ADVANCES IN ENDOCRINE THERAPY FOR BREAST CANCER*

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ABSTRACT

Endocrine therapy is used frequently in breast cancer management, particularly in the setting of adjuvant care, but outstanding questions remain in choosing between available endocrine agents and the management of patients receiving long-term endocrine therapy. This article will discuss the current options in endocrine therapy and the relevant data that guide the decision to incorporate these agents into therapeutic strategies for breast cancer. Common questions that clinicians face in prescribing endocrine therapy also will be addressed. (Adv Stud Med. 2007;7(16):511-516)

Endocrine therapy is used throughout the spectrum of breast cancer disease, encompassing patients with a high risk of developing breast cancer, those with premalignant disease (such as ductal carcinoma in situ), breast cancer requiring adjuvant care, and metastatic disease. However, important controversies do exist in the choice of endocrine therapy, such as tamoxifen versus an aromatase inhibitor (AI), as well as the appropriate use of endocrine therapy in different settings. Importantly, the decision to use endocrine therapy in the adjuvant care setting can be challenging because of toxicity concerns and the fact that these agents must be administered over long periods of time. Also, the choice of agent in adjuvant care can have an impact on the long-term disease course and the characteristics of those who present with metastatic disease.

HORMONAL THERAPY IN ADJUVANT CARE

The use of hormonal therapy in the adjuvant setting is based on compelling data that demonstrate a substantial survival benefit with the use of these agents. The Early Breast Cancer Trialists’ Collaborative Group conducted a meta-analysis of approximately 37 000 women with early-stage breast cancer who were enrolled in 55 randomized clinical trials before 1990 that investigated the use of tamoxifen. Patients found to have estrogen receptor (ER)-negative disease were excluded from the analysis. Researchers found that the use of tamoxifen therapy for 5 years after cancer surgery significantly reduced the risk of recurrence and all-cause mortality in patients with both node-negative and node-positive disease. At 10 years postsurgery, patients with node-negative disease experienced a reduction of 14.9% (2-sided P < .00001) in the risk of recurrence, and a 5.6% reduction in the risk of all-cause mortality (2P < .00001). Patients with node-positive disease demonstrated a 15.2% reduction in the risk of recurrence (2P < .00001) and a 10.9% reduction in the risk of all-cause mortality (2P < .00001). However, it is important to note that the curves demonstrating a reduction
in risk began to level off after 5 years, emphasizing the chronic nature of breast cancer and the fact that opportunities certainly exist to improve outcomes (Figure 1). Overall, this analysis demonstrated the strength of tamoxifen data in terms of disease-free survival and overall survival benefits, resulting in the widespread use of this agent in the adjuvant care of patients with ER-positive disease.

In the First 5 Years Postdiagnosis, Is Initial Therapy with Tamoxifen Followed by an AI Better Than Tamoxifen or AI Monotherapy?

Although multiple trials have been conducted in an attempt to incorporate AI, it is important to note that most of the available trials had slightly different designs and included different patient populations. However, it has been demonstrated in several studies that the inclusion of an AI after an initial period of tamoxifen therapy does reduce event rates.

One meta-analysis by Jonat et al compiled data from 3 trials, including Arimidex/Nolvadex 95, Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8, and Italian Tamoxifen Anastrozole studies, all of which investigated a switching regimen from tamoxifen to anastrozole in postmenopausal patients with hormone receptor-positive early-stage breast cancer. The switch to anastrozole therapy resulted in a significant improvement in total recurrence events \( (P < .0001) \), including local recurrence, distant recurrence, and contralateral breast cancer, compared with those who remained on tamoxifen therapy (Figure 2). A modest overall survival benefit \( (P = .038) \) also was demonstrated with the switch to anastrozole, and this therapeutic strategy is now common in Europe. Another 5-year analysis of the ABCSG 8 trial alone likewise found that those who were treated with anastrozole demonstrated a 94.4% event-free survival rate compared with 92.9% in the tamoxifen monotherapy group \( (P = .068) \).

The Breast International Group (BIG) 1-98 study was different in that 4 treatment arms were compared, including those receiving tamoxifen for 5 years, those receiving letrozole for 5 years, those receiving 2 years of tamoxifen followed by 3 years of letrozole, and those receiving 2 years of letrozole followed by 3 years of tamoxifen. A modest improvement in disease-free and overall survival was found with letrozole \( (P = .003) \), but the event rate was very low in both groups at 5 years. A longer follow-up period in this patient population would be needed to reveal a more substantial outcomes benefit with a letrozole therapeutic switch.

Based on the current data, the 5-year tamoxifen regimen and switch strategy are both valid options. The switch strategy may be more attractive in younger women for whom menopausal status has not been absolutely confirmed. The important point is that...
therapeutic options are available to allow clinicians to tailor therapy to individual patient needs.

**In the Setting of Extended Adjuvant Therapy with Letrozole, Do Patients Really Need 5 Years of Treatment?**

Although no definitive answers exist in response to this question, initial data are available in the setting of extended adjuvant therapy that may provide some insight. The MA.17 trial, which investigated the use of letrozole after 5 years of tamoxifen, clearly demonstrated a benefit in terms of disease-free survival with letrozole therapy compared with placebo. Also, a significant decreasing trend in hazard ratios was observed over the course of the analysis period ($P < .0001$), suggesting a greater letrozole benefit with time. A similar pattern was observed in demonstrating a benefit with letrozole in terms of disease-free survival ($P = .013$) and overall survival (not significant).

These data suggest that the clinical benefits are indeed related to the length of therapy, and that patients benefit over time with a full 5-year course of treatment.

**After a Standard Course of Tamoxifen Has Been Completed, Can Therapy with Letrozole or Another AI Be Initiated, Even If There Has Been an Extended Period (Years) Without Any Hormonal Therapy?**

An analysis from the MA.17 trial also looked at outcomes after the unblinding of the study, when placebo-treated patients were given the option of continuing letrozole therapy. Those with more aggressive disease tended to be more likely to choose to switch to letrozole, therefore these patients were expected to have worse outcomes. Those switching from placebo to letrozole were also more likely to be younger and to have received adjuvant chemotherapy. Disease-free survival was significantly improved in patients proceeding to letrozole after placebo compared to those who had received placebo and had not continued with therapy ($P < .0001$). Also, a strong protective benefit was shown with letrozole therapy with respect to contralateral breast cancer.

The results of this study demonstrate the benefits of long-term letrozole therapy, even if years have elapsed since tamoxifen was administered.

**Should Clinicians Use Progesterone Receptor Status to Decide on an Initial Adjuvant AI Strategy?**

An analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial raised the issue of progesterone receptor (PR) status in deciding whether to initiate hormonal therapy with tamoxifen or an AI. In the ATAC analysis, patients with ER-positive, PR-negative tumors demonstrated striking benefit in terms of disease-free survival with anastrozole compared with tamoxifen ($P < .001$). Meanwhile, only narrow differences in disease-free survival were observed between treatment groups in the subset of patients who had ER-positive, PR-positive tumors. However, these results have not been reproducible. In the Intergroup Exemestane Study (IES), which investigated a switch in therapy from tamoxifen to exemestane, no differences in outcomes were observed between those with ER-positive, PR-negative disease and those with ER-positive, PR-positive disease. A lack of difference in outcomes between PR-negative and PR-positive patients has also been reported in other trials of AI therapy.

Overall, although data from the ATAC study demonstrated a differential benefit with AI therapy in patients with ER-positive, PR-negative disease, these results have not been confirmed in other analyses to the extent that a clear benefit of AI therapy can be predicted by PR status.

**Should HER2 Status Be Used to Determine an Initial Adjuvant AI Strategy?**

Patients with ER-positive, human epidermal growth factor receptor 2 (HER2)-positive disease have higher event rates and proliferation rates than those who do not exhibit these markers. This higher incidence in events has been demonstrated regardless of whether these patients receive tamoxifen or AI therapy. In these patients, the addition of trastuzumab, a HER2-receptor antagonist, to the therapeutic regimen is more important than the decision of which hormonal therapy to incorporate. In fact, the response to trastuzumab therapy is not linked to ER status. However, because many patients who are HER2-positive have high-risk disease, AI therapy is a reasonable initial choice, pending additional data.
SHOULD CLINICIANS CHOOSE BETWEEN AVAILABLE AIs BASED ON DIFFERENTIAL EFFECTS ON LIPID LEVELS OR BONE TOXICITY?

Most patients receiving hormonal therapy will experience some degree of adverse effects, and clinicians should be prepared to encounter problems, such as hot flashes, myalgia, fracture risk, and an increased risk of cardiovascular disease, in patients managed with long-term AI therapy.

BONE TOXICITY

An analysis of data from the ATAC trial was conducted to determine the relative risk of fracture, a predefined adverse event, in patients receiving anastrozole or tamoxifen. A significantly greater number of patients receiving anastrozole therapy reported fractures compared with those receiving tamoxifen (7.1% vs 4.4%, \( P < .001 \)). The IES study also reported a higher rate of fractures in patients receiving exemestane compared with those receiving tamoxifen (3.1% vs 2.3%), although this was an observed trend that did not reach significance (\( P = .08 \)). Another analysis reported a trend in increased fracture rates in patients receiving letrozole versus placebo (3.6% vs 2.9%), although these differences were not significant (\( P = .24 \)).

Patients receiving AI therapy should receive bone mineral density (BMD) screenings at appropriate intervals to determine the need for additional therapy to protect against bone density loss and fractures. The American Society of Clinical Oncology guidelines for the management of treatment-related bone loss suggest an initiation of drug therapy in patients with BMD scores of -2.5 or lower. The importance of vitamin D monitoring in these patients should be emphasized, as many patients with breast cancer may present with low levels of vitamin D. The correction of vitamin D deficiency with supplementation may avoid the need for bisphosphonates.

HYPERCHOLESTEROLEMIA

Clinical trials have raised some concern about the risk of hypercholesterolemia in patients receiving letrozole. In the BIG 1-98 trial, 43.5% of patients who received letrozole experienced hypercholesterolemia (based on nonfasting single measurements), compared with 19.1% of tamoxifen patients. However, tamoxifen may have a slight cholesterol-lowering effect that could have contributed to these differences.

Another study comparing changes in baseline cholesterol and triglyceride levels with the administration of anastrozole, letrozole, or exemestane reported that exemestane resulted in the greatest reduction in total cholesterol from baseline to 12 weeks (not significant), an effect that continued at 24 weeks despite a lack of considerable change in cholesterol levels from baseline with anastrozole or letrozole. Triglyceride levels increased with letrozole therapy at both timepoints, whereas treatment with the other AIs resulted in lower triglycerides at 12 weeks and negligible triglyceride changes from baseline to 24 weeks. These results suggest that there could be differences between AI therapies in terms of effect on lipid profiles, but additional data will be needed to determine the clinical importance of these effects, or indeed whether these findings are reproducible.

Overall, the effects of AI therapy on lipid profiles should be interpreted with caution, as most trials compared an AI to tamoxifen, which may possess cholesterol-lowering and cardioprotective benefits that confound any comparisons. Patients receiving AI therapy should have regular lipid assessments and should be managed accordingly with appropriate supportive therapy; those with particularly high baseline cholesterol levels may be considered for tamoxifen as an alternative to AI therapy.

CONCLUSIONS

Hormonal therapy has considerably advanced the therapeutic options for patients with breast cancer, but questions still remain in choosing the right regimen for each individual patient. Ongoing studies are tracking response to neoadjuvant hormonal therapy and performing detailed genomic tumor analyses postsurgery to determine the initial response to hormonal therapy, particularly in those with ER-positive and HER2-positive disease. The addition of these data to the literature will help clinicians make more consistent, informed choices when prescribing long-term hormonal management in their patients.

DISCUSSION

Dr Stearns: In a patient who is node-positive and received tamoxifen followed by AI therapy or AI therapy alone, how long would you continue AI therapy?

Dr Ellis: We do not really have a definitive answer for this question, but it has been suggested that new data may expand the recommendations for hormonal
therapy to 10 years in most patients. In my practice, in women who were switched from tamoxifen to AI, I continue to administer AI therapy after 5 years in high-risk patients.

**Dr Isaacs:** In all cases, therapy should be individualized, considering the potential risks and benefits in a particular patient. Also, the issue of side effects should be addressed with the patient, including the fact that side effects are not well characterized after 5 years of therapy.

**Dr Ellis:** Bone health is one of the most important issues in terms of side effects with AI therapy, therefore I carefully monitor the patient with regular BMD screenings as well as the need for vitamin D supplementation or bisphosphonate therapy.

**Dr Isaacs:** The long-term cardiovascular and cognitive effects of estrogen deprivation with hormonal therapy are also important issues, and I am interested in data that reveal more about the effects on cognitive function in particular.

**Dr Ellis:** Data have also been published to suggest that estrogen replacement therapy caused worsening cognitive function, thus I think our long-standing assumptions continue to be challenged with new data.

**Dr Isaacs:** Hormone replacement therapy is an excellent example of a drug that was initially considered to provide great benefits, and that has now been shown to have the potential to cause considerable harm. I think that this should signal us to proceed with caution when it comes to the potential long-term side effects with therapies such as AI agents.

**Dr Stearns:** Moving on to another important issue, how common is the use of vaginal hormone replacement therapy?

**Dr Partridge:** Although I avoid the use of exogenous hormone in all breast cancer survivors regardless of ER status, I believe that the estradiol vaginal ring 2 mg may have relatively low levels of systemic absorption, and I am comfortable prescribing these when necessary.

**Dr Blackwell:** If vaginal dryness is the only issue that is driving the consideration of a vaginal hormone replacement therapy, then I may just switch the patient from an AI to tamoxifen based on the lesser degree of this effect with tamoxifen. Also, arthralgia has been an important issue with AI therapy in my practice.

**Dr Partridge:** Arthralgia can lead to noncompliance, in my experience.

**Dr Ellis:** Vitamin D deficiency may also contribute to arthralgia and myalgia, based on recent data. Although this may not be an issue in all patients, vitamin D supplementation may resolve these effects in some women.

**Dr Isaacs:** How do you approach pharmacogenetics in clinical practice?

**Dr Stearns:** In my practice, I generally initiate AI therapy in postmenopausal women. If I am unsure about a patient’s menopausal status, I will begin with tamoxifen therapy. I am not willing to withhold tamoxifen based on pharmacogenetic testing, because we still do not have definitive answers on this front. Generally, I do not order pharmacogenetic testing.

**Dr Ellis:** What about the issue of ovarian suppression?

**Dr Partridge:** In young, high-risk patients with cancer who have a low risk of becoming postmenopausal, I have offered ovarian suppression as a treatment option, particularly in those who are interested in taking shorter courses of tamoxifen because they still want to try to get pregnant later on. I have also offered ovarian suppression in very young patients who do not want chemotherapy.

**REFERENCES**


7. Dowsett M, on behalf of the ATAC Trialists’ Group. Royal Marsden Hospital, London, United Kingdom. Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status. Presented at: 26th Annual San Antonio Breast Cancer Symposium; December 3-8, 2005; San Antonio, TX. Abstract 4.


