Treatment on the Edges: Discordance Between Stage and Biology

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One of the more difficult issues that clinicians face when helping patients make adjuvant therapy decisions is what to do when discordance exists between two important predictors of relapse risk: tumor stage and tumor biology [Albain KS. SABCS 2012 (abstr CS1-1)]. Patients with higher-stage tumors (ie, large tumors, multiple positive lymph nodes) of favorable biology (eg, luminal A tumors) and those with the opposite situation (ie, small tumors with aggressive biology) can render adjuvant therapy choices difficult. In this session, Kathy S. Albain, MD, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA, discussed issues surrounding the treatment of patients with discordant tumor stage and biology.

Dr. Albain began by discussing the scenario of tumors with advanced anatomic stage but favorable biology. The current standard of care for such patients usually includes systemic chemotherapy plus endocrine therapy (if indicated) and human epidermal growth factor receptor 2 (HER2)-targeted therapy (if indicated). However, many patients may be overtreated if this protocol is routinely followed.

Historically, many patients with higher-stage early disease but favorable biology (usually estrogen receptor [ER]-positive) remain free of breast cancer recurrence after surgical treatment and endocrine therapy, and live a normal life expectancy. The risk and time course of distant metastases generally varies by tumor size, but not all large tumors recur. Nevertheless, it is not currently possible to reliably identify those cancers with bad stage that could be cured by surgery and endocrine therapy, or which patients could be spared chemotherapy.

Standard factors that define bad stage are higher T stage, positive axillary nodes, and the number of positive nodes. Nonetheless, this high-risk status could potentially be overruled by high ER levels, low-grade/well-differentiated tumors, low proliferative rate by Ki67, low 21-gene recurrence score assay, or a good-risk 70-gene signature (ie, favorable biology). Beyond this, the treatment of ER-positive breast cancer can be complicated by issues of tumor heterogeneity, de novo and acquired drug resistance, and tumor HER2 status.

Some ER-positive tumors with large tumor size and/or nodal involvement are indolent and may be cured by endocrine therapy alone, separating them from luminal B-like tumors that may still have added benefit from chemotherapy. These indolent tumors include luminal A-like cancers and others that may be cured by endocrine treatment monotherapy.

ER-positive tumors with adverse tumor and nodal features that are classified as having less favorable biology (eg, luminal B-like tumors) remain high risk and require creative strategies to circumvent tumor growth and progression driven by multiple pathways. This biology may still be relatively resistant to standard chemotherapy, and endocrine monotherapy has insufficient efficacy in these unique tumors. Inhibition of cross talk with pathways that take over driving tumor growth when hormone receptors are blocked is necessary to treat these luminal B tumors.

In higher-stage HER2 nonamplified subgroups that are endocrine responsive with low proliferation (variably defined by low 21-gene recurrence score, luminal A, or low-risk 70-gene signature), avoidance of standard chemotherapy may be justified due to relative resistance. Dr. Albain concluded, "The highest risk scenarios that also present with this biologic profile require alternate strategies to increase cure rates."

In the same session, Martine J. Piccart-Gebhart, MD, PhD, Jules Bordet Institute, Brussels, Belgium, discussed the issues surrounding treatment of patients with a low stage but adverse tumor biology. Prof. Piccart-Gebhart provided key messages about the natural history of T1a,bN0M0 breast cancers.

First, the number of T1a,bN0M0 tumors identified is increasing due to mammographic screening. When patients with T1a,bN0M0 tumors are examined in large population databases and unselected for adverse biology, the specific mortality rate associated with these tumors at 10 years is <5%. Women aged >50 years with T1a,bN0M0 tumors have significantly higher death rates from causes other than breast cancer. Furthermore, breast cancer-specific survival is >90% at 12 to 15 years for women with unselected screen-detected T1a,bN0M0 tumors. For patients with small lobular/ductal cancers, about 25% of all relapses occur beyond 10 years, and the number of distant relapses is comparable to locoregional relapses. For these tumors, discrimination between T1a and T1b may have little clinical relevance.

Despite these relatively good outcomes for the T1a,bN0M0 population as a whole, certain biological features may be considered adverse in these breast cancers, including ER negativity, HER2 positivity, high grade, vascular invasion, and high proliferation. Characteristics of an adverse genomic

landscape for T1a,bN0M0 breast cancer are still being investigated. In addition, patient age may also serve as an important factor in defining tumor biology. After adjusting for breast cancer subtype and other tumor characteristics, patients aged ≤35 years have been reported as having 2.51 (95% CI, 1.21 to 5.22; p=0.013) times lower chance of recurrence-free survival (RFS) and 2.60 (95% CI, 1.05 to 6.46; p=0.04) times lower chance of distant RFS compared with patients aged >50 years [Theriault RL et al. *Clin Breast Cancer* 2011]. Clinicians should also consider whether a T1a tumor may be underestimated in size due to tissue processing and fixation [Pritt B et al. *Hum Pathol* 2005]. Factors that may lead to underestimating of tumor size include preoperative biopsies, handling of the specimen, and paraffin temperature. Pritt et al. [*Hum Pathol* 2005] found that tumor shrinkage occurred in 40% (20) of samples from the fresh to final processed stage.

Currently for small luminal breast cancers the National Comprehensive Cancer Network (NCCN) Guidelines recommend that clinicians consider chemotherapy only if there are nodal micrometastases present for a T1a tumor or if a patient has an intermediate or high 21-gene recurrence score in T1b [NCCN Panel. *NCCN Guidelines Version 3.2012*: *Breast Cancer* 2012]. For small triple-negative and HER2-positive breast cancers, the NCCN Guidelines recommend considering chemotherapy for T1a lesions with nodal micrometastases or T1b lesions.

Careful analysis of outcomes specifically for patients with small tumors with adverse biologic features is critical to further defining adjuvant treatment strategies, as an understanding of the risk of recurrence helps define the magnitude of absolute benefits to be gained from chemotherapy. In the literature, data from a few large population-based studies and many small single-institutional studies (which are subject to bias) are available for T1a,bN0M0 breast cancer. All of these studies are retrospective and few have truly mature follow-up data. In parallel, greater understanding of the biology of these small tumors is needed. Two hypotheses about the genomic landscape of T1a,bN0M0 disease are that "HER2-positive tumors probably have acquired their full mutational/rearrangement landscape" by the time they reach the T1a stage and "triple-negative tumors probably have acquired some—but not all—of their mutational/rearrangement landscape when <1 cm."

Since clinical trials are often not open to patients with T1a,bN0M0 tumors, Prof. Piccart-Gebhart concluded that more initiatives like the ones at the Dana-Farber Cancer Institute (eg, investigating novel adjuvant regimens for patients with T1a/b HER2-positive disease) are needed to gain more knowledge about the benefits versus harm of treatments.