

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Estrogen and Progesterone Receptors in Breast Cancer

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H&O Can you provide some background on estrogen receptor and progesterone receptor pathways in breast cancer?

CM Estrogen receptor (ER) and progesterone receptor (PR) signaling plays an important role in the pathogenesis of breast cancer. In addition, ER and PR expression in breast cancer cells has prognostic and predictive implications. Approximately two-thirds of breast cancer cases express ER and PR. ER- and PR-positive breast cancers tend to have a longer time to disease recurrence, whereas ER- and PR-negative cancers tend to have a more rapid growth rate and worse clinical outcome. In the ER-positive breast cancer population, PR negativity carries a worse prognosis. Importantly, ER and PR expression is required for tumor response to endocrine therapy, including antiestrogens, such as tamoxifen or flutestran, and estrogen deprivation, such as aromatase inhibitors, ovarian ablation, or gonadotropin-releasing hormone agonists.

H&O How do ER and PR interact to cause increased cell growth and increased breast cancer risk?

CM The Women's Health Initiative study showed that estrogen in combination with progesterone, but not estrogen alone, for 5 or more years increased the risk of breast cancer, indicating an interaction of ER and PR in

the pathogenesis of breast cancer. The mechanisms of this activity remain to be determined. In a report published in the June 2010 issue of *Nature*, Joshi and colleagues describe their discovery that progesterone induces adult mammary stem cell expansion in mice, possibly through the activation of a series of events involving the Wnt and RANKL signaling pathways. Estrogen was necessary to induce PR expression for the effect of progesterone to occur. This study provides a possible mechanism for the increased risk of breast cancer when progesterone is added to estrogen.

H&O What are the challenges seen with testing for ER and PR status?

CM Currently, we use immunohistochemistry (IHC) to test ER and PR expression. There are pre-analytical, analytical, and post-analytical factors that could affect the validity of the results. For example, pre-analytical variations may occur due to time spent from tumor removal to tissue fixation and the type of fixative used. The types of antibodies, assay methods, and reagents could influence the assay results. In addition, pathology interpretation and the cut-off points for ER and PR positivity can be subjective or variable. It is important to create a standardized method for each step. These challenges have resulted in inaccurate test results in at least 10% of cases in some reports. This is a critical problem in patient management.

H&O What were the CAP/ASCO guideline recommendations for ER/PR testing?

CM Because of the challenges discussed above, the College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO) created guidelines to try to improve the accuracy of ER and PR testing. The guidelines recommend standardized tissue processing, including the time limit from tumor removal to initiation of fixation, the fixative, and fixation procedures. The guidelines also state that ER and PR testing should be done in a CAP-accredited laboratory that meets the accreditation requirements. Furthermore, the CAP and ASCO discussed the cut-off points for what is considered positive. The guidelines suggest that if at least 1% of the tumor in the sample tests positive, then the ER/PR is considered positive. In addition, tumors should be retested at recurrence. Overall, the guidelines were created to make sure the IHC test is uniformly performed across different laboratories in order to provide reliable and reproducible assays.

H&O Are there any studies of interest that have incorporated ER/PR status, and what have these studies found?

CM The TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial was a study conducted in ER- or PR-positive breast cancer patients who were randomized to tamoxifen versus exemestane. The study evaluated whether the expression level of PR or ER had any role in predicting benefit of aromatase inhibitors versus tamoxifen. The study showed that PR expression, regardless of whether it was negative or positive, did not predict preferential benefit from exemestane. These were confirmatory findings, as they were similar to what was seen in the ATAC (Anastrozole Tamoxifen Alone or in Combination) trial and the Breast International Group 1-98 trial.

H&O Where is future research headed?

CM ER-positive breast cancer is a heterogeneous group of diseases. Although ER is the most robust predictor of treatment benefit, not every ER-positive cancer is responsive to endocrine manipulation. Additional markers of response are needed. HER2 positivity has been an established marker of endocrine resistance. In recent years, several multigene signatures including *Oncotype DX* and *MammaPrint* have become available in clinical practice to identify patients who are likely not going to do well with just hormonal therapy. Using molecular profiling, ER-positive breast cancer is subdivided into luminal

A and luminal B subtypes and occasionally nonluminal subtypes (such as basal-like or HER2-enriched breast cancer) by molecular profiling, which has been shown to be prognostic. Perhaps one of the most exciting areas of research lies in the genomic sequencing of ER-positive breast cancer that is analyzed in the context of clinical outcomes. At the 2011 American Association of Cancer Research meeting, Dr. Matthew Ellis presented the whole genome sequencing data of 50 ER-positive breast cancers. He compared the genome sequencing data of ER-positive cancers that had either a favorable or unfavorable clinical outcome. With this type of research we will be able to obtain not only more informative predictors, but also potential therapeutic targets for the development of more effective agents. At this time, accurate prediction of outcome based on baseline tumor characteristics and biomarkers is lacking, and there is continued research in the area.

Recent studies of neoadjuvant trials indicate that tumor response (such as on-therapy Ki67 and end-of-therapy preoperative endocrine prognostic index score) in the neoadjuvant setting provides an *in vivo* assessment of endocrine sensitivity and predicts long-term outcomes. This allows for the identification of resistant disease early in the treatment course so that strategies can be developed to prevent recurrence.

In the metastatic setting, strategies to inhibit various growth factor receptor signaling pathways are being tested in clinical trials to overcome endocrine resistance. In addition, there has been intense interest in targeting the PI3K pathway, as enhanced PI3K pathway activity has been implicated in treatment resistance. The prevalence of the PIK3CA mutation in ER-positive breast cancer (30–40%), even at recurrence, provides further impetus to target the PI3K pathway. Clinical trials are ongoing to test various agents, including inhibitors of mTOR, AKT, and PI3K, in metastatic disease.

Suggested Readings

Sanchez CG, Ma CX, Crowder RJ, et al. Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. *Breast Cancer Res.* 2011;13:R21.

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Ellis MJ, Ding L, Shen D, et al. Analysis of luminal-type breast cancer by massively parallel sequencing. Presented at the 102 Annual Meeting of the American Association for Cancer Research; April 2–6, 2011; Orlando, Florida.

LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. *JAMA.* 2011;305:1305-1314.