ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Novel Targets for Triple-Negative Breast Cancer

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H&O Can you provide some background on triple-negative breast cancer (TNBC)?

LC TNBC has existed forever, but it was not identified as a separate category of breast cancer until approximately 10 years ago, because there was no routine testing for HER2 until the late 1990s/early 2000s. There are several reasons that the TNBC subtype became important. Over time, it became the standard of care to obtain 3 markers in all breast cancers: the estrogen receptor, the progesterone receptor, and HER2. This became the standard because we had developed drugs for each category of breast cancer—antiestrogen therapy options to treat hormone receptor–positive breast cancers and HER2-targeted drugs to treat HER2-positive breast cancers. It became evident that the patients for whom we did not have targeted treatments were the triple negative subgroup of breast cancers. Hence, part of the clinical and research interest in this group is due to the lack of targeted treatment for these patients. Concurrently, scientists who were working on molecular profiling began to identify subclasses of breast cancer from a biologic standpoint, called the intrinsic subtypes or the molecular profiles of breast cancer. They demonstrated that what we call *TNBC* clinically comprises at least 2 molecular subtypes, similar to how ER-positive breast cancer is made up of 2 or 3 subtypes. So, there was an overlapping of an emerging understanding of the scientific underpinning of the biology of breast cancer with the clinical development of drugs for breast cancer. Because we now recognize that there is a unique biology to some of the breast cancer subtypes—like the basal subtype that makes up the majority of TNBC—this may provide a direction in terms of treatment strategies.

H&O What is the current treatment approach?

LC The current treatment approach for patients with TNBC is chemotherapy. The good news is that as chemotherapy got more advanced, it got better, particularly for the triple negative and HER2-positive subtypes. There are some drugs like bevacizumab (Avastin, Genentech) that seem to work to the same degree across subtypes, including TNBC. At the San Antonio Breast Cancer Symposium, results from the GeparQuinto study were presented. These findings suggested that in the neoadjuvant setting, the addition of bevacizumab to chemotherapy may help improve treatment of the tumor while it is still in the breast. Thus, this combination may play a role in early breast cancer. We will know much more about this when the larger trials testing agents in TNBC are completed.

H&O Why is TNBC a subset that is more challenging to treat compared to other subsets?

LC TNBC is a more aggressive subtype when left untreated, and it carries a poorer prognosis in general. There are a number of subtypes of breast cancer that appear to be more aggressive, but TNBC has a bad com-

bination of being inherently more aggressive and having fewer treatment options. When TNBC is being treated in the metastatic setting, it tends to grow faster and have a shorter time of response than other subtypes.

H&O What targets are currently being investigated? What kinds of studies are ongoing in TNBC?

LC Poly (ADP-ribose) polymerase (PARP) inhibition has been an area of great interest in the past year. There is an overlap of TNBC—particularly the basal type that comprises the majority of TNBC—with BRCA-associated breast cancer. Women who carry an inherited form of breast cancer from the BRCA gene most frequently develop basal-like breast cancer when they get TNBC. This fairly new class of drugs, PARP inhibitors, have particular promise in BRCA1- or BRCA2-associated breast cancer and ovarian cancer. Because there are some similarities between basal-like breast cancer in women who do not have the inherited form and BRCA-associated breast cancer, some have considered whether these PARP inhibitors may also work in regular basal-like breast cancer. There are several small studies in which only oral PARP inhibitors were given to breast cancer patients to see if there was a benefit. The studies found that PARP inhibitors by themselves did not result in much benefit unless the patient had a BRCA1 or BRCA2 mutation. Although these studies were small and not very definitive, these findings call into question the assumption that basal-like breast cancer will behave the same whether it is BRCA-associated or sporadic.

Another drug being investigated is iniparib (Sanofi-Aventis). It has some PARP inhibitor activity but we are not very clear on its mechanism of action. A randomized phase II study that evaluated gemcitabine and carboplatin versus the 2 drugs with iniparib was published in the *New England Journal of Medicine* in January 2011. The findings showed that adding iniparib to these 2 chemotherapeutic agents has a significant improvement in progression-free survival and overall survival. However, the phase III trial presented at the 2011 American Society of Clinical Oncology meeting did not confirm these results. If there was an impact of iniparib added to chemotherapy, it was very small. At this point we are uncertain of the role of this drug and in whom it should be used.

There are a number of other targeted agents that are being investigated. There are inhibitors of other growth factor pathways that are of great interest in TNBC subtypes; those studies are currently ongoing. There was a series of studies looking at EGFR inhibition, as it appeared to be a very hopeful area of research. There was a randomized study presented last year called BALI-1 (Randomized Phase II Trial With Cetuximab and Cisplatin in the Treatment of ER-negative, PgR-negative, HER2-negative Metastatic Breast Carcinoma ["Basal Like"]), which found that the response rate to platinum chemotherapy (cisplatin) and the progression-free survival were augmented with the addition of an EGFR inhibitor (cetuximab). However, it was only a modest change, and so it is evident that solely using triple negative as a selection strategy is not going to lead to development of effective targeted therapies. It will be necessary to more carefully examine what is happening within TNBC in order to identify patients who have tumors that are appropriate for certain approaches.

H&O What kind of research is being done with predictive markers?

LC There are a number of groups working on predictive profiles for chemotherapy benefit; we do not really have any yet for ER-negative breast cancer. The profiles that have been used that were prognostic and, to a degree, predictive in ER-positive breast cancer—such as Recurrence Score or MammaPrint—do not seem to work in ER-negative breast cancer. The development of that type of profile is much further behind in ER-negative breast cancer. Therefore, identifying the predictive profiles of patients that are most likely to benefit from this approach is the goal.

H&O What are the main goals in the diagnosis and treatment of TNBC?

LC Improving screening is important for TNBC because this type of cancer tends to affect younger women more frequently. In terms of prevention, this is a weak area. If we can better identify who is at risk for getting a particular type of breast cancer, then we can go back to the drawing board to figure out prevention strategies.

There are some population-based studies coming from the earliest phases of the Carolina Breast Cancer Study, which is a population-based study that oversampled premenopausal breast cancer and breast cancer in African American women. When the investigators looked at the tumors by subtype, the risk factors differed from one subtype to another. Breast-feeding was a much stronger protective factor for basal-like breast cancer than it was for luminal A breast cancer. Similarly, there was a switch of the effect of having many children and having children at a young age; obesity was also a much stronger risk factor. Hence, there is a suggestion that we can really get smarter about how to prevent breast cancer if we can get a handle for who is at risk for the different kinds of breast cancers. There are numerous groups working on some of the genetic risk factors that may be different for ER-negative

subtypes of breast cancer, and that information combined with populations at risk—like young women or African American women—will give us a much more tailored approach to prevention.

Many women with early-stage TNBC will do well and may not even need chemotherapy. Figuring out good prognostic profiles in that group in order to avoid chemotherapy in those who do not need it would be great. Also, establishing who needs what kind of chemotherapy is a very worthwhile pursuit. Finally, there is a strong, ongoing effort to find appropriate targeted agents in all the specific subtypes of breast cancer.

Suggested Readings

O'Shaughnessy J, Osborne C, Pippe JE, et al. C. Iniparib plus chemotherapy in cetastatic triple-negative breast cancer. *N Engl J Med.* 2011;364:205-214.

Baselga J, Gomez P, Awada A, et al. The addition of cetuximab to cisplatin increases overall response rate and progression-free survival in metastatic triple-negative breast cancer: results of a randomized phase II study (BALI-1). *Ann Oncol.* 2010;21:viii96–viii121. Abstract 2740.

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Untch M, Loibl S, Bischoff J, et al. Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: primary efficacy endpoint analysis of the GEPARQUINTO Study (GBG 44). Presented at the San Antonio Breast Cancer Symposium; December 10, 2010; San Anotonio, TX.