



Christine Zalewski. *White Blush Tulip III*. Photograph.

*Three multicenter trials have shown improved disease-free survival and good tolerability with aromatase inhibitors as adjuvant treatment for early-stage breast cancer:*

## Current Status of Aromatase Inhibitors in the Management of Breast Cancer and Critique of the NCIC MA-17 Trial

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**Background:** *The third-generation aromatase inhibitors reduce circulating estrogen levels in postmenopausal women and are well tolerated orally for breast cancer. Their role in the management of advanced breast cancer has already been recognized. This article reviews the evidence for their role in the adjuvant treatment of early-stage disease.*

**Methods:** *Three large multicenter trials are reviewed. The ATAC trial compared anastrozole and tamoxifen or a combination of the two, for 5 years from the point of diagnosis. The NCIC trial published the results of letrozole compared with placebo after the completion of 5 years of tamoxifen. Most recently, the Intergroup Exemestane Study reported a comparison of 5 years of tamoxifen vs 2 years of tamoxifen followed by 3 years of exemestane.*

**Results:** *The aromatase inhibitor arm in each of these studies was associated with improved disease-free survival and good tolerability. Because of the three different settings, cross-trial comparisons of the different aromatase inhibitors are impossible, but in each case the novel therapy appears promising.*

**Conclusions:** *This review is critical of the early stopping of the NCIC study and recommends more mature follow-up in each case until distant disease-free or overall survival rates can be measured and then correlated with adverse events. The late onset of osteoporotic fractures is a concern that must be addressed before tamoxifen can be abandoned in favor of the aromatase inhibitor in each of the three clinical points: at diagnosis, at midway through a course of tamoxifen, and as an extension to the conventional 5-year period of endocrine therapy.*

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*Abbreviations used in this paper:* ATAC = anastrozole, tamoxifen, alone or in combination; ER = estrogen receptor; PR = progesterone receptor; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; EBCTCG = Early Breast Cancer Trialists' Collaborative Group.

## Introduction

Over the last 15 years there has been a dramatic fall in mortality from breast cancer in both the United Kingdom and the United States. Most commentators attribute this to the direct or indirect effect of adjuvant hormonal manipulation.

In 1952, approximately 50 years after Beatson's landmark series of surgical castration,<sup>1</sup> Huggins and colleagues<sup>2</sup> first described surgical adrenalectomy as second-line endocrine therapy. Both of these studies were empirical observations with little or misguided understanding of the biological rationale underlying the responses. Within the last 50 years, we have seen a concentrated effort by both endocrinologists and clinicians to understand and exploit these mechanisms to enhance clinical benefit.

"Medical adrenalectomy" induced by the interruption of steroidogenesis at the level of the conversion of cholesterol to pregnenolone can achieve objective responses in metastatic breast cancer among women without ovarian function to a similar extent as a surgical adrenalectomy and thus can be more widely applicable to a woman who is a poor operative risk.<sup>3</sup> Recent developments in medical adrenalectomy have followed the discovery of the aromatase inhibitors, which act by blocking aromatase, the enzyme that catalyzes the final and rate-limiting step in the synthesis of estrogens.<sup>4</sup>

Aromatase is expressed in non-ovarian tissues such as muscle and fat in both premenopausal and postmenopausal women. These non-ovarian tissues become the dominant sources of estrogen in postmenopausal women. Currently, the available aromatase inhibitors fall into two classes. The class I inhibitors bind aromatase irreversibly, and the available agents have a steroidal structure (eg, exemestane). The class II agents bind aromatase in a reversible manner, and the available agents are nonsteroidal (eg, anastrozole and letrozole). Because of the specificity of its mode of action, this class of compound is well tolerated and thus lends itself to the management of both early- and advanced-stage disease. Although the first adjuvant trial (ATAC) to report data started recruitment before the publications of trials from the advanced settings, the trials of the aromatase inhibitors as first-line therapy for metastatic breast cancer are discussed first.

Both anastrozole and letrozole have been shown to be superior to megestrol acetate in second-line endocrine therapy after failure with tamoxifen. However, more importantly, both drugs have been shown as superior to tamoxifen in efficacy and tolerability in the first-line therapy of locally advanced or metastatic disease for postmenopausal women with hormone receptor-positive disease.<sup>5-7</sup> It is now widely accepted that an aromatase inhibitor should be the treatment of first choice in this setting.

## Aromatase Inhibitors in the Adjuvant Setting

In the early breast cancer setting, tamoxifen is the established treatment for postmenopausal women with hormone-sensitive disease (ER<sup>+</sup> and/or PR<sup>+</sup>) and shows significant benefits compared with control/placebo.<sup>8-10</sup> Although tamoxifen is generally well tolerated and relatively nontoxic, an increased incidence of endometrial cancer has been reported in association with tamoxifen treatment, and the level of risk appears to be time- and dose-dependent.<sup>11</sup> Other side effects related to the estrogenic properties of tamoxifen include the increased risk of thromboembolic disorders.<sup>12</sup> For these reasons, the third-generation of oral aromatase inhibitors are ideal candidates to either enhance the activity of tamoxifen or replace it entirely in the adjuvant setting. A number of active trials are exploring the roles of both the steroidal and nonsteroidal agents, used either head-to-head, sequentially, or in combination with tamoxifen.

## ATAC Trial

The ATAC trial was the first to complete recruitment, be presented in public, and be published in full.<sup>13,14</sup> This trial of anastrozole or tamoxifen alone or in combination in postmenopausal breast cancer patients with early breast cancer represents the first report of a new generation aromatase inhibitor compared with tamoxifen in the early breast cancer setting. A unique feature of this trial was the inclusion of the combination arm, thus allowing the investigation of any possible additive effects through the use of two drugs with different modes of action. The ATAC trial is the largest adjuvant breast cancer study conducted in postmenopausal patients with early breast cancer.

In addition to the main trial endpoints, the differing pharmacologic effects of the two drugs alone or in combination were addressed within a number of subprotocols. These subprotocols included assessment of effects on the endometrium, bone mineral density and bone markers, quality of life, and the possible pharmacokinetic and pharmacodynamic interactions when anastrozole was given in combination with tamoxifen.

Candidates who were randomized (with their informed consent) into the ATAC trial included postmenopausal patients who had operable invasive breast cancer and had completed their primary treatment (which included chemotherapy in approximately 20% of cases who were judged to be at high risk of relapse) and who were candidates to receive adjuvant hormonal therapy. Between July 1996 and 2000, a total of 9,366 patients from 380 centers in 21 countries were recruited and randomized into one of three treatment arms: (1) active anastrozole 1 mg per day plus tamoxifen placebo, (2)

active tamoxifen 20 mg per day plus anastrozole placebo, or (3) active anastrozole 1 mg per day plus active tamoxifen 20 mg per day.

### **Efficacy Results**

Analysis of the data was formally triggered at the advice of the Data Monitoring and Safety Committee after the predetermined number of events (1,050) had been reached, with a further analysis a year later at 1,350 events and a median follow-up of approximately 4 years.

At this relatively early stage of follow-up, anastrozole shows superior efficacy to tamoxifen, with a 17% relative risk reduction in disease-free survival in the intention-to-treat population and a 19% improvement when compared to the combination arm. The result is even more impressive in the subgroup known to be hormone receptor-positive, where the relative risk reduction for anastrozole against tamoxifen is 27%. After all, this is the target population in future therapeutic decisions for adjuvant endocrine therapy. It is too early to measure outcomes in terms of all-cause and cause-specific mortality, but the threshold number of events to trigger that analysis will possibly occur later in 2004.

Perhaps the most surprising result was the failure of arm 3, the combination treatment, which fared no better than tamoxifen alone and less well than anastrozole alone. One explanation, favored by the majority when made aware of these data, is that in an estrogen-deprived environment, tamoxifen is "seen" as an agonist, whereas in a normal estrogen-rich environment, tamoxifen can exert its classic antiestrogen effect.

### **Contralateral Disease**

Perhaps the most impressive result at this stage is the striking reduction in the incidence of contralateral invasive cancers for anastrozole compared with tamoxifen. Yet, since 1985 tamoxifen has been associated with a significant reduction in contralateral disease compared with a control population. In the latest overview, 5 years of tamoxifen is associated with a 50% reduction in contralateral breast cancer.<sup>10</sup> If these trends persist, then anastrozole has the potential to prevent (or delay) up to 75% of all new breast cancers.

### **Subgroup Analyses**

By chance, a significant proportion of patients admitted with unknown ER status have been demonstrated as ER<sup>-</sup> after retrieval of archival material. Not surprising was the observation that both tamoxifen and anastrozole were *equally* ineffective in this subgroup. Of more interest is the most recent observation, presented at the San Antonio Breast Cancer Symposium in December 2003, which demonstrated the greatest relative risk reduction for anas-

trozole vs tamoxifen in the subgroup of patients whose tumors were ER<sup>+</sup>/PR<sup>-</sup>.<sup>15</sup>

In patients with heavy lymph node involvement, most of whom had chemotherapy before randomization to the endocrine treatment, no differences have emerged between anastrozole and tamoxifen. This might be real evidence of interaction between treatments or simply an issue of "statistical power" resulting from the small number of women at risk in this population.

### **Tolerability and Side Effects**

The ATAC trial was powered to demonstrate "equivalence" on the basis that anastrozole has demonstrated a better tolerability profile than tamoxifen in the advanced setting.<sup>5,6</sup> It could therefore be argued that if this is the case in the adjuvant setting, then anastrozole could become the treatment of choice. As it is, anastrozole already shows greater efficacy than tamoxifen and at a relatively short period of follow-up and, it could be argued, better tolerability. Among the predetermined adverse events analyzed, anastrozole is significantly less likely to contribute to hot flushes, vaginal discharge, vaginal bleeding, endometrial cancer, strokes, and thromboembolic disease. Although endometrial cancer associated with exposure to tamoxifen is rare, the fear of this association means that most of those women with gynecologic symptoms might have been subjected to unnecessary invasive investigations. This advantage for anastrozole could save both anxiety and health service costs in the long term.

The disadvantages of anastrozole compared with tamoxifen are found in the contrast between women with chronic estrogen deprivation compared with women on a drug with weak agonist effect. Women taking anastrozole are more likely to suffer from "musculoskeletal" problems. Prominent among these is a curious form of polyarthralgia, which seems to be a specific side effect of this class of compound. Its mechanism is obscure but might be related to aromatase inhibition in the small muscles of the distal limbs. More serious is the excess of bone fractures already observed in the anastrozole group. It is currently unknown whether this is a result of the protective effect of tamoxifen on bone compared with an untreated population or whether it is due to estrogen deprivation due to aromatase inhibition. It is the subject of intense scrutiny in another subprotocol that has been prospectively studying bone mineral metabolism in a sample population of the main study. In pragmatic terms, it does not matter what the mechanism is because women will have to make an informed choice between one drug and the other — no treatment being an inferior option. Nevertheless, this is a side effect that can be managed if anticipated. Clinicians opting to prescribe anastrozole should request a base-line bone density scan that should be repeated at approximately 12-month intervals. A variety of options can be considered for women whose bone density starts to fall into

the osteopenic range. For example, stop the drug if they have been taking it for more than 3 years, or prescribe a bisphosphonate, which in addition to protecting the skeleton might even reduce the risk of skeletal metastases.

## NCIC CTG Intergroup Trial MA-17

A recent publication<sup>16</sup> has created interest and controversy. The NCIC CTG Intergroup Trial MA-17 studied women who were alive and symptom-free after completing 5 years of tamoxifen. They were then randomized to receive placebo or 5 years of letrozole. The trial was stopped prematurely because of a significant improvement in disease-free survival favoring the letrozole group. Those on placebo were then offered letrozole. In my opinion this is a pity, for although it is of scientific interest to note that the natural history of the disease can be perturbed after 5 years of tamoxifen, this study will never be able to address the issue of clinical utility in overall survival or provide a proper harm-benefit analysis. I would like to explore this point in greater detail as there are important generic issues at stake that go beyond this trial or even this disease setting. I also wish to look at the matter in two ways: the clinical relevance of the findings and the ethical implications of this and future trials. I will start with the latter but first I must emphasize I have absolutely no stake in one aromatase inhibitor over another. My strictures would apply equally if the drug in question was anastrozole instead of letrozole and I am not alone in this criticism.<sup>17,18</sup>

The authors of the paper claimed the moral high ground in obeying the stopping rules of their protocol. This may indeed be the case, but as I will argue they had become hostages to fortune by accepting such strict stopping rules to start with, which in my opinion are contrary to the *implicit contract* they had with their volunteers. In clinical science, there are only two meaningful outcome measures — length and quality of life. All other outcome measures are surrogate, and that includes disease-free survival. The reason for that is the false assumption that disease-free survival automatically translates into overall survival. For example, unexpected adverse events may increase deaths from other causes in the novel treatment arm, thus obliterating the benefit in cause-specific deaths. Regarding quality of life, there is often a trade-off to be made between disease-free and overall survival and tolerability of the treatments that can influence the balance in quality of life. In my opinion, the early stopping of MA-17 because of ill-judged stopping rules is a breach of contract with the client and therefore unethical. The implications of this are magnified by the negative influence that the decision has had on other trials. I am concerned by the decision of the NSABP to abort their B-33 protocol, which was evaluating exemestane, on the basis of preliminary results of the MA-17 trial. There is an imminent threat to the future of aromatase inhibitor trials and

management decisions of countless women for generations to come on the basis of only 29 life-threatening events in one trial (vide infra). This might mean that North American oncologists are too fearful of litigation or vilification from an ill-informed and mendacious legal profession. If that were the case, then I would argue that North America is not an ideal place for the conduct of randomized clinical trials and that the rest of the world should resist this type of ethical imperialism!

Finally just as with NSABP P-1,<sup>19</sup> the data were released to the lay media before there was time for mature medical professional consideration. CNN and the Washington Post are not appropriate mouthpieces for the announcement of scientific progress.

The rather outspoken comments above can be amplified when studying in detail the clinical outcomes described. Only 20 patients have been followed for 4 years, at which point there is an absolute difference of 2% in the number of events. Removing the 40 cases of contralateral breast cancer leaves the significance level borderline, and in life-threatening distant metastases there are 47 patients in the letrozole arm vs 76 in the placebo arm out of a total population of 5,189. It would be churlish of me to deny the authors their legitimate pride and excitement to learn that we can perturb the natural history of breast cancer after 5 years of tamoxifen. I share their excitement, but can we be sure it is not simply the duration of the endocrine therapy that we are seeing? There is a false assumption in the introduction to the paper that we know the optimum duration of tamoxifen; this is not the case. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) 2000 showed that the optimal duration of tamoxifen remains unresolved. This is indirectly hinted at by the fact that the two largest trials on duration of tamoxifen (Adjuvant Tamoxifen Longer Against Shorter [ATLAS] and Adjuvant Tamoxifen Treatment Offer More [aTTom]) are still open for recruitment.<sup>20</sup> That aside, I have little doubt that there is a real difference in disease-free survival that will stand the test of time, but early stopping inevitably exaggerates the magnitude of the difference as seen before in the comparison of NSABP P-1<sup>19</sup> and in the overview of all the tamoxifen prevention trials.<sup>21</sup> Finally, as already noted, the unbinding and crossover of placebo to active therapy means we will never learn the real benefit in overall survival or the total burden in adverse side effects and their impact on quality of life.

## Intergroup Exemestane Study

The Intergroup Exemestane Study, coordinated by the Breast International Group, is the most recent study of adjuvant aromatase inhibitors. Patients were randomized to receive either 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of the steroidal aromatase inhibitor exemestane.<sup>22</sup> After a median follow-up of less

than 3 years in a study involving nearly 5,000 patients, there was a significant advantage for the group switching to the aromatase inhibitor in disease-free survival. The authors urge caution in overinterpretation and premature adoption of this policy before long-term toxicity data are available. Nevertheless, this is welcome news for women who find tamoxifen difficult to tolerate in the long term.

Although the data from these trials are not yet fully mature, it is possible that the aromatase inhibitors will eventually have a role in the three scenarios: newly diagnosed patients, those halfway through their course of tamoxifen, and those who are close to finishing the conventional 5-year course of tamoxifen.

## Conclusions

What can we advise newly diagnosed patients with breast cancer? We now have a choice of adjuvant endocrine therapy for postmenopausal hormone receptor-positive patients. For example, if tamoxifen is specifically contraindicated because of a previous history of thromboembolic disease, then anastrozole could be considered. However, beyond that, I consider it too early for a proper risk-benefit analysis to be calculated until we have the overall survival result. This should become available in the third quarter of 2004. At that time, we should be in a good position to calculate a balance of benefits vs harm to allow a selective approach based on age, prognostic factors, and biological predictive measurements. As far as switching from prescribing 5 years of tamoxifen to an aromatase inhibitor, we may never know the outcome unless the NSABP B-33 protocol is reopened to recruitment. However, I would like to challenge the scientific community to conduct a large and pragmatic trial of all the women in the world who have completed tamoxifen of any duration at any time in the past and then randomizing them to either control, restarting tamoxifen, or taking any of the third-generation aromatase inhibitors. What a magnificent trial for worldwide collaboration of clinicians and their industrial partners that would be!

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