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Current Developments in the Management of Solid Tumor Malignancies

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Subtyping of Triple-Negative Breast Cancer

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H&O What are the known subtypes of triple-negative breast cancer, and how common are they?

IM These are not considered official categories at this point, but in an article published in the *Journal of Clinical Investigation* in 2011, a team led by Lehmann and Pietenpol described 6 subtypes: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor (LAR). "Unclassified" is considered to be a seventh subtype.

Between 10% and 20% of breast cancers are triple-negative, meaning that they do not express estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 (HER2) genes. Of these, approximately 40% fall into the basal-like 1 or 2 subtype, and approximately 10% fall into the LAR subtype.

H&O How are the subtypes of triple-negative breast cancer determined?

IM In the Lehmann/Pietenpol study, the subtypes were determined using genomic array technology. This technology is able to identify tumors that have a similar genetic pattern and cluster them together for analysis. The genetic pattern is like a bar code; some tumors will cluster into one kind and others will cluster into a different kind.

Genomic array gets beyond what we can see simply by looking at a tumor through a microscope. Although we can see certain differences in the laboratory, those differences do not tell the whole story because tumors behave so differently from each other.

In some cases, we have other ways to determine the subtype. For example, we have been able to detect the LAR subtype by using immunohistochemistry to determine the presence or absence of androgen receptors.

H&O What are the benefits to knowing the subtype of triple-negative breast cancer?

IM Although there is a lot of excitement about what these different subtypes mean, the classifications do not have a solid clinical application at present. Even if they did, we are not able to determine in the clinic what a patient's subtype is via standard tests.

A lot of resources right now are being devoted to laboratory studies of which drugs produce the best response in tumor cells of various subtypes. For example, the fact that the basal-like 1 and 2 subtypes are more dependent on genes that control cell cycling and DNA replication could suggest that patients with these tumors might benefit from platinum agents or other drugs that directly affect cell cycling and DNA replication.

Some of the characteristics that we are finding in the laboratory do not have a corresponding drug, however. For example, the mesenchymal subtype seems to be

dependent on tumor growth factor-β and other types of molecular pathways, such as the insulin growth factor pathway, and potentially the PI3K pathway.

The immunomodulatory subtype has high levels of immune cell signaling, but we do not know whether this makes the tumors respond better to some of the newer drugs, such as anti–PD-1 agents. All of this is speculation, but clinical trials to investigate this will be starting soon.

The one subtype that seems to stand out as a separate entity is the LAR subtype. It is possible that this type of breast cancer will respond to androgen receptor (AR) blocker combinations. In a phase 2 trial by Gucalp and associates, 424 patients with metastatic triple-negative breast cancer were tested for AR positivity. About 50 patients tested positive; these patients received bicalutamide—an AR blocker—as a single agent until they either developed disease progression or had unacceptable side effects from the drug. The results of this trial were not impressive: after more than 6 months of treatment, only 19% of the patients had a complete or partial response or demonstrated stable disease. However, the team led by Lehmann and Pietenpol has shown that about 70% of LAR triple-negative tumors also have a mutation in the *PIK3CA* gene. Therefore, we are now launching a phase 2 clinical trial for patients with AR-positive triple-negative metastatic breast cancer that explores the combination of bicalutamide with a PI3K inhibitor.

H&O Do the different subtypes of triple-negative breast cancer differ in how well they respond to treatment?

IM The subtypes may have different responses to chemotherapy, as demonstrated in a study that was presented at the most recent American Society of Clinical Oncology meeting. In this retrospective study, Masuda and colleagues tested tumor samples from 130 patients who had undergone treatment for triple-negative breast cancer with standard sequential taxane and anthracycline-based regimens. Tumor samples were analyzed and classified using the same methods and subtypes described by Lehmann/Pietenpol and colleagues.

The researchers found that the pathologic complete response rate was highest for the basal-like 1 subtype (52%) and lowest for the basal-like 2 and LAR subtypes

(0% and 10%, respectively). These findings suggest that the basal-like 1 subtype is more responsive to chemotherapy than the other subtypes. However, the Masuda study was retrospective and the numbers were small, so these results should be taken with a grain of salt. Here at Vanderbilt, we are launching trials in which we will prospectively determine the subtypes and hopefully be able to tease out these differences in a more convincing way.

H&O Could you talk more about your research?

IM The study that just launched in September is a randomized, phase 2 clinical trial led by one of my partners at Vanderbilt, Dr Vandana Abramson. This trial is looking at patients with metastatic triple-negative breast cancer who are undergoing first- or second-line treatment. We are testing the patients' tumors to detect the presence or absence of AR, as well as the different genomic subtypes of triple-negative breast cancer. If patients have the LAR subtype, they will receive a combination of bicalutamide with a PI3K inhibitor in a phase 2 single-arm clinical trial. If they do not have the LAR subtype, patients will be enrolled on a randomized phase 2 clinical trial of single-agent cisplatin with or without a PI3K inhibitor.

The rationale behind this approach is that the cisplatin by itself should be effective against basal-like subtypes, which overall are quite sensitive to platinum agents. The addition of the PI3K inhibitor appears to be effective against the mesenchymal subtype in the laboratory. Patients whose disease progresses on cisplatin alone will be able to cross over to receive cisplatin with the PI3K inhibitor. We are hoping that the above combination therapy will provide the most substantial responses in the AR-negative/triple-negative metastatic breast cancer group of patients.

Suggested Readings

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767.

Masuda H, Baggerly KA, Wang Y, et al. Differential pathologic complete response rates after neoadjuvant chemotherapy among molecular subtypes of triple-negative breast cancer [ASCO abstract 1005]. *J Clin Oncol*. 2013;31(suppl 15).

Gucalp A, Tolaney S, Isakoff SJ, et al; the Translational Breast Cancer Research Consortium (TBCRC 011). Phase II trial of bicalutamide in patients with androgen receptor positive, hormone receptor negative metastatic breast cancer [published online August 21, 2013]. *Clin Cancer Res*. doi:10.1158/1078-0432.CCR-12-3327.