The Fall of Tamoxifen?

a report by
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Dramatic changes are taking place in the way post-menopausal patients with early-stage breast cancer are treated. Tamoxifen has been the cornerstone for treating hormone-responsive breast cancer of all stages in both pre- and post-menopausal women for over two decades.[1] However, serious problems with tamoxifen including side effects, such as the fact it increases the risk of uterine cancer,[1] and the fact that many patients develop tamoxifen resistance, led to identification of new hormonal therapies. Aromatase inhibitors, which block the formation of estrogen in post-menopausal women, are not a new class of drug, but older aromatase inhibitors, such as aminogluthethimide were not selective in purely blocking the conversion of androgens to estrogens, and were somewhat abandoned as breast cancer therapies when tamoxifen was noted to have a superior toxicity profile. The newer aromatase inhibitors are all selective, and, in general, have an excellent safety profile.

Following encouraging data from trials[2–6] examining the use of selective aromatase inhibitors in patients with advanced breast cancer, several trials were initiated to evaluate their use in post-menopausal patients with early-stage breast cancer. These trials can be broadly divided into those evaluating aromatase inhibitors head to head with tamoxifen, and trials in which aromatase inhibitors are used following some duration of tamoxifen. The first adjuvant aromatase inhibitor trial to report efficacy data was a head to head trial comparing the aromatase inhibitor, anastrozole, with tamoxifen. The Arimidex, Tamoxifen and Combination (ATAC) trial randomized over 9,000 post-menopausal patients with early-stage breast cancer using anastrozole, tamoxifen, or a combination of the two agents, for a total of five years. The combination of tamoxifen and anastrozole did not result in a statistically significant better outcome than tamoxifen alone.[7] However, significantly fewer patients with hormone receptor-positive breast cancer treated with anastrozole, compared with tamoxifen, have experienced disease relapse.[7,8] At four years, disease-free survival is improved by almost 3% in patients treated with anastrozole, compared with patients treated with tamoxifen.[8] Based on these results, anastrozole was approved in 2002 as adjuvant treatment for hormone

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2. *Bonneterre J, Thurlimann B, Robertson J F, Krzakowski M, Mauriac L, Koralewski P, et al., "Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study",[see comment]* J.Clin. Oncol. *(2000), 18 (22): pp. 3,748–3,757.*
3. *Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al., "Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group", [see comment][erratum appears in* J.Clin. Oncol. *(2001), Jul 1; 19 (13): p. 3,302],* J.Clin. Oncol. *(2001), 19 (10): pp. 2,596–2,606.*
4. *Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al., "Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group",* J.Clin. Oncol. *(2003), 21 (11): pp. 2,101–2,109.*
5. *Nabholtz J M, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al., "Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group", [see comment],* J.Clin. Oncol. *(2000), 18 (22): pp. 3,758–3,767.*
6. *Paridaens R D L, Lohrisch C, et al., "Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy fro postmenopausal women with metastatic brease cancer",* Ann. Oncol. *(2003), 14: pp. 1,391–1,398.*
7. *Baum M, Budzar A U, Cuzick J, Forbes J, Houghton J H, Klijn J G, et al., "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", [see comment][erratum appears in* Lancet *(2002), Nov 9; 360 (9344): p. 1,520],* Lancet *(2002), 359 (9324): pp. 2,131–2,139.*
8. *Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, et al., "Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses",* Cancer *(2003), 98 (9): pp. 1,802–1,810.*

receptor-positive breast cancer in post-menopausal patients. Five-year follow-up from the ATAC trial will be presented at the San Antonio Breast Cancer Symposium in December 2004. Survival data from the ATAC trial and data from several other trials that compare tamoxifen head-to-head with the other two aromatase inhibitors are eagerly awaited.

Over the past 12 months, several trials that examine the use of aromatase inhibitors after various durations of tamoxifen have reported preliminary efficacy data. The National Surgical Adjuvant Breast and Bowel Projects (NSABP) B-14 trial extension trial[9] compared five years with 10 years of adjuvant tamoxifen in patients with node-negative early-stage breast cancer. Disease-free survival was statistically worse, and survival was not improved in patients who continued tamoxifen for 10 years, compared with patients who stopped tamoxifen at five years.[9] It is clear that patients with estrogen receptor (ER)-positive breast tumors can experience recurrences many years after diagnosis, and the Oxford Overview Analysis[1] has demonstrated that patients are at a high risk of recurrence after five years of tamoxifen. Therefore, it was essential to evaluate the use of newer hormonal agents in patients completing five years of tamoxifen. The MA-17 trial randomized about 4,500 patients to letrozole or placebo after they had completed five years of adjuvant tamoxifen. This trial was closed after the first interim analysis, due to a highly significant difference in estimated four-year disease-free survival in favor of the patients randomized to receive letrozole.[10] The final analysis of this trial[11] at 30 months follow-up demonstrates an absolute improvement in four-year disease-free survival of 7.5% and 2.7% in patients with node-positive and node-negative breast cancers, respectively, treated with letrozole, compared with those treated with placebo. Both distant disease-free and overall survival were significantly improved in patients treated with letrozole with node-positive tumors, but no statistical difference was seen in patients with node-negative tumors.[11] In summary, the use of letrozole after tamoxifen improved outcome, particularly in patients with node-positive tumors. One issue with this trial is that the majority of patients randomized had not received the assigned five years of therapy when the trial was closed. Therefore, it is not clear what duration of letrozole is optimal after five years of tamoxifen. The NSABP B-33 trial, which randomized patients to exemestane or to placebo after five years of tamoxifen, was closed when the results of the MA-17 trial were made available. Based on the results of the MA-17 trial, letrozole was approved for extended adjuvant therapy in October 2004.

However, it remains unclear as to whether all patients require the complete five years of tamoxifen. Data from three trials now suggest that patients who switch to an aromatase inhbitor after two to three years of tamoxifen are less likely to experience disease recurrence than patients who receive five years of tamoxifen. An Italian group[12] randomized approximately 400 patients who had completed about three years of adjuvant tamoxifen to either continue tamoxifen for the entire five years, or to switch to the aromatase inhibitor, aminogluthethimide. Patients who switched to the aromatase inhibitor were less likely to experience a visceral relapse, and had an improved overall survival and a trend to improved breast cancer survival, compared with patients receiving five years of tamoxifen.[12] The same Italian group subsequently randomized approximately 450 patients with node-positive breast cancers, who had received about three years of adjuvant tamoxifen, to either continue tamoxifen for the entire five years, or to switch to anastrozole. At a short follow-up of 36 months, patients who switched to anastrozole were significantly less likely to experience a breast cancer relapse, compared with the patients who continued to take tamoxifen.[13] A much larger trial, the Intergroup Exemestane Study (IES), randomized approximately 4,500 patients who had completed just more than two years of adjuvant tamoxifen, to continue tamoxifen for the entire five years or to switch to exemestane. At a short follow-up of 31 months, patients who switched to exemestane had an absolute improvement in three-year disease-free survival of 4.7% compared with patients completing five years of tamoxifen.[14]

9. *Fisher B, Dignam J, Bryant J and Wolmark N, "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", [see comment],* J. Nat. Cancer Inst. *(2001), 93 (9): pp. 684–690.*
10. *Goss P E, Ingle J N, Martino S, Robert N J, Muss H B, Piccart M J, et al., "A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer", [see comment],* N. Eng. J. Med. *(2003), 349 (19): pp. 1,793–1,802.*
11. *Goss P E, "Final results of MA-17 trial", Special Presentation ASCO 2004.*
12. *Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Romeo D, Caroti C, et al., "Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study",* J. Clin. Oncol. *(2001), 19 (22): pp. 4,209–4,215.*
13. *Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Massobrio M, Porpiglia M, et al., "Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment", Breast Cancer Res. Treat. 2003; 82(Supplement 1): S6.*
14. *Coombes R C, Hall E, Gibson L J, Paridaens R, Jassem J, Delozier T, et al., "A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer",* N. Engl. J. Med. *(2004), 350 (11): pp. 1,081–1,092.*

One of the reasons that tamoxifen was chosen as an agent to examine as a breast cancer preventive was the discovery that it reduced the risk of contralateral breast cancer by about 50%.[1,15] All of the adjuvant trials outlined above[7,8,10,14] demonstrate that the aromatase inhibitors are more effective than tamoxifen at decreasing the risk of contralateral breast cancers. For example, switching to exemestane in the IES trial resulted in a 56% reduction in contralateral breast cancers, compared with patients completing a total of five years of tamoxifen.[14] These findings suggest that the aromatase inhibitors should be evaluated as breast cancer preventives, and two placebo-controlled trials examining the aromatase inhibitors in this setting are on-going.

The side effects of both tamoxifen and the aromatase inhibitors could have been predicted based on their respective mechanisms of action. Tamoxifen, secondary to its estrogenic effects on differential target tissues, increases the risk of uterine cancer in post-menopausal women, and increases the incidence of thromboembolic disease.[1,15] In contrast, the aromatase inhibitors have no estrogenic effects, and therefore do not increase the risk of uterine cancer, and are associated with a lower risk of thromboembolic events.[8] However, unlike tamoxifen, the aromatase inhibitors do not have estrogenic effects on bone, and are associated with a decrease in bone mineral density and an increase in fractures.[8] The adjuvant trials have clearly demonstrated an increase in musculoskeletal complaints, particularly joint pain, in patients taking aromatase inhibitors.[8,10,14] It is important to remember that, unlike tamoxifen, long-term toxicities associated with the aromatase inhibitors are unknown. Do the results of these trials herald the end of tamoxifen? And how do these trials help us decide the best therapeutic approach for our individual patients? In considering the best hormonal therapy for patients, it is worth taking into account some of the sub-group analyses available from these trials. For example, the ATAC trial failed to demonstrate a significant difference in disease-free survival in patients with node-positive cancers treated with anastrozole, compared with those treated with tamoxifen.[7,8] In contrast, as outlined above, the use of letrozole after five years of tamoxifen significantly improved both disease-free and overall survival in patients with node-positive disease.[11] The IES trial demonstrated an improved disease-free survival in patients switching to exemestane regardless of lymph node status.[14] Based on these subgroup analyses, patients with node-positive disease may be best treated with some duration of tamoxifen, followed by an aromatase inhibitor. The on-going Breast International Group/Femera®-Tamoxifen (BIG-FEMTA) trial will address the question of whether five years of letrozole alone is better than the sequence of tamoxifen and letrozole. A retrospective analysis of the ATAC trial[16] demonstrated that there was no significant difference in disease-free survival in patients with tumors expressing both ER and progesterone receptor (PR) treated with anastrozole or tamoxifen. In contrast, patients with ER-positive, PR-negative tumors treated with anastrozole had a highly significant 50% improvement in disease-free survival compared with those treated with tamoxifen.[16] To date, it is unclear why the absence of PR renders tumors less sensitive to tamoxifen, and more sensitive to anastrozole. There is currently no data from any of the adjuvant trials on the association of tumor HER2/neu-status and outcome.

In summary, available results from these adjuvant trials do not definitively specify how to best treat patients. It seems reasonable to state that five years of tamoxifen alone is no longer adequate adjuvant treatment for most post-menopausal patients with hormone receptor-positive tumors. However, it does appear that some duration of tamoxifen should be recommended in most patients. The BIG-FEMTA trial should determine whether patients need some duration of tamoxifen, or whether they can be treated with an aromatase inhibitor alone. Five years of tamoxifen remains the adjuvant therapy of choice in pre-menopausal patients.[1] The addition of ovarian ablation to tamoxifen is being evaluated in the Suppression of Ovarian Function Trial (SOFT). This trial also evaluates the use of the aromatase inhibitor exemestane, in combination with ovarian ablation in pre-menopausal women. It is important to remember that aromatase inhibitors should not be used in women with intact ovarian function. Therefore, patients who become amenorrheic during adjuvant chemotherapy should not be treated with an aromatase inhibitor. Decisions regarding the optimal hormonal therapy should be made on an individual patient basis, taking into account differences in efficacy and in side effects between the different agents. Clearly, the aromatase inhibitors are considerably more expensive than tamoxifen. Additionally, because of the decrease in bone mineral density resulting from the use of aromatase inhibitors, many patients will require bisphosphonate therapy, which will increase the cost of their treatment.

In conclusion, incremental improvements have clearly been made in the treatment of post-menopausal patients with early-stage breast cancer. Many questions, however,

15. *Fisher B, Costantino J P, Wickerham D L, Redmond C K, Kavanah M, Cronin W M, et al., "Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study", [see comment],* J. Nat. Cancer Inst. *(1998), 90 (18): pp. 1,371–1,388.*

16. *Dowsett M, Group obot A T, "Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen and progesterone receptor status", Breast Cancer Res. Treat. 2003; 82 (Supplement 1): S7.*

remain to be answered. Do post-menopausal women need any tamoxifen at all and, if so, what duration should be prescribed? How long should patients receive adjuvant aromatase inhibitors, and how should bone mineral density loss be best managed? Finally, and most importantly, what are the long-term side effects of the aromatase inhibitors, and do they improve survival? Until these questions are answered, tamoxifen will likely remain a component of adjuvant hormonal therapy in both post- and pre-menopausal patients. ■