ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer In Focus

PARP Inhibition Outside of BRCA Mutation Carriers

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H&O What is triple negative breast cancer?

SI Triple negative breast cancer (TNBC) is a term that has been used for almost a decade that refers to the immunohistochemical staining pattern of approximately 15–20% of breast cancer patients that is defined by a lack of expression of the estrogen receptor, the progesterone receptor, and HER2. It is the lack of these 3 markers that led to the term *triple negative.* Breast cancer (BRCA)1 mutation carriers who develop breast cancer most commonly develop TNBC. However, BRCA2 mutation carriers develop the full spectrum of subtypes, including estrogen receptor–positive and HER2-positive breast cancers. Although most BRCA1-associated breast cancers are triple negative, the converse is not true, as most TNBC is not associated with any BRCA mutation; it is usually a sporadic (nonhereditary) development that is not completely understood. The triple negative subtype of breast cancer is seen more frequently in certain populations, such as premenopausal African American women. The incidence may be as high as 30–40% in these higher risk populations. Histologically and clinically, TNBC is higher grade, with a propensity to spread to visceral organs earlier in the disease course. Recurrence often occurs within the first several years after treatment. TNBC is seen more commonly in younger women, which may explain why younger women sometimes have a more aggressive form of breast cancer.

H&O What have studies of PARP inhibitors found?

SI Poly(ADP-ribose) polymerase (PARP) inhibitors are drugs that obstruct the ability of cells damaged by chemotherapy or through genetic mutations to repair themselves, causing tumor cell death. PARP inhibitors have exhibited antitumor activity in breast, ovarian, and prostate cancers associated with breast cancer BRCA1 and BRCA2 mutations.

The data that have been presented so far have shown that iniparib (BSI-201, BiPar Sciences), a compound currently under investigation, is active in the TNBC population when combined with chemotherapy. A phase II study was recently updated at the 2010 European Society of Medical Oncology meeting. The study showed that the addition of iniparib to gemcitabine and carboplatin improved the response rate and increased progression-free survival from 3.6 months to 5.9 months. Interestingly, there also appeared to be an overall survival benefit of approximately 4.6 months. This trial led to the development of a phase III, randomized, placebo-controlled trial that completed enrollment earlier this year; we are eagerly awaiting confirmation from this study. So far, there have not been many other compounds to show activity in the population without a BRCA gene mutation. There was a presentation by Dr. Karen Gelmon at the 2010 American Society of Clinical Oncology meeting of a study in which a subset of ovarian cancer patients without a BRCA1 or BRCA2 mutation had some benefit from PARP inhibition with olaparib (AstraZeneca). However, in that study, there did not seem to be any single-agent activity with olaparib in the non-BRCA TNBC population. The research is still in its early stages, and many of the PARP inhibitors are being looked at in combinations with chemotherapy. We are hopeful that these combinations will produce some activity in the non–BRCA-associated breast cancer population.

H&O What is synthetic lethality and how is it applicable in breast cancer?

SI The term *synthetic lethality* has roots that stem from classic bacterial and fruit fly genetics. It is a term that describes the concept that individual mutations by themselves do not seem to cause any particular phenotype, but when combined, they result in the expression of a phenotype. The way this term has been applied to the use of PARP inhibitors in BRCA-associated cancer has to do with the DNA damage response and repair pathways. Normally, we inherit 1 copy of the BRCA1

and BRCA2 genes from each parent. In mutation carriers, one of those copies of either BRCA1 or BRCA2 is not functional. These patients are at higher risk of developing breast cancer when the normal copy of the BRCA gene also develops some mutation that prevents it from working. All cells undergo some DNA damage as they are growing and dividing; this damage is often repaired through the BRCA pathway. However, when that pathway is nonfunctional, there are redundant pathways that complement the BRCA pathway. One of them is the base excision repair pathway, which requires an intact PARP pathway. The notion of synthetic lethality is that each of these 2 interventions alone—either inhibiting the PARP enzyme or making the BRCA genes nonfunctional—will not cause a major problem in DNA repair, but both interventions combined cause catastrophic DNA damage that the cell cannot repair, which leads to tumor cell death.

H&O What are some of the promising PARP inhibitors being studied?

SI Iniparib is the furthest along in development in the triple negative subgroup of patients. Olaparib has been studied in a phase II trial in BRCA carriers that showed a significant response of 41%. In addition, veliparib (ABT-888, Abbott) is also in clinical trials. We recently completed a trial of veliparib with temozolomide to evaluate their combined activity in metastatic breast cancer unselected for subtype. In this trial we found that only BRCA carriers appear to respond to the drug combination. There are a number of companies developing various PARP inhibitors that are in preclinical or early-stage testing, and there are early trials with compounds from Pfizer and Merck. Structurally, veliparib and olaparib are in a similar family and are good inhibitors of PARP1 and PARP2, whereas iniparib has a different chemical structure and may preferentially inhibit PARP1.

Many of the ongoing early-phase studies are looking at combinations of PARP inhibitors and chemotherapy. Some of the compounds are being investigated not just in the metastatic setting, but also in other areas of importance such as early-stage treatment with preoperative therapy; for primary prevention in patients at high-risk for BRCA-associated breast cancer; and in challenging settings such as in the case of brain metastases from breast cancer. Some of these compounds are able to cross the blood-brain barrier, and there is a lot of interest in trying to combine these PARP inhibitors with agents that might also pass into the brain to determine whether they can create a more effective attack strategy.

H&O What do we hope to see with PARP inhibitors in non-BRCA carriers?

SI We are all very hopeful that PARP inhibitors will find some role in adding another effective treatment to TNBC. TNBC tends to have higher response rates to chemotherapy because of its high-grade nature, but it also tends to progress more quickly. Some studies have shown that this breast cancer subtype responds to first-line therapy for only 3 months, and responds to subsequent lines of therapy for an even shorter duration. Based on some of the early data from the iniparib trials, we are very optimistic that we will see some significant improvements in the metastatic and early-stage settings with this agent. Although we have a lot of work to do to determine which subsets of triple negative patients are likely to get the most benefit from PARP inhibitors, we hope that this class of drugs will add to the arsenal of effective therapies for BRCA-competent and -deficient patients.

One of the attractive things about PARP inhibitors in the BRCA-carrier population is that when they are used as single agents they have very little toxicity and appear to be very well tolerated. However, when they have been combined with chemotherapy, their administration has been more challenging due to hematologic toxicity. Thus, another area of active research is determining the best way to combine these drugs with chemotherapy to produce the most effective doses with the least toxicity. One of the challenges in the field is the question of whether to maximize the chemotherapy dose and gradually increase the PARP inhibitor dose, or to maximize the PARP inhibitor dose and administer lower doses of chemotherapy to induce DNA damage but reduce toxicity. I think these types of studies are going to be critical in the early stages of development in order to produce the most safe and effective compounds. So far, PARP inhibitors have been studied primarily in BRCA carriers and triple negative patients. However, as we learn more about different molecular subsets of breast cancer, there is good reason to think that we will see activity with PARP inhibitors combined with other chemotherapy in different types of breast cancer. I also expect that we will see rational combinations of PARP inhibitors with various targeted therapies. The good news is we are only at the beginning of using PARP inhibitors in breast cancer and have already had some very promising clinical results, so I am very optimistic that we will see some significant improvements in the near future.

Suggested Readings

Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361:123-134.

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Tutt A, Robson M, Garber JE , et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet.* 2010;376:235-244.