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EDITORIAL

Problems With the Progesterone Receptor in Practice?

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The estrogen receptor (ER) has proven to be the best target for the treatment and prevention of breast cancer.[1] The link between ER status and response to endocrine ablation originally was observed in women with metastatic breast cancer[2] long before tamoxifen was first marketed in the United States in 1978. The development of tamoxifen for long-term adjuvant therapy[3] and the evaluation of tamoxifen efficacy in worldwide randomized clinical trials led to a substantial increase in disease-free survival and overall survival, but only in the patients with ER-positive tumors.[4,5] Unfortunately, as with all targets in cancer, not all ER-positive tumors respond, despite the fact that initially, the assay was rigorously quality controlled in cooperative groups.

The solution seemed so easy because estrogen is necessary to induce the progesterone receptor (PgR), and therefore, those patients with ER+/PgR+ breast tumors should be more likely to respond to tamoxifen therapy.[6,7] Extrapolation of these data from the metastatic breast cancer setting to adjuvant therapy has been less rewarding. There was initial promise that PgR status correlated well with disease-free and overall survivorship in stage II breast cancer.[8] However, the Early Breast Cancer Trialists' Collaborative Group Overview analysis of randomized clinical trials has found strong correlation between ER status and response to adjuvant tamoxifen but no further benefit associated with positive PgR status.[4,5]

The development of therapeutic agents targeted specifically to block the aromatase enzyme, thereby creating a "no estrogen state," has introduced a new dimension in breast cancer therapeutics.[9] A multitude of recent clinical studies have compared and contrasted several new aromatase inhibitors to adjuvant tamoxifen.

In this issue of the *Journal*, Goss et al[10] report an analysis of ER/PgR status and breast cancer responsiveness to extended adjuvant antihormonal therapy. Following the successful completion of 5 years of adjuvant tamoxifen treatment, the MA.17 trial evaluated 5 additional years of letrozole compared with a placebo control. Patients with ER+/PgR+ breast tumors constituted 73% of the patient population, whereas patients with ER+/PgR− tumors constituted 12% of the study population. The authors found that patients whose tumors are ER+/PgR+ are more likely to benefit from an additional 5 years of letrozole than are those with ER+/PgR− tumors. Should we be surprised?

The authors contend that their result is controversial in light of the fact that a recent retrospective analysis of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial[11] showed that patients with ER+/PgR− tumors are more likely to benefit from anastrozole than tamoxifen. However, the BIG (Breast International Group) 1-98 trial[12] showed that the PgR status did not influence the magnitude of benefit of letrozole compared with tamoxifen.

Patients with advanced breast cancer have a higher response rate to endocrine therapy if they have ER+/PgR+ tumors, compared with ER+/PgR− tumors.[13,14] There is also a strong inverse relationship between S phase fraction (SPF) and steroid receptor classification. Tumors with both ER and PgR expression have low SPF, and SPF increases significantly with loss of PgR.[15] What is the mechanism? We have known for nearly two decades that enhanced epidermal growth factor signaling reduces PgR levels[16] and these ER+ tumor cells respond less completely to antiestrogen treatment than ER+/PgR+ tumor cells.[17,18] These concepts have recently been confirmed and extended with reference to human epidermal growth factor receptor 2–*neu*[19] and insulin-like growth factor receptor signaling.[20] Laboratory studies also suggest that when drug resistance develops during long-term tamoxifen treatment[21] and treatment is stopped, the undetected nascent tumors will still respond to either estrogen or tamoxifen for growth.[22] These data explain the effectiveness of the letrozole after tamoxifen treatment was stopped in MA.17.

The controversy arises when the sequential adjuvant study MA.17 is compared with adjuvant antihormone treatments that are initiated immediately after surgery. Unlike either the comparative ATAC or BIG 1-98 study populations, the MA.17 study investigates responsiveness in an enriched population after tamoxifen. The enrichment is evidenced by the high proportion of ER+/PgR+ tumors (73%) compared to either the ATAC (62%) or BIG 1-98 studies (63%). In other words, the ER+/PgR− tumors are more likely to recur during tamoxifen treatment. A patient can only be included in MA.17 if tamoxifen therapy is successful.

The controversy really centers on the apparent conflict in outcomes of subgroup analyses between ATAC and BIG 1-98. Based on a small study of neoadjuvant therapy[23] in which aromatase inhibitors performed better than tamoxifen in a growth factor–rich environment, the analysis of the ATAC data according to ER/PgR status[11] supported the hypothesis that PgR− status could be used to select a cohort of patients with ER+ disease who would benefit most from adjuvant aromatase inhibitors. The

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observation in BIG 1-98 that the degree of benefit from letrozole compared with tamoxifen did not differ according to PgR status at this point seemed to be counterintuitive. Central pathology review of ER and PgR in tumor samples for 58% of randomized cases[24] (subsequently increased to 79% [M. Regan, personal communication, January 2007]) confirmed this lack of enhanced effectiveness of letrozole compared with tamoxifen for the ER+/PgR− cohort in BIG 1-98. In fact, the benefit of letrozole compared with tamoxifen was numerically larger for the ER+/PgR+ cohort compared with the ER+/PgR− cohort based on the centrally reviewed receptor values. Furthermore, 2.3% of the BIG 1-98 cases enrolled on the basis of locally determined receptor-positive breast cancer were found to have no expression of either ER or PgR on central review. This small cohort of false-positive receptor cases had a substantially worse disease-free survival compared with the centrally reviewed receptor-positive cohort, and did not benefit from letrozole compared with tamoxifen. Thus, misclassification of true receptor status can influence observed results. Obtaining quality-controlled quantification of ER and PgR values is essential to assure that patients enrolled in endocrine therapy trials have the targeted disease and also that those cared for outside of clinical trials receive proper adjuvant therapy.

Recently, Dowsett and Allred[25] presented time-to-recurrence results according to a centrally reviewed assessment of ER and PgR conducted on 32% of patients enrolled on the monotherapy arms in the ATAC trial. In contrast to the original ATAC report, which was based on data provided on the case report forms,[11] the centrally reviewed ER+/PgR− cohort did not demonstrate a differentially greater benefit of anastrozole. Notably, the centrally reviewed cases were highly selected according to geographic region, with almost 80% of United Kingdom cases included, but with less that 10% of the cases from the United States and other non-United Kingdom centers submitted for central review. It is possible, therefore, that the method of PgR determination in different parts of the world could have influenced the results.

It is also quite reasonable to conclude that the apparent differences in outcome between ATAC and BIG 1-98 reported initially are due primarily to the play of chance. The importance of PgR− status to predict markedly superior response to aromatase inhibitor compared with tamoxifen may have been exaggerated in the original ATAC subgroup analyses. The current report from MA.17 shows that the ER+/PgR+ cohort benefits more from letrozole following tamoxifen than the ER+/PgR− cohort, while BIG 1-98 suggests little difference in the magnitude of the letrozole effect according to PgR status. We fully support the recommendation of Goss et al[10] who, in their study in this issue of the *Journal*, "caution against using these results for clinical decision-making."

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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