

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Advances in Triple Receptor-negative Breast Cancer

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**H&O** What are the clinical and pathologic characteristics of triple receptor-negative breast cancer?

**AG-A** Triple receptor-negative breast cancer is defined as disease found by immunohistochemistry and/or fluorescence in situ hybridization to be negative for expression of the estrogen and progesterone receptors and amplification of the *HER2/neu* gene. It seems that the majority of triple receptor-negative breast cancers have features consistent with those of basal-like breast cancers due to overexpression of basal-like markers. Triple receptor-negative breast cancer, accounting for 25% of all breast cancers, is more common in African-American patients, especially young, or premenopausal, African-American patients compared with premenopausal white patients. Approximately 40% of premenopausal African-American patients with breast cancer have triple receptor-negative disease compared with 16% of premenopausal non-African-American patients.

Clinically, 62% of patients present with at least stage II disease, 41% present with positive lymph nodes, and 84% have ductal carcinomas. Additionally, 84% of triple receptor-negative tumors are grade III, which indicates that the tumors grow rapidly. Patients with triple receptor-negative breast cancer appear to have more aggressive disease and experience worse outcomes than patients with HR-positive tumors or patients with *HER2*-positive tumors treated with trastuzumab (Herceptin, Genentech). However, triple receptor-negative tumors are very responsive to chemotherapy. Between 25% and 45% of

these patients experience a pathologic complete response when given adjuvant chemotherapy. The problem facing clinicians is that some patients are very responsive whereas others are resistant to therapy. When patients are sensitive to chemotherapy, they tend to have a good outcome, but when they are not sensitive and residual disease remains after chemotherapy, it seems that the outcome is very poor. Therefore, it is clear that nonresponsive patients require different therapies, but at present we do not know what the best treatment for such patients would be.

**H&O** What is the rate of relapse in this setting?

**AG-A** The majority of patients with triple receptor-negative disease relapse within 2–3 years after diagnosis, but the rate of relapse depends on the response to the treatment they have received. The 5-year disease-free survival rate regardless of therapy received in this setting is approximately 65%, with a 35% risk of recurrence. It seems that the risk of recurrence is higher in these patients than in those with hormone receptor-positive disease or with *HER2*-positive disease treated with trastuzumab. Data indicate that *HER2*-positive tumors historically have relapsed more than triple receptor-negative tumors, but with the clinical introduction of trastuzumab, these rates of relapse have reversed, with triple receptor-negative disease now more likely to recur. It has also been observed that recurrence in patients with triple receptor-negative breast cancer is more likely to be in the lung compared to recurrence in patients with other types of disease.

**H&O** What research is ongoing into new treatment options?

**AG-A** The current treatment options for patients with triple receptor-negative breast cancer are limited to chemotherapy. Other options are under investigation, however. It is thought that certain specific chemotherapies, such as platinum compounds, may be more efficacious

than nonspecific chemotherapies because of the molecular characteristics of the tumors. Two studies are ongoing with specific chemotherapies in this setting. A neoadjuvant study of therapy with a platinum-based regimen organized by a cooperative group is expected to begin soon. The usefulness of targeting angiogenesis using medications like bevacizumab (Avastin, Genentech) or tyrosine kinase inhibitors is also under investigation. Still other studies are investigating inhibitors of epidermal growth factor receptor (EGFR), such as the monoclonal antibody cetuximab (Erbix, Bristol-Myers Squibb/ImClone) or erlotinib (Tarceva, Genentech/OSI). The results of a study of cetuximab in this setting will be presented in December at the San Antonio Breast Cancer Symposium. Additionally, researchers are evaluating the utility of targeting the *BRCA1* gene because a large proportion of breast cancers in carriers of mutations in *BRCA1* are basal-like—although most basal-like breast cancers are not in carriers of mutations in *BRCA1*. The enzyme poly(ADP-ribose) polymerase (PARP) aids DNA repair; therefore, it is a target in the *BRCA* mutant tumors, which have problems in their repair capacity. PARP inhibitors given to patients with triple receptor-negative breast cancer can make these cells more susceptible to DNA damage, leading to cell death. Src inhibitors, such as dasatinib (Sprycel, Bristol-Myers Squibb), and mTOR inhibitors, such as RAD001 (Novartis), are under investigation in this setting. One neoadjuvant study is ongoing at The University of Texas M. D. Anderson Cancer Center using standard chemotherapy with or without an mTOR inhibitor. Finally, it seems that some patients with triple receptor-negative breast cancer overexpress the androgen receptor, which means that targeting this receptor could be a useful approach, and research is ongoing in this regard at Memorial Sloan-Kettering Cancer Center.

**H&O** Are patients' molecular characteristics being assessed before assignment to investigational therapies?

**AG-A** Researchers are investigating inhibitors of EGFR, PARP, *Src*, and mTOR because the molecular characteristics of these tumors indicate that these targets appear to

be appropriate for treatment. At present, however, it is unknown whether different patients express these targets differently. Through the general study of triple receptor-negative breast cancer, researchers have discovered that there is a group of patients, for example, who overexpress the androgen receptor, whereas others do not. Other patients—though not all—have defects related to *Src* and *BRCA1*. Thus, we have tried to focus our research efforts on the abnormalities seen in molecular studies.

**H&O** How can immunohistochemical markers of prognosis be used in this setting?

**AG-A** Besides the markers for ER, PR, and *HER2*, we have used antibodies against cytokeratins 5, 6, and 17, as well as EGFR. Immunohistochemistry is a technique that has significant problems with standardization, although we use it all the time and it may be practical. Ideally, we should begin to use techniques that are more precise even if they require considerable effort at the outset, such as genomics and proteomics.

### Suggested Readings

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