BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Is Precision Medicine Ready for Use in Breast Cancer?

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H&O How do you define *precision medicine*?

LP The term *precision medicine* is often used as shorthand for personalizing or tailoring treatment recommendations to the individual patient, taking into account the molecular characteristics of the cancer, the patient's personal preferences, and other medical conditions the patient may have. This term frequently is used interchangeably with *personalized medicine*, but one could argue that medicine, at its best, always has been about personalizing treatment. What has changed is that we are getting better at it because of new molecular diagnostic technologies and biologically targeted drugs.

H&O What types of molecular testing are already routine in breast cancer?

LP The answer depends on the stage of the disease. Every patient with breast cancer that is localized to the breast or regional lymph nodes—that is, stage I, II, or III disease—is tested for the presence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) on the tumor's surface. Results from these tests, which have been routine for more than 20 years, define the subtype of breast cancer and have important implications for therapy.

For patients with ER-positive cancer, we also commonly perform additional molecular tests that provide an estimate of how sensitive the tumor is to chemotherapy and the likelihood of future recurrence and metastasis without chemotherapy. Several tests exist in this space that are more or less equivalent, although some are supported by more data than others. These include Oncotype Dx, MammaPrint, the Breast Cancer Index, and Prosigna. All of these are commercially available, although they are not all cleared by the US Food and Drug Administration or endorsed in practice guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network. The use of these tests has become routine over the past 5 to 10 years. As Hassett and colleagues found in a study that was published in the *Journal of Clinical Oncology* in 2012, the use of gene expression profile testing with Oncotype Dx in nonmetastatic breast cancer reduced the use of chemotherapy from 84.3% to 45.3% in clinically high-risk patients, but increased the use of chemotherapy from 2.9% to 17.0% in clinically low-risk patients. It is important to remember that the value of these tests does not lie in decreasing or increasing adjuvant chemotherapy use per se, but in enabling the tailoring of chemotherapy use to those who need it.

Women who have a strong family history of breast cancer or other cancers, or who develop cancer at a young age, also need to be tested for genetic predisposition to breast cancer through germline *BRCA* testing or genetic risk panel testing. The results of these tests are used to help decide on the right type of surgery for the patient, and to determine the intensity of surveillance needed after completion of treatment. In addition, these tests are increasingly being used to assist in the selection of adjuvant chemotherapy and also to determine eligibility for certain clinical trials. Cancers that carry a *BRCA* mutation show above-average sensitivity to platinum chemotherapy agents (cisplatin and carboplatin) and to a new class of drugs called poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. The PARP inhibitor olaparib

(Lynparza, AstraZeneca) has been approved for use in ovarian cancer, and this and other PARP inhibitors are being studied for use in *BRCA*-mutated breast cancer in both the adjuvant and metastatic settings.

Some women with metastatic breast cancer also receive molecular tumor profiling based on a needle biopsy sample of the cancer. This involves the use of next-generation DNA sequencing to look for mutated cancer genes that could be targeted with various existing or experimental drugs. All major academic centers can perform these profiling tests in-house in their molecular diagnostic laboratories, and several companies also provide these assays, including Foundation Medicine and Caris Life Sciences. We have not yet determined the value of this approach in breast cancer, but a number of studies are testing the validity of this concept.

H&O What are some of the most important ongoing studies in breast cancer that are incorporating molecular testing?

LP The most important studies in the context of molecular testing are the basket studies, which enroll patients with any type of cancer as long as their tumor contains a mutation for which a corresponding drug exists. All clinical trials are important, however, because they provide an opportunity for patients to receive tomorrow's therapies today. Trials in patients with metastatic cancer are structured in such a way that we learn whether or not the drug is working for an individual patient within 6 to 8 weeks of therapy, so patients only continue treatment if there are signs of benefit. It also is important to keep in mind that no existing therapy works 100% of the time, and that cure remains elusive in the metastatic setting with current therapies.

The NCI-MATCH trial (NCI Molecular Analysis for Therapy Choice) is an important nationwide study that is testing the clinical value of molecular tumor profiling to guide treatment selection across many cancers, including breast cancer (NCT02465060). Patients with metastatic cancer of any kind have a biopsy sample taken that is sent to one of 4 reference laboratories, which include our molecular pathology laboratory here at Yale. A total of 110 genes are sequenced, and if a mutation is found that can be treated with an existing drug—an actionable mutation—the National Cancer Institute supplies the drug. The study will include approximately 1000 women with breast cancer, although the various cohorts may expand depending on the results seen in the first 20 or 30 patients. More than 15 drugs are being used in this trial, but that will change as more agents become available and others are shown to be less effective. At the moment, the number of patients with cancer who qualify for treatment on the trial because they have an actionable mutations is still small, at approximately 10%.

Table. Variable Successes in Trials That Tested Molecularly Targeted Agents in Molecularly Defined Patient Subsets

Mutation/Predictive Biomarker	Agent	Cancer Type
Positive Association		
HER2	Trastuzumab	Breast, gastric
BCR/ABL	Imatinib	CML
c-KIT/PDGFR	Imatinib	GIST
EML4/ALK	Crizotinib	NSCLC
BRAF	Vemurafenib	Melanoma, thyroid, NSCLC
No Association Between Marker and Drug Activity		
BRAF	Vemurafenib	Colorectal
PI3K	Everolimus	Breast
CDK4/6	Palbociclib	Breast
HER2	Trastuzumab	Lung, ovarian
ER	Tamoxifen	Ovarian

CML, chronic myeloid leukemia; ER, estrogen receptor; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; NSCLC, non–small cell lung cancer; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase.

ASCO is undertaking a similar study called TAPUR (The Targeted Agent and Profiling Utilization Registry; NCT02693535). One difference between NCI-MATCH and TAPUR is that NCI-MATCH requires that all biopsy samples be tested at one of 4 central laboratories, whereas TAPUR uses results generated by hospital or commercial testing. Another difference is that NCI-MATCH provides experimental as well as approved drugs, whereas TAPUR provides only targeted drugs that are commercially available—for indications other than breast cancer.

Several pharmaceutical companies are also conducting similar trials to test the efficacy of individual drugs or drug portfolios in molecularly selected patients. These include the Novartis Signature Trial Program (multiple studies) and Genentech's My Pathway trial (NCT02091141). A large number of ongoing phase 2 and 3 clinical trials also require the patient's cancer to be positive for a particular biomarker that serves as a known or potential target for the experimental drug that is being tested. I would estimate that at least 20% of all clinical trials require that patients test positive for some biomarker in order to be eligible.

H&O When do we expect preliminary results from NCI-MATCH to be available?

LP I would expect to see the first results within the next 2 to 3 years. These basket studies are popular. When NCI-MATCH opened, for example, it quickly accrued a large number of patients. The molecular profiling laboratories were overwhelmed with more specimens than they were prepared to handle.

The underlying principle behind NCI-MATCH and TAPUR is that once you identify a cancer-driving molecular abnormality in a given tumor, it should no longer matter what histologic type of cancer the person has. For example, trastuzumab (Herceptin, Genentech) was first approved for women with breast cancer that has HER2 amplification or overexpression, but HER2 amplification or overexpression also can occur in gastric cancer, lung cancer, and ovarian cancer. Does trastuzumab work in these patients as well? Studies have shown that it can work in gastric cancer, but it has turned out to be less successful in lung and ovarian cancer (see the table). That is the type of question that basket studies try to answer. Although I believe we will see some successes, I do not think that this approach is going to be an unqualified success across the board.

H&O Would you say that precision medicine for breast cancer has arrived?

LP I would say that it has arrived, but it has yet to cross the finish line. The evolution of medicine means that we continue to add more and more precision and personalization of treatments. We provide much more precise medicine today than we did 20 years ago, and I think that in another 20 years we will do even better.

H&O What do you see happening with precision medicine over the next few years?

LP I think that the basket trials that are ongoing today will define some new, small molecular subcategories of breast cancer that can benefit from a particular drug. However, most of the molecularly targeted drugs that we currently are testing may not turn out to be effective, however, despite our attempts to molecularly select the patient population. I think that the molecular and cellular context of a presumed driver mutation matters. It seems to me that whether or not a given molecular alteration is a driver depends on the constellation of other abnormalities that the cancer has. If the basket trials find that one out of 10 drugs works as predicted in a small molecularly defined subset, however, that is an important step forward.

Disclosures

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