Endocrine Therapy Trials of Aromatase Inhibitors for Breast Cancer in the Adjuvant and Prevention Settings

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ABSTRACT

The recent past has witnessed the appearance of substantial data relating to endocrine therapy of breast cancer. In the adjuvant therapy setting in early breast cancer, several large, well-conducted, randomized, double-blind clinical trials have provided evidence for the value of the third-generation aromatase inhibitors (AI) anastrozole, exemestane, and letrozole. The three major studies to date [i.e., Arimidex, tamoxifen alone, or in combination (ATAC), International Exemestane Study (IES), and letrozole after 5 years of tamoxifen (MA.17)] evaluated three different populations of women from the standpoints of duration of prior tamoxifen and thus time since the treatment of the primary breast cancer. A consistent pattern of improvement in disease-free survival was seen whether the control arm was tamoxifen (ATAC and IES) or placebo following tamoxifen (MA.17). From a toxicity standpoint, the major findings with the AIs were a decreased incidence of thromboembolic events and endometrial cancers but an increase in musculoskeletal complaints and potential for decreasing bone density. The last issue should be clarified with ongoing studies addressing the impact of the three AIs on bone density and fractures. In summary, based on ATAC, IES, and MA.17, respectively, the following conclusions can be drawn relating to postmenopausal women with hormone receptor positive early breast cancer: anastrozole is a reasonable choice for initial endocrine adjuvant therapy, exemestane should be considered for women who have received 2 to 3 years of tamoxifen, and letrozole should be considered for those who have completed about 5 years of tamoxifen.

In the prevention setting, tamoxifen has been evaluated in multiple trials involving >28,000 women and, despite clear evidence of benefit, the level of acceptance of this agent by women seems to be low. Two recently developed prevention trials, IBIS 2 and MAP3, involve the study of aromatase inhibitors against a placebo control rather than tamoxifen. Whereas the recent adjuvant trials have established the value of the third-generation aromatase inhibitors in early-stage breast cancer, the marked reductions in contralateral breast cancers seen in these trials suggest they will be of value in the prevention setting in women at increased risk of developing the disease.

INTRODUCTION

Endocrine therapy offers the potential for substantial benefit in the majority of postmenopausal women with breast cancer who are candidates based on presence of hormonal receptor [estrogen and/or progesterone receptor (ER and/or PR)] in the tumor. In the advanced disease setting, tamoxifen has had U.S. Food and Drug Administration approval since 1977, but the third-generation nonsteroidal aromatase inhibitors (AI) anastrozole and letrozole and, more recently, the steroidal AI exemestane have been shown to be preferable to tamoxifen in phase III clinical trials (1, 2). Given the superiority of AIs in the advanced disease setting, it was logical that these agents would receive intensive study in earlier stages of disease. In the adjuvant setting in early breast cancer, tamoxifen had been the standard of therapy since it was approved by the Food and Drug Administration in 1986 for postmenopausal women with resected node-positive breast cancer and in 1990 for premenopausal and postmenopausal women with resected node-negative disease. Multiple clinical trials were developed to evaluate the AIs in the adjuvant setting (3), and substantial data has been presented in the recent past relating to these trials, which provide evidence for their use in the management of patients in standard clinical practice.

Tamoxifen, at present, is the only endocrine agent approved by the Food and Drug Administration for prevention of breast cancer, specifically “Reduction in Breast Cancer Incidence in High Risk Women” in the Food and Drug Administration labeling. In women at high risk of developing breast cancer, there is a wealth of clinical trial data showing that tamoxifen reduces breast cancer incidence, but there seems to be low acceptance of this agent by women in the prevention setting. This review will consider the recent results from the major clinical trials that provide evidence for use of anastrozole, exemestane, and letrozole as adjuvant endocrine therapy in early breast cancer and the basis for their study in the prevention setting.

AROMATASE INHIBITORS AS ADJUVANT THERAPY IN EARLY BREAST CANCER

Three large, well-conducted, randomized, and placebo-controlled trials have recently been reported that provide evidence upon which decisions can be based regarding the use of the third-generation AIs as adjuvant endocrine therapy in women with early breast cancer. The three trials are Arimidex, tamoxifen alone, or in combination (ATAC; refs. 4, 5), International Exemestane Study (IES; ref. 6), and MA.17 (7). As the trial schemata shown in Fig. 1 indicate, each trial...
examined the AI in a different clinical setting. ATAC compared anastrozole with tamoxifen for 5 years as initial treatment; IES compared exemestane with tamoxifen in women who had already received 2 to 3 years of tamoxifen for a total of 5 years of endocrine adjuvant treatment; and MA.17 compared letrozole with placebo in women who had already received 4.5 to 6 years of tamoxifen. The setting of each of the trials is superimposed on a recurrence-free survival curve estimated from the Oxford Overview data (8) in Fig. 2, showing that the population of patients examined in these three trials differed in terms of disease-free survival (DFS) and extent of prior tamoxifen exposure. Thus, it can be assumed that the proportions of patients who were hormonally insensitive differed between the studies with that proportion increasing from the MA.17 to IES to ATAC trials. These differences in patient characteristics between the trials make direct cross-study comparisons impossible. However, examination of the trials reveals a consistent pattern of benefit and toxicities and each provides level I evidence for use in clinical practice. The findings from each of these pivotal studies will be reviewed and the implications for patient management considered.

**ATAC.** The ATAC trial (4, 5) involved 9,366 postmenopausal women randomized to tamoxifen alone, anastrozole alone, or the combination. The study was double blind and treatment length was planned for 5 years, but the median follow-up of the most recent report was 47 months (5). As the combination arm was no better than tamoxifen alone, attention has focused on the comparison of anastrozole with tamoxifen. The most informative analysis involved the patients whose hormone receptor status was known to be positive, as it is the patients whose tumor is ER and/or PR positive for whom endocrine adjuvant therapy is indicated. Receptor results were available for about 85% of the patients entered. There was a substantial difference in HR for disease recurrence (anastrozole/tamoxifen) between the ER-positive and PR-positive patients and the ER-positive and PR-negative patients with HR = 0.82 (NS) and HR = 0.48 (statistically significant), respectively. These HRs indicated that anastrozole was associated with an 18% reduction in hazard for recurrence when both ER and PR were positive, but a 52% reduction in those patients who had a positive ER but negative PR. The authors emphasized that these were exploratory analyses that should not influence patient management. Whereas this analysis is primarily of value for hypothesis generation by virtue of its retrospective nature, some may wish to consider these findings as a part of the total evaluation of a patient’s clinical situation. If one is persuaded to use anastrozole preferentially in a patient with an ER-positive tumor, then the issue of PR status is moot. Although retrospective, the experience with the ER and PR status involves over 2 logs more patients than the 39 patients with HER2-positive tumors treated with letrozole or tamoxifen in the report by Ellis et al. (10) that has stimulated much debate on whether HER2 status should be considered in the decision whether to use anastrozole or tamoxifen.

### Fig. 2 Schematic representation of the clinical settings for the ATAC, IES, and MA.17 adjuvant therapy trials. Schemata of the ATAC, IES, and MA.17 adjuvant therapy trials.

R, randomization; yr, years.
The second recent presentation of note was that by Howell for the ATAC Trialists’ Group at the European Breast Cancer Conference in Hamburg in March 2004. In response to the IES publication (discussed below), results were presented of an analysis of events during the first 2.5 years of therapy for the ATAC trial. The main findings were that the event rate peaked during the first 2 years and that local/regional recurrences, distant recurrences and contralateral invasive cancers were all lower in the anastrozole-treated patients than in those treated with tamoxifen. In addition, the worrisome toxicities of venous thromboembolism, ischemic cardiovascular events, and endometrial cancer were also all lower during the first 2.5-year time frame.

**IES.** The IES study (6) involved 4,742 postmenopausal women who had already received 2 to 3 years of adjuvant tamoxifen who were randomized in a double-blind fashion to receive either tamoxifen or the steroidal AI exemestane to complete a 5-year course of therapy. The primary end point was DFS with the same criteria as that of the ATAC trial (i.e., recurrence of breast cancer at any site, a second primary breast cancer or death from any cause). About 81% of the patients were known as ER-positive with most of the remaining being ER unknown. With a median follow-up of 30.6 months, DFS was significantly superior for those women switched to exemestane with the unadjusted HR (exemestane/tamoxifen) being 0.68 (95% CI, 0.56-0.83; \(P < 0.001\)). Thus, switching a woman from tamoxifen to exemestane was associated with a 32% reduction in risk of an event over continuing the tamoxifen. Considering contralateral new breast cancer primaries, there was a 56% reduction for exemestane relative to tamoxifen (odds ratio, 0.44; 95%, CI 0.20-0.98; \(P = 0.04\)). Of note is that there was no indication of heterogeneity of effect according to PR status in the ER-positive patients that was found in the ATAC trial data. As with the ATAC trial, the toxicity profiles differed. Switching to exemestane was associated with a significantly lower incidence of thromboembolic events, gynecologic symptoms, vaginal bleeding, and muscle cramps but a significantly higher incidence of arthralgias and diarrhea. The assigned treatment was stopped for reasons other than relapse or death in 365 patients on exemestane and 302 patients on tamoxifen.

**MA.17.** Five years of tamoxifen has generally been considered the standard for therapy in the adjuvant setting. The Oxford Overview considered numerous trials which examined 1, 2, and 5 years of tamoxifen and found a highly significant trend toward greater benefit with the longer duration of therapy (8). The trial that had the major influence on setting tamoxifen therapy duration at 5 years was the National Surgical Adjuvant Breast and Bowel Project B14 trial, which evaluated 5 versus 10 years of tamoxifen in women with ER-positive, node-negative breast cancer and found an advantage that achieved significance in disease-free survival (\(P = 0.03\)) and approached significance in overall survival (\(P = 0.07\)) for those who received tamoxifen for 5 years (11). MA.17 (7) evaluated the concept of extended adjuvant endocrine therapy in a setting where no therapy was available to offer patients, and thus a placebo-controlled trial was appropriate and necessary. This trial involved 5,187 postmenopausal women who had already received 4.5 to 6 years of adjuvant tamoxifen therapy and were randomized in a double-blind fashion to receive either letrozole or placebo for a planned 5-year period. The primary end point was also DFS but the definition did not include women who had died without either recurrence of breast cancer or new diagnosis of a contralateral breast cancer, as these patients were censored. At the time of the first interim analysis, the Data and Safety Monitoring Committee recommended unblinding and reporting of the study because of extreme results in favor of the use of letrozole. The published results (7) were based on a median follow-up of 2.4 years and DFS was significantly superior for those who received letrozole, with the HR (letrozole/placebo) being 0.57 (95% CI, 0.43-0.75; \(P = 0.00008\)). Thus, women who received letrozole had a 43% reduction in risk of an event compared with those who received placebo. Considering contralateral new primary tumors alone, the incidence was cut almost in half with the use of letrozole: 14 cases in the letrozole group and 26 cases in the placebo group. From the toxicity standpoint, MA.17 differed from ATAC and IES in that the control group received a placebo rather than tamoxifen. The major finding was that joint and muscle complaints, hot flushes, and patient-reported new diagnoses of osteoporosis were more common with letrozole, but vaginal bleeding was less frequent. More patients on letrozole experienced a bone fracture but the difference between letrozole-treated and placebo patients was not significant. About half of the patients in each group had node-positive disease and half node-negative disease, and the effect of letrozole on the HR for an event was at least as great in the node-negative patients. In an update presented at the American Society of Clinical Oncology (ASCO) meeting in June 2004, Goss noted that distant DFS, an analysis which had not been done for the initial publication, was significantly better when the entire study population was considered. Although overall survival for the entire study population was not significantly different, it was significantly better for letrozole-treated patients who had positive nodes.

Quality of life remains an important consideration when any adjuvant therapy is considered. Whelan et al. (12) reported the findings from the MA.17 quality of life study at the ASCO meeting in June 2004. This study involved almost 3,600 women who were evaluated with the Medical Outcomes Study 36 Item Short Form General Health Survey and the Menopause Specific quality of life questionnaire. The conclusions from this study, the largest to date involving AIs, were that letrozole did not have a substantial adverse impact on quality of life; small effects were seen in some domains consistent with a minority of patients experiencing adverse effects. Thus, this large study, with a high level of compliance of the participants, provides additional support for the conclusion that letrozole is well tolerated in the extended adjuvant setting.

**PRACTICE IMPLICATIONS**

The results from the ATAC, IES, and MA.17 trials have clearly established the value of AIs as adjuvant endocrine therapy for postmenopausal women with early breast cancer. The ASCO Technology Assessment Working Group on AIs has addressed the role of anastrozole on two occasions (13, 14) and concluded that tamoxifen remained a reasonable standard, a position supported by the St. Gallen Conference Panel (15). These position statements were developed prior to the release of the MA.17 results in October 2003 and the IES results in March.
2004. An update from the ASCO Technology Assessment Working Group is expected in the latter part of 2004. This author's opinion is that the ATAC, IES, and MA.17 provide the basis for recommendations regarding the use in the clinical settings examined by the three different trials.

- Based on ATAC, anastrozole is a reasonable choice as initial therapy based on an improved DFS and a lower incidence of thromboembolic events and endometrial cancers relative to tamoxifen, with the understanding that there is an increased risk of fractures requiring monitoring of bone density and potentially additional therapy (e.g., bisphosphonates) and an increased risk of musculoskeletal complaints. For patients who have concern regarding any of these issues or the less complete knowledge regarding long-term side effects, tamoxifen remains an option with proven efficacy.

- Based on IES, women who have received 2 to 3 years of tamoxifen should be considered for switching to exemestane based on an improved DFS and lower incidence of thromboembolic events and gynecologic symptoms compared with continuation of tamoxifen for a 5-year course of treatment.

- Based on MA.17, women who have completed 5 years of tamoxifen should be considered for treatment with extended adjuvant therapy with letrozole based on an improved DFS, including distant DFS, taking into account the patient's residual risk of recurrence. A full discussion should be held regarding potential risks of therapy and limitations of knowledge regarding long-term side effects.

ENDOCRINE THERAPY FOR PREVENTION OF BREAST CANCER

Tamoxifen has received extensive study in the prevention setting. In an overview analysis of four major studies involving 28,419 women, Cuzick et al. (16) found a 38% (95% CI, 28-46; \( P < 0.0001 \)) reduction in incidence of breast cancer; no impact on ER-negative breast cancer but a reduction in ER-positive breast cancer by 48% (95% CI, 36-58; \( P < 0.0001 \)); an increase in endometrial cancer rates [consensus relative risk of 2.4 (95% CI, 1.5-4.0), \( P = 0.0005 \)]; and an increase in venous thromboembolic events [relative risk 1.9 (95% CI, 1.4-2.6), \( P < 0.0001 \)]. Although tamoxifen has received approval as a preventive therapy from the Food and Drug Administration, there are indications that the level of acceptance of this agent is low. Port et al. (17) from Memorial Sloan-Kettering Cancer Center evaluated 43 women with a mean age of 53 years who were at increased risk of developing breast cancer by virtue of a Gail Score of at least 1.7 (i.e., at least 1.7% risk of developing breast cancer over the next 5 years) and only 2 (5%) decided to take tamoxifen. This decision was not influenced by educational sessions; the reasons most cited for the decision not to take tamoxifen were concerns regarding endometrial cancer, venous thromboembolism, and menopausal symptoms.

Findings from the ATAC, IES, and MA.17 trials have provided a strong impetus for the study of AIs in the prevention setting. Substantial reductions in contralateral breast cancers, which represent prevention in the previously unaffected breast, were seen in all three trials. The odds ratio (AI/tamoxifen) for developing a contralateral breast cancer and the 95% CI were 0.56 (95% CI, 0.32-0.98) for ATAC, 0.44 (95% CI, 0.20-0.98) for IES and, in updated data from presentation by Goss at ASCO, 0.62 (95% CI not given) for MA.17. The reductions of 44% for anastrozole in ATAC and 56% for exemestane in IES are particularly remarkable given that the AI was being compared with tamoxifen, which is associated with a 38% reduction in breast cancer incidence, as noted in the overview by Cuzick et al. (16), and a halving of the breast cancer incidence in the largest study to date, the National Surgical Adjuvant Breast and Bowel Project P-1 prevention trial (18).

The National Surgical Adjuvant Breast and Bowel Project will complete the Study of Tamoxifen and Raloxifene with 19,000 women that will provide information on the selective estrogen receptor modulator raloxifene, which was not associated with an increased incidence of endometrial cancer in the Multiple Outcomes of Raloxifene study (19). Despite the reduction in breast cancer incidence with tamoxifen, the toxicities observed and low patient acceptance have led to new strategies in prevention. There are two large ongoing trials of endocrine therapy for prevention in postmenopausal women at increased risk of breast cancer in which the control arm is placebo, a strategy which has been advocated by an ASCO Technology Assessment Panel (20). International Breast Cancer Intervention Study 2 (IBIS 2) involves a randomization between anastrozole and placebo, and MAP.3 (also known as EXCEL for exemestane plus celecoxib) is a double-blind trial with a randomization between exemestane plus celecoxib, exemestane plus placebo and two placebos. The latter study involves the cyclooxygenase-2 inhibitor celecoxib because of data indicating a relationship between cyclooxygenase-2 activity and prostaglandin E2 synthesis, which in turn can induce aromatase activity (21); at least additive antitumor effect when celecoxib is combined with exemestane in a preclinical model (22); and celecoxib's ability to inhibit an ER-negative breast cancer cell line, MDA-MB-231 (23).

CONCLUSIONS

The third-generation AIs, anastrozole, exemestane, and letrozole, have become firmly established as effective in the adjuvant therapy of postmenopausal women with early-stage breast cancer. Multiple questions remain, as is generally the case when a new modality of therapy is introduced. Among the major questions are optimal duration of AI treatment, optimal sequencing, if any, of tamoxifen and an AI, long-term side effects, and whether there is a “best” AI. Ongoing clinical research will address many of the questions. The AIs offer the potential for increased benefit to patients in terms of reducing the burden of breast cancer recurrence, and prevention of breast cancer is the next focus of AI research.

OPEN DISCUSSION

Dr. Stephen Johnston: In regards to the aromatase inhibitors as initial therapy, in the UK, we are waiting for the results of BIG-FEMTA, which will provide the randomized comparison of an AI upfront versus tamoxifen upfront versus the switch in therapy at 2 years. In the animal model, the better...
long-term outcome was with an AI upfront, but the BIG-FEMTA will provide the clinical data.

Dr. James Ingle: In the US at least, the acceptance of AIs is growing, and I think it is going to be the unusual patient in the US who will get tamoxifen upfront. The new ASCO guidelines will basically reflect the view that an AI as initial therapy is a reasonable option.

Dr. Kent Osborne: I am told that BIG-FEMTA will not have progesterone receptor data. We are ignoring biological and clinical data that suggest that most of the aromatase inhibitor advantage can be explained by HER2 positivity and PR negativity. In ATAC there was only a very small difference in outcome between the two treatments in the ER-positive, PR-positive, HER2-negative group. I wouldn’t be surprised if there are certain subgroups where it is still better to give tamoxifen first and then switch later when tamoxifen resistance may have developed, when many of those patients are still sensitive to aromatase inhibitors. The majority of relapses occur after 5 years. So, if you can salvage a greater percentage of those than you lose during the first 5 years by initial tamoxifen therapy compared to an initial aromatase inhibitor, the absolute benefit from giving tamoxifen first followed by aromatase inhibitor might be greater.

Dr. Steven Come: But that assumes you’re stopping at 5 years on the AI.

Dr. Osborne: That’s another question. We have no idea what would happen with prolonged AI therapy, and we are not going to know that for another 5 to 10 years, so we have to deal with what we know today. Now, people in the States are going to assume that long-term AIs are better and give them after 5 years. They did that with tamoxifen.

Dr. Johnston: The bone issue is not a concern, then, in the States?

Dr. Ingle: I think the bone issue is still a concern. In my practice I have put a number of women receiving an AI on bisphosphonates, and I haven’t seen the recovery of bone density that one might hope. Dr. Osborne raised the very important point of the modulating effect of progesterone receptor, and I must say I was surprised at the way that the results from that study were dismissed because it was a retrospective analysis [Breast Cancer Res Treat 2003;82:S7]. When you have data for 1370 patients in a subset (ER positive, PgR negative) from a well-controlled study, you should at least pay some attention to it.

Dr. Aman Buzdar: We just published a study of 11,000 women on tamoxifen [Bardou et al. J Clin Oncol 2003;21:1973-9], and there are many other studies in advanced breast cancer and the adjuvant setting showing that in an ER-positive, PR-negative patient, tamoxifen is half as effective as it is in an ER-positive, PR-positive patient. The only unknown is whether the aromatase inhibitors fall into that same model or not. Judging from the ATAC trial, they don’t.

Dr. Ingle: Let me bring up one other point. What concerns me about the International Exemestane Study is the women who have been on tamoxifen for 2 1/2 years, then switched to exemestane and who then stop endocrine therapy after 5 years. I think duration is an issue with the aromatase inhibitors, and the long-term outcomes might be like Trevor Powles’ study where the hazard rate reversed itself after the women stopped the aminoglutethimide [J Clin Oncol 1992;10:1547–52].

Dr. Osborne: Two years of goserelin seem to provide the optimal benefit, at least in premenopausal women. The data are remarkable, and so it may be that with aromatase inhibitors or estrogen deprivation therapy you get whatever benefit there is very quickly. I think it’s an open question.

Dr. Per Lønning: On the other hand, there is no direct comparison of 2 years of an LHRH analogue to 5 years. I think in response to Dr. Ingle’s question, until somebody has done a head-to-head comparison, we don’t know. In regard to the BIG-FEMTA trial and receptor status, I believe that the blocks should be available from the departments of pathology in most of the participating countries, so they should be able to retrieve those data.

Dr. Osborne: The blocks are available in the ATAC trial, except it is very difficult to get them. That is what Dr. Dowsett is trying to do in the UK and Dr. Allred is trying to do it in the States.

Dr. Johnston: You may not get them all, but if you get them in a proportion then you can actually address this question. It’s such a fundamental issue.

Dr. Osborne: Today there is no question and, in fact, we said so in the consensus statement for this meeting in 2002 [Clin Cancer Res. 2003;9:443S–6S], that these large clinical trials should not be undertaken without including access to tissue blocks in the trial design.

Dr. Richard Santen: Let me change the tack from an oncologic discussion to an endocrinologic discussion. In selecting therapy, we really need to know about the patient’s baseline bone density, which can be used to decide between two practical options. If a woman has very low bone density you might pick tamoxifen. Alternatively, you might add a bisphosphonate in the patient on an aromatase inhibitor. When we get to the practical world of treating patients, I think it is this analysis of all of the factors that we are talking about. These women are going to survive 20 years, so the long-term bone health issues with aromatase inhibitors are very important.

Dr. Aman Buzdar: The adverse events associated with AIs can be monitored (for example, by bone density study) with tests and there are available interventions to treat these events (i.e., osteopenia or osteoporosis). Whereas, if a woman develops endometrial carcinoma, stroke or a pulmonary embolus on tamoxifen, there are no predictive tests or effective interventions. So, I think we have to put all these issues in proper prospective to say what are the net gains and net losses.

Dr. Johnston: Are there other trials that need to be done if we are not going to get the answer from BIG-FEMTA? The guidelines that are coming out are not going to be that prescriptive. The wording you are using is that an aromatase inhibitor is a reasonable choice, but that perhaps will leave a lot of oncologists still very confused.

Dr. Ingle: An aromatase inhibitor is a reasonable choice. It is a choice for which we don’t really know the optimal duration and where are still a lot of unanswered questions. Dr. Brodie’s work has predicted the outcomes in a number of these large clinical trials, as you know. So, in BIG-FEMTA [BIG 1-98], the arm of letrozole followed by tamoxifen shouldn’t work. They have some 8,000 patients in that study, but I don’t know that the outcome is going to change things much.

Dr. Johnston: We could take ER-positive, PR-negative and/or HER2-positive patients and give them an AI upfront, and likewise the ER-positive, PR-positive, HER2-negative patients,
then compare tamoxifen versus switching to AI after 2 to 3 years. To me, that would be an obvious question we could perhaps address, because the issue with the hormone-sensitive disease is whether we can use the sequential switch, when and for what duration, to prevent them from relapsing. In the tumors that are PR negative and/or HER2 positive, it may be that we should go for an AI upfront. Is that something that any study is addressing or should be addressing?

**Dr. Ingle:** MA.27 is a North American Intergroup study that took a year to write. It will take 4 years to complete accrual. To write a study to do what you described, which is to use the ER/PR status to define a population and look at the strategies, I don’t know if many of us would be around to see the results of such a study.

**REFERENCES**

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