3 years

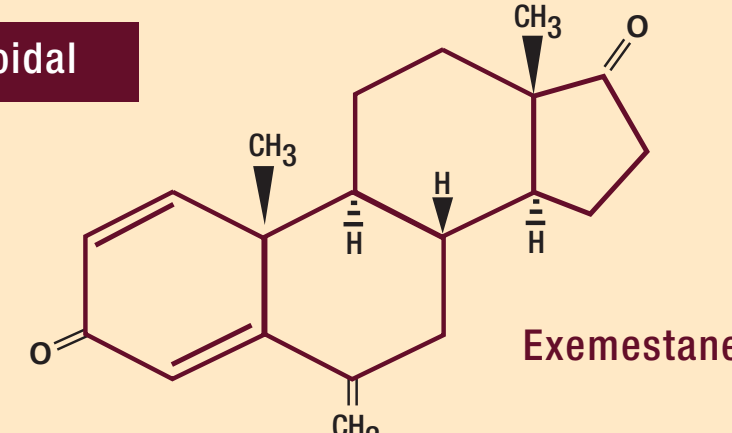
Source: NCI Physician Data Query, October 2002

3RD GENERATION AROMATASE INHIBITORS

Non-steroidal



Steroidal



ONGOING PHASE III RANDOMIZED TRIALS EVALUATING THE CONTINUATION OF ADJUVANT HORMONAL THERAPY WITH AN AROMATASE INHIBITOR

Protocol ID	Eligibility	Randomization Arms
NSABP B-33	Stage I, II or IIIA; 57-66 months adjuvant tamoxifen	ARM 1 Exemestane x 2 years ARM 2 Placebo x 2 years
SWOG-JMA17/ BIG 97-01/ CLB-49805	4.5-6 years adjuvant tamoxifen	ARM 1 Letrozole x 5 years ARM 2 Placebo x 5 years

Source: NCI Physician Data Query, October 2002

ONGOING PHASE III RANDOMIZED TRIALS EVALUATING THE OPTIMAL DURATION OF ADJUVANT TAMOXIFEN

Protocol ID	Eligibility	Randomization Arms
CRC-TU-ATTOM/ EU-98042	≥ 2 years of adjuvant tamoxifen	ARM 1 Stop tamoxifen ARM 2 Continue tamoxifen for at least 5 extra years
ATLAS/ EU-96064	5 years adjuvant tamoxifen	ARM 1 Stop tamoxifen ARM 2 Continue tamoxifen for at least 5 extra years

Source: NCI Physician Data Query, October 2002

SELECT PUBLICATIONS

The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet* 2002;359(9324):2131-2139.

Baum M. A vision for the future? *Br J Cancer* 2001;85(Suppl 2):15-18.

Boeddinghaus IM, Dowsett M. Comparative clinical pharmacology and pharmacokinetic interactions of aromatase inhibitors. *J Steroid Biochem Mol Biol* 2001;79(1-5):85-91.

Brodie A. Aromatase inhibitors in breast cancer. *Trends Endocr Metab* 2002;13(2):61-65.

Buzdar AU. Anastrozole (Arimidex®) — an aromatase inhibitor for the adjuvant setting? *Br J Cancer* 2001;85(2 suppl):6-10.

Buzdar A, Howell A. Advances in aromatase inhibition: Clinical efficacy and tolerability in the treatment of breast cancer. *Clin Cancer Res* 2001; 7:2620-2635.

Fisher B et al. Five versus more than five 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.

Wellington K, Faulds DM. Anastrozole in early breast cancer. *Drugs* 2002;62(17):2485-2492.