Individualizing Care for Women With Early-Stage Breast Cancer: The Role of Molecular Assays

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Traditionally, a variety of factors were used to make adjuvant treatment decisions in breast cancer, but none of those factors, except grade, has a consistent association with sensitivity to chemotherapy or endocrine therapy. However, oncologists now are able to use molecular assays as a component of decision making for adjuvant therapy. This article focuses on the use of two of those molecular assays and their implications for nurses.

Breast cancer is the most common cancer affecting women in the United States. In 2013, an estimated 232,340 new cases will be diagnosed in the United States (American Cancer Society [ACS], 2013). Several well-established factors are associated with an increased risk of breast cancer, including family history, nulliparity, early menarche, advanced age, and a personal history of breast cancer (ACS, 2013).

Of all women with breast cancer, 5%-10% may have a germline mutation of the BRCA1 and BRCA2 genes (ACS, 2013). Cancer genetics primarily focuses on the likelihood of developing cancer, but genomics is the study of how genes interact and are expressed as a whole. Certain genomics and gene expression profiling tools focus on the cancer itself and can determine the aggressiveness of the cancer (prognosis) and the likely benefit from treatment (prediction).

Breast cancer has several biologic subtypes that have distinct behavior and responses to treatment, including estrogen receptor-negative (ER) or progesterone receptor (PR)—positive, HER2-positive, and triple-negative (ER/PR/HER2-negative) (see Figure 1). ER is expressed in 75% of breast cancers overall and is slightly more common in postmenopausal women and less in younger women (Osborne & Schiff, 2011). ER expression is related to patient age and correlates with lower tumor grade, lower tumor proliferation, less aneuploidy, less frequent amplification of HER2 and concomitant loss of the p53 tumor suppressor gene, positive expression of PR, metastases, and lower rates of disease recurrence (Osborne & Schiff, 2011).

In the past, oncologists struggled to determine prognosis and chemotherapy treatment for patients with early-stage, ER-positive breast cancer. Traditionally, factors used to make treatment decisions included patient age, size of tumor, lymph node status, histologic grade, ER or HER2 status, and comorbid illness (Paik et al., 2004) (see Figure 2). Unfortunately, none of those factors, with the exception of grade, has a consistent association with sensitivity to chemotherapy or endocrine therapy. Weighing those factors, oncologists would provide subjective recommendations for treatment, leading to variable recommendations among oncologists. Based on those recommendations, many patients received adjuvant systemic chemotherapy with limited benefit but substantial toxicity.

Breast oncologists now are able to use molecular assays as a component of decision making for adjuvant therapy and to distinguish the patients that might benefit most from a combination of endocrine therapy and chemotherapy versus endocrine monotherapy. Molecular markers promise the ability to estimate prognoses and predict responses to particular treatments with greater precision than is possible with clinical findings alone. The markers ultimately would allow the care of patients with cancer to be more individualized (Bast & Hortobagyi, 2004).

Available data suggest that information generated from genomic tests has resulted in a change in treatment decision making in 25%-30% of breast cancer cases (Lo et al., 2010).

Two of the molecular assays for breast cancer treatment are Oncotype DX® and MammaPrint®. They provide better data to predict clinical outcome than the traditional anatomic and pathologic data and standards.

**21-Gene Assay**

Oncotype DX is a 21-gene reverse transcription polymerase chain reaction assay that measures the expression of 21 genes. Those genes include 16 cancer-related genes and five reference genes. The genes are identified in the RNA extracted from formalin-fixed, paraffin-embedded samples of tissue from primary breast cancer.

To establish the level of expression of the 21 genes, the genes are manipulated by an empirically derived, prospectively defined mathematical algorithm to calculate a recurrence score (RS). That score is used to assign a patient to one of three groups by estimated risk of distant...
recurrence: low, intermediate, or high (Harris et al., 2007) (see Table 1).

Based on results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, those recurrence scores contribute to the prediction of 10-year recurrence probability in women with ER-positive, node-negative breast cancer treated with tamoxifen alone (Paik et al., 2004). The greatest benefit from tamoxifen was observed in women with a low or intermediate RS, with minimal benefits in women with a high RS (Paik, 2007).

In the NSABP B-20 trial, Oncotype DX demonstrated a substantial benefit in ER-positive, node-negative women randomly assigned to receive tamoxifen alone or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) followed by tamoxifen. That benefit was demonstrated in the reduction of distant recurrence from CMF in high-RS tumors, no benefit in low-RS tumors, and an uncertain benefit in intermediate-RS tumors (Paik et al., 2006). Incorporating Oncotype DX into decision making for patients with early-stage breast cancer has allowed oncologists to make more informed and tailored decisions based on the biology of the tumor.

Treatment recommendations for a woman with an intermediate score are not clear. The Trial Assigning Individualized Options for Treatment (TAILORx) was designed to address this group of patients. The large trial focused on women who had an intermediate score and who met standard clinical criteria for recommending adjuvant chemotherapy for their ER-positive, HER2-negative, node-negative disease, randomized to chemotherapy versus no chemotherapy. The results of the study will not be available for several years (Benowitz, 2008). For intermediate score patients, Oncotype DX is recommended in the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and St. Gallen International Breast Cancer Expert Panel guidelines (Benowitz, 2008; Harris et al., 2007).

70-Gene Assay

MammaPrint, a 70-gene assay, is another molecular assay used widely in Europe. The assay requires a fresh sample of tissue with a minimum of 30% malignant cells. The sample must be sent to the company using its kit and received within five days of obtaining the tissue sample (Harris et al., 2007).

MammaPrint is the first U.S. Food and Drug Administration (FDA)–cleared breast cancer recurrence assay. A gene signature was developed from a series of 78 patients with node-negative, stage I–II breast cancer who had received no adjuvant systemic therapy. Using DNA microarrays, the assay measures the expression of 70 genes and calculates a prognostic score that categorizes patients in “good” and “poor” risk groups (van’t Veer et al., 2002).

The assay signature was validated in a set of 295 consecutive patients with stage I or II primary breast carcinomas (151 node-negative and 144 node-positive), and demonstrated that the gene-expression profile was a more powerful predictor of the outcome of disease in young patients with breast cancer than the standard systems based on clinical and histologic criteria (Harris et al., 2007). Those results were further validated in another set of 307 patients who did not receive adjuvant systemic therapy (Buysse et al., 2006). Although approved by the FDA, ASCO guidelines suggest that more definitive clinical recommendations for use of this assay require data from more clearly directed retrospective studies, such as the Microarray in Node Negative Disease May Avoid Chemotherapy (MINDACT) study currently underway (Harris et al., 2007).

Implications for Oncology Nurses

The role of genomics in guiding treatment decisions is no longer solely investigational. ASCO and NCCN support the use of Oncotype DX as a component of treatment decisions. Nurses are well-positioned to educate patients on the role of molecular assays in making adjuvant treatment decisions for women with early-stage breast cancer. Nurses can help identify appropriate patients for assay evaluation: stage I or II, ER-positive, HER2-negative. If molecular profiling clinical trials are available to patients, nurses also can help identify potential trial candidates and assist with enrollment. Enrollment to clinical trials is crucial because ongoing studies are trying to better understand the molecular profiling of tumors.

Future Directions

Great strides have been made in the adjuvant treatment of women with early-stage breast cancer, but challenges continue. Current molecular assays are not beneficial for women with triple-negative breast cancer or HER2-positive breast cancer. In addition, ongoing trials are studying women who fall into the intermediate category; whether these patients derive additional benefit or risk from adjuvant chemotherapy in addition to endocrine therapy is unclear. The TAILORx and...
MINDACT clinical trials, conducted in the United States and Europe, respectively, may help answer this question. Another study, Rx for Positive Node Endocrine Responsive Breast Cancer, is designed to investigate patients with node-positive disease (Hayes, 2012).

Conclusion

The use of molecular assays—particularly the Oncotype DX assay—has fundamentally changed the conceptual approach to treating women with early-stage breast cancer. The test augments conventional prognostic indicators with its ability to predict breast cancer outcome and response to treatment. The Oncotype DX assay quantifies the likelihood of recurrence in women with node-negative, ER-positive disease and predicts the magnitude of chemotherapy benefit.

By using genomic profiling, fewer women receive potentially toxic chemotherapy. Molecular assays used to establish early-stage breast cancer treatment strategies fill a previously unmet diagnostic niche, which is becoming a cornerstone of routine care.

TABLE 1. Oncotype DX® Scores Estimating Risk of Distant Recurrence

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk of Distant Recurrencea</th>
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<tbody>
<tr>
<td>Low</td>
<td>Less than 18</td>
</tr>
<tr>
<td>Intermediate</td>
<td>18–30</td>
</tr>
<tr>
<td>High</td>
<td>31 or higher</td>
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Scores can range from 0–100.

Note. Based on information from Harris et al., 2007.

References


Benowitz, S. (2008). Revised guidelines signal that gene expression profiles are coming of age. Journal of the National Cancer Institute, 100, 916–917. doi:10.1093/jnci/djn228


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