ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

Treatment Options for Triple-Negative Metastatic Breast Cancer

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H&O Can you discuss the triple-negative subtype of breast cancer?

JO There are 3 main molecular subtypes of triple-negative breast cancer (TNBC). The first is the fastest growing kind, referred to as basal-like; most triple-negative tumors are basal-like. Among other molecular abnormalities, this subtype has problems with DNA repair machinery. Basal-like breast cancer may be amenable to treatment with DNA-damaging agents such as cisplatin. The second molecular subtype is the mesenchymal breast cancers; these are triple-negative (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and human epidermal growth factor receptor [HER]-negative) and sometimes have stem cell features. Mesenchymal breast cancers are also highly proliferative.

The third molecular subtype is luminal apocrine; this subtype is triple-negative and androgen receptor–positive, which is rare. The luminal apocrine subtype has a distinct clinical phenotype; these cancers tend to be accompanied by bone metastases and lymph node involvement, and are more indolent.

From a clinical practice standpoint, there are no breast cancer subtypes that are associated with changes in treatment approaches. Researchers are attempting to understand, at the scientific level, the various breast cancer subtypes and their molecular abnormalities. In the near future, we hope to conduct clinical trials to match up the cancer subtypes with specific therapies. However, at present there are no subtypes of proven clinical utility.

H&O What are the main goals of treatment of metastatic TNBC?

JO In early breast cancer, the goal is cure. In metastatic breast cancer, the goal is prolongation of life and improvement of cancer-related symptoms. We aim to use the least toxic therapy possible to get the most improvement in symptoms, but the overarching goal is improvement in survival. There is no difference in goals in treatment of TNBC versus ER-positive or HER2-positive breast cancers.

H&O What factors are evaluated when deciding on treatment in patients with metastatic TNBC?

JO Upon presentation, oncologists have to confirm that the patient's cancer is in fact ER-, PR-, and HER2-negative. Regardless of whether the testing is done at an academic or a community laboratory, there is still variation in identifying ER, PR, and HER2 status. Hence, it is important to biopsy metastatic disease to confirm that the metastatic clone from the original primary is not different from the original breast cancer.

H&O What are the treatment options for women with metastatic TNBC?

JO When a woman presents with metastatic TNBC, the main priority is to enroll her onto a clinical trial, as our current treatment options are inadequate. The use of bevacizumab (Avastin, Genentech) benefits this particular breast cancer subtype. The data in triple-negative patients have been very positive, and bevacizumab is the only drug we have that is non–cross-resistant with chemotherapy. Unfortunately, chemotherapy is very limited in its effectiveness in women who have recurred rapidly within 1 or 2 years of adjuvant therapy. For these women, bevacizumab has been, and continues to be, a mainstay of treatment, and we hope that it will be approved again in the future by the US Food and Drug Administration for metastatic breast cancer. Because of the lack of targeted treatments, clinical trials are very important, as they bring additional treatment options to light.

There are several options for treatment of metastatic TNBC, for which we have level 1 evidence from phase III trials. For women who have already received adriamycin, cytoxan, and a taxane in the adjuvant setting, the choices are weekly paclitaxel and bevacizumab, gemcitabine and carboplatin, or ixabepilone (Ixempra, Bristol-Myers Squibb) and capecitabine (Xeloda, Genentech). These combinations are well supported by clinical data. There are large phase III trials.

H&O What are some interesting areas of research?

JO An important issue to address is the bevacizumab question. We need to evaluate women who have higher plasma levels of vascular endothelial growth factor A (VEGF-A), which is the ligand to which bevacizumab binds. The hypothesis is that patients with higher VEGF-A levels, such as those with aggressive cancers like TNBC, will benefit from bevacizumab. This hypothesis is going to be tested in a trial that is being conducted by Genentech.

Another interesting area of investigation is the combination of MEK and AKT inhibitors. MEK inhibitors inhibit the RAS pathway, and AKT inhibitors inhibit the PI3 kinase pathway. We believe that both the RAS and PI3 kinase pathways are important in metastatic TNBC. There are currently ongoing combination studies looking at RAS and PI3 kinase inhibitors. There have been some patients who have already responded to therapy, but this research is still in the earliest phase.

Another area of research is the DNA-damaging agent iniparib (Sanofi-Aventis/BiPar Sciences). This drug used to be considered a poly (ADP-ribose) polymerase (PARP) inhibitor, but in fact it is not a PARP inhibitor in the physiologically delivered doses. Iniparib is again in phase I testing to determine whether it will function as a PARP inhibitor at higher doses. We are also attempting to determine which subset of TNBCs benefit from iniparib. This is a very active area of study, and we hope to see a subsequent trial in a molecularly selected group of TNBC patients.

There is also research, led by Dr. Kornelia Polyak, originating from the Dana Farber Cancer Center looking at the JAK2/STAT3 pathway in TNBC. Dr. Polyak and colleagues are conducting a phase II study with a JAK2 inhibitor in this specific patient population.

Finally, my colleagues and I collaborated with Dr. Lisa Carey on a study looking at epidermal growth factor receptor (EGFR) inhibition in TNBC. We found that a very small percentage (5–8%) of metastatic TNBC patients may have a prolonged benefit in multi-year remission with the anti-EGFR agent cetuximab (Erbitux, Eli Lilly/Bristol-Myers Squibb). We have performed molecular analyses to identify the "super responders," and we are considering a prospective trial, which will molecularly select for this population.

H&O What were some noteworthy findings presented at the recent meetings?

JO Understanding the molecular pathways that are permitting the survival of lethal breast cancer is of critical importance. The results of the phase III trial of iniparib in TNBC, which I presented at this year's American Society of Clinical Oncology (ASCO) meeting, were a big disappointment, especially because the data were positive in the phase II trial.

At the 2011 San Antonio Breast Cancer Symposium (SABCS), I presented our study on whole genome sequencing in 12 metastatic TNBC patients. In our study, we harvested tissue from metastatic TNBC patients and performed complete genomic and RNA sequencing. I presented the clinical outcomes of 6 of the patients; there were abnormalities in both the RAS and PI3 kinase pathways. Based on the mutations discovered through sequencing, these patients are being offered treatment with combined MEK and AKT inhibitors on an ongoing phase I study. I think there was interest in this presentation because it is indicative of the strategy we need to be taking in these patients. We need to understand the molecular abnormalities in metastatic TNBC, and to enroll patients on national clinical trials.

The ability for clinicians to access broad-based genomic assessments of a patient's metastatic cancer is rapidly approaching. Several diagnostic companies are prepared to launch molecular analyses, but clinical trials are

needed to show clinical utility. Increasingly, women who want to participate in clinical research will be able to get these molecular tests, including whole genome sequencing.

Also presented at SABCS was a report from the working group of The Cancer Genome Atlas (TCGA) Program. In collaboration with the International Genome Consortium, TCGA is working on assembling a database of gene sequencing and RNA profiles on breast cancers, which can be shared among scientists and clinicians. We are now discovering the molecular abnormalities driving the TNBCs that recur (20–25% of patients recur after adjuvant chemotherapy). The diagnostics are here, but the challenge is creating enough clinical trials of novel agents and making them more widely available in the United States and across the world, so that women can have easier access to promising clinical trials for their specific breast cancer.

Suggested Readings

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

Yau C, Benz S, Sanborn JZ, et al. SuperPathway analyses of luminal and basaloid breast cancers from the Cancer Genome Atlas (TCGA) Program. Presented at the 2011 San Antonio Breast Cancer Symposium. December 6-10, 2011. San Antonio, Texas.

Shrestha Y, Schafer EJ, Boehm JS, et al. PAK1 is a breast cancer oncogene that coordinately activates MAPK and MET signaling. *Oncogene.* 2011. Nov 21 [Epub ahead of print].