Adjuvant Endocrine Therapy for Breast Cancer: A Commentary


The review by Drs. Ruta Rao and Melody Cobleigh in this issue of ONCOLOGY summarizes the state-of-the-art adjuvant hormonal therapy for breast cancer concisely and appropriately. However, there are some areas in which available data could be used to build on current recommendations.

One area that some might see differently is the role of ovarian ablation in the adjuvant treatment of premenopausal women. The original Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview showed that ovarian ablation, mainly surgical or radiation-based in those days, improved disease-free survival and overall survival even in a setting in which patients had not been selected (on the basis of estrogen receptor [ER] status) to be hormonally sensitive.[1,2] The current use of tamoxifen as the standard—and its inclusion as the standard in the National Comprehensive Cancer Network (NCCN),[3] American Society of Clinical Oncology (ASCO),[4] Cancer Care Ontario (CCO) Program in Evidence-Based Care (PEBC),[5] and St. Gallen[6] guidelines—relates more to current practices than to the evidence available. That the randomized trials of luteinizing hormone–releasing hormone (LHRH) agonists alone, as outlined by Drs. Cobleigh and Rao, do not demonstrate a significant improvement in overall survival likely relates to the limited power of this relatively small meta-analysis.[7] If all trials of ovarian ablation by surgery, radiation, or LHRH agonists are meta-analyzed together, then both disease-free and overall survival are indeed significantly reduced.[7,8] There have never been direct comparisons of ovarian ablation vs tamoxifen in the adjuvant setting, and most trials of one of these therapies versus both have used tamoxifen as the single agent. Thus, the current concept that tamoxifen is the standard is based more on the current trend toward the use of pills and on the far greater number of trials using tamoxifen, perhaps driven in part by pharmaceutical funding and interests. The SOFT trial has once again chosen tamoxifen (T) as a standard, with T plus ovarian ablation (OA) and OA plus an aromatase inhibitor (AI) as the other two arms, so that the role of OA alone may never be completely addressed.

Another area that remains controversial is the paradox of “the first 2 years” in the adjuvant therapy of postmenopausal women. Cobleigh and Rao clearly describe the facts that (1) women receiving tamoxifen have recurrences during the first 2 years that do not occur in women receiving an AI, and (2) that patients randomized after 2 years to an AI vs continuation of tamoxifen do not have the same tumor characteristics as those randomized at the time of initial primary surgery, since a number of higher-risk tumors will already have recurred. In spite of this, the concept that beginning with tamoxifen and switching to an AI may be superior lingers in practice and in the Cobleigh and Rao article. In fact, starting with an AI is better, and while this may be even more the case in higher-risk patients, that observation may again relate to lower power of the data on lower-risk patients, due to there being fewer events in these patients, and consequently less of an opportunity for a differential benefit to be demonstrated for the somewhat better agent, the AI.

Cobleigh and Rao also describe the possibility of switching from one AI to another if a patient is intolerant of the first AI. While this is something we all try in practice, there is little literature to suggest that the side effects are different when a patient switches. Many of us who have followed this path in practice find that any AI produces the same or similar musculoskeletal effects and that most women in the end either decide to “live with” these side effects or discontinue AIs completely. Furthermore, the authors express a desire to see a randomized trial of an AI vs placebo in order to clarify the rate of musculoskeletal effects; there is one—MA.17.[9] In this randomized, placebo-controlled study, 33% of those receiving an AI have musculoskeletal complaints (arthralgias plus myalgia) vs 26% of those receiving placebo. However, the most important point to be stressed in this setting is that a patient who cannot tolerate an AI is much better off taking tamoxifen for 5 years than receiving no endocrine therapy at all.

Cobleigh and Rao’s interpretations of the data on the length of endocrine therapy are conventional but perhaps should be questioned. There are now data to suggest that more than 5 years—and
perhaps more than 7 or 10 years—of endocrine therapy may be superior in women with endocrine-responsive disease. We know from the Oxford Overview[10] and from other long-term follow-up studies, such as that of Saphner et al,[11] that women who have been treated for 5 years with tamoxifen continue to have appreciable rates of risk of recurrence after between 5 and 15 years of follow-up. These rates are on the order of 1% to 2% per year for patients who initially had node-negative disease and 3% to 4% per year for patients with node-positive disease.[10] Thus, the concept that 5 years of an AI alone, or 5 total years of endocrine therapy consisting of tamoxifen followed by an AI or vice versa, is sufficient is not totally supported by a comprehensive view of the literature, where there are clear data showing that adding 5 years of an AI after tamoxifen[9] or adding additional tamoxifen beyond 5 years[12,13] provides prolonged disease-free if not prolonged overall survival. Furthermore, data from MA.17[14] suggest that for every additional year of therapy with an AI there is an additional benefit. From this one might infer that until further data become available, continuing AIs beyond 5 years may be a reasonable choice. The ATLAS[13] and aTTom[12] trials both suggest that at least disease-free survival is improved by longer tamoxifen therapy. Thus, for women who are still premenopausal or who cannot afford an AI, certainly more than 5 years of tamoxifen should be considered, although clearly such a regimen is associated with an increased risk over time of endometrial cancer for those women who still have a uterus.

In sum, the points we want to make are as follows:

1. There are plenty of data to suggest that ovarian ablation may be a reasonable option as a single-agent treatment for premenopausal women in the adjuvant setting. Of course, tamoxifen or ovarian ablation plus tamoxifen are also excellent options. Ovarian ablation plus an AI may be equivalent or better, but the data from Gnant et al suggest that this may not be the case.[15]

2. AIs are probably the better choice for all women in the postmenopausal setting. While the difference between an AI and tamoxifen in low-risk patients may not seem to be significant, this may be the result of the data's weaker power, stemming from the low risk in this group, rather than the result of a treatment/tumor biology interaction. As AIs become generic and thus much less expensive, there is less reason to consider them as a second choice for any reason.

3. It is clearly better to have a patient take some adjuvant endocrine therapy in the postmenopausal setting than none. While trying other AIs of the same class or AIs of another class may be helpful in patients who demonstrate intolerance of AIs, there are few data and limited clinical experience to support this strategy. Thus, a switch to tamoxifen, with its fewer musculoskeletal effects, should certainly be seriously considered. Leaving the patient with no endocrine therapy is the least desirable choice of all.

4. The value of extended endocrine therapy may currently be underestimated. We know that patients with endocrine-sensitive breast cancer continue to run high risks of recurrence between 5 and 15 years after treatment with 5 years of tamoxifen. Probably the same is true after 5 years of an AI, after 5 years of a combination, and even after 7 to 10 years of endocrine therapy of any type. Furthermore, consideration of the extended use of AIs should include the illustration from MA.17 that for every additional year of AI therapy, patients obtained additional benefit.[14] Thus, increasing the duration of endocrine therapy, whether it be tamoxifen in premenopausal women, tamoxifen followed by an AI or vice versa in postmenopausal women, or an AI in postmenopausal women, should be considered much more seriously in routine practice, at least until data from a number of randomized trials of longer therapy give us further information.

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