Metastatic Breast Cancer: The Individualization of Therapy

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The goals of breast cancer therapy are to reduce the risk of disease recurrence, minimize toxicity, and improve overall survival. Recent advances in research of the biology of breast cancer tumors have resulted in more targeted therapies. The therapies can increase survival and help maintain the quantity and quality of life for patients with metastatic breast cancer. The targeted therapies for breast cancers that are HER2 positive are presented, including the indications and expected benefits for patients and implications for nurses involved in the care of such patients. Emerging research in triple-negative breast cancer also is discussed.

In 2000, the American Cancer Society (ACS) estimated a 21% long-term survival rate (10 years or longer) for metastatic breast cancer (MBC). The current long-term survival rate is an estimated 27% (ACS, 2008). Several factors have contributed to the modest but steady gain in long-term survival (ACS, 2007). Part of the progress is attributable to the recognition that breast cancer is not a single disease—it has many subtypes and each can require different treatment (Burstein, Paik, Ravdin, & Albain, 2006). The improvement in MBC long-term survival is the result of the use of pathologic information and biomarkers to individualize care and the development of new treatment agents.

The purpose and results of breast cancer pathology should be discussed with patients. Nurses can help their patients understand why specific tests are ordered and how their results will impact treatment decisions. A pathology report provides information about features of a tumor that might predict a response to a particular therapy and prognosis (see Table 1). The information is an important step in individualizing therapy.

The systemic treatment of breast cancer has advanced toward a more targeted approach, which is aimed at specific molecular targets, rather than treatment with relatively nonspecific cytotoxic chemotherapy or hormonal therapy. Theoretically, this will minimize treatment risks and side effects and optimize benefits, particularly quality of life and overall survival. The goal is to perfect the approach so that each patient receives therapy targeted at her specific breast cancer subtype. Patient resources for information on MBC, including targeted therapy, are shown in Figure 1.

This article describes the biomarkers that individualize MBC therapy and provides an overview of two targeted agents, trastuzumab and lapatinib, which often are used in the treatment of MBC. Information about triple-negative breast cancer also is provided in this article.

At a Glance

- The goal of targeted therapy is to provide optimal treatment for specific breast cancer subtypes based on biologic characteristics of the tumor.
- Women with HER2-positive breast cancer may benefit from treatment with trastuzumab or lapatinib.
- Research is under way into treatment for triple-negative breast cancer—estrogen receptor negative, progesterone receptor negative, and HER2 negative.

Considerations for Individualizing Therapy

To optimize treatment for any cancer, the ability to predict how a patient will respond to a given therapy is invaluable. Pathology results, previous treatments, and medical history can provide information that is an important component in developing an effective, individualized treatment plan.

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Biomarkers, such as estrogen receptor (ER), progesterone receptor (PR), and HER2 are indicators of breast cancer prognosis and are considered in the selection of treatment. Individualized therapy for breast cancer is not a new concept. Selected ER modulators (SERMs) are among the earliest examples of targeted, individualized breast cancer therapy. Tumors that have a high proportion of ERs and PRs are sensitive to estrogen and progesterone, which are associated with the pathogenesis and growth of the breast cancer. Tamoxifen was the first SERM approved by the U.S. Food and Drug Administration (FDA) to block ERs. It has been used widely as a targeted agent since 1977, when it was approved for the treatment of MBC. Following that initial indication, tamoxifen was approved for the adjuvant treatment of breast cancer and for breast cancer prevention in individuals at high risk (National Comprehensive Cancer Network [NCCN], 2008).

HER2 status is another characteristic of breast cancer that can be used to guide individualized therapy, and current research is focusing on identifying other biomarkers, particularly those such as topoisomerase 2 (TOPO2) that will help individualize care for women with triple-negative breast cancer (Di Leo, Licitra, Claudino, & Biganzoli, 2008). Table 2 provides an overview of the current American Society of Clinical Oncology (ASCO) recommendations for the use of biomarkers in breast cancer.

Previous therapy is another factor that must be considered in individualized treatment plans. Cumulative toxicities and/or resistance to agents used earlier may occur. For example, taxanes and anthracyclines used in the adjuvant setting can increase the likelihood of resistance at disease recurrence. Assessment of any comorbidities and other factors that might impact the quality of life associated with a particular treatment can affect choice of therapy.

Helping patients with breast cancer understand the results of their pathology evaluations, why particular therapies are recommended, and what side effects might be expected is an important aspect of oncology nursing care.

### HER2-Positive Disease

Approximately 20% of patients with breast cancer have HER2-positive disease (Wolff et al., 2007). Research has shown...
that women with HER2-positive breast cancer have a more aggressive disease, greater likelihood of recurrence, poorer prognosis, and decreased survival compared with women with HER2-negative breast cancer (Wolff et al., 2007). Although their prognosis is worse, effective therapies that directly target HER2 are available (Piccart-Gebhart et al., 2005).

Pathophysiology of HER2-Positive Breast Cancer

The HER2 transmembrane receptor is encoded by the HER2neu gene. It is part of a family of receptors including epidermal growth factor receptor (EGFR). It also includes HER1, HER2, HER3, and HER4 (Burstein, 2005). When the gene is amplified, it causes an increase in the amount of HER2 receptors expressed on the cell (Burstein). HER2-positive tumors have a genetic alteration in the HER2 gene that produces an increased amount of the growth factor receptor protein on the tumor cell surface. The overexpression can cause cells to divide, multiply, and grow more rapidly than normal. Anti-HER2 therapies interrupt the cellular processes that the receptors initiate.

Measurement of HER2 in Breast Cancer

Accurate assessment of HER2 status is critical in determining an effective therapeutic approach and deciding which patients will benefit from anti-HER2 therapy. Currently, up to 20% of HER2 test results may be inaccurate (Wolff et al., 2007). Typically, HER2 is measured by immunohistochemistry (IHC), which uses an antibody that recognizes the HER2 protein on the surface of cancer cells, or fluorescent in situ hybridization (FISH), a molecular test that identifies actual gene amplification. NCCN and ASCO have guidelines on how HER2 should be measured.

With IHC, HER2 is reported as 0, 1+, 2+, or 3+. The 3+ is considered positive (Wolff et al., 2007). FISH reports are more complicated and detailed. If more than six HER2 gene copies per nucleus are detected or if the FISH ratio (HER2 gene signals to chromosome 17 signals) is more than 2.2, FISH is considered to be positive (Wolff et al., 2007). According to the current standard of care, only patients who are HER2 positive by IHC or FISH benefit from anti-HER2 therapy (Hayes, 2008; NCCN, 2008).

Research on HER2 testing and the implications of testing are active areas of breast cancer research (Wolff, Paik, & Press, 2008). A HER2 test that consistently and accurately identifies patients who would benefit from anti-HER2 therapy would be helpful. Two anti-HER2 therapies are available: trastuzumab and lapatinib. Trastuzumab is effective in reducing the risk of relapse in approximately 50% of women with disease that is HER2 positive, which suggests that other factors also mediate tumor progression (Wolff et al., 2008). Research is ongoing to identify better markers for patients who would benefit from targeted therapy and to develop additional targeted agents.

Trastuzumab

Mechanism of Action

Trastuzumab is the first molecular targeted therapy developed for the treatment of breast cancer (Johnson & Seidman, 2005). It is approved for use in the adjuvant and metastatic settings. Most patients with early-stage HER2-positive breast cancer receive trastuzumab as adjuvant therapy (Johnson & Seidman). Studies are ongoing, but the results to date from clinical trials show that adjuvant treatment with trastuzumab for one year with...
Chemotherapy reduces the risk of cancer recurrence by about half as compared to women with HER2-positive disease who do not receive trastuzumab therapy (Joensuu et al., 2006; Piccart-Gebhart et al., 2005; Romond et al., 2005; Slamon et al., 2005). Resistance to trastuzumab can occur, which must be a clinical consideration in treatment plans for women with HER-positive breast cancer that has recurred.

Trastuzumab is a monoclonal antibody that binds to the HER2 receptor outside the cell and inhibits it from signaling cellular processes that help cancer cells survive (Harkins & Geyer, 2007). However, the exact mechanism of action of trastuzumab is not fully understood. Trastuzumab does not cross the blood-brain barrier.

**Efficacy**

Clinical trials have shown improved clinical outcomes when trastuzumab is used in combination with a variety of chemotherapeutic agents as first-line and later-line therapy for MBC (Longo, Torino, & Gasparini, 2007). In patients whose tumors overexpress HER2 and who previously received cytotoxic chemotherapy, single-agent trastuzumab resulted in a response rate of 21% (Cobleigh et al., 1999). In a prospective trial, patients with metastatic disease were randomized to chemotherapy alone (doxorubicin and cyclophosphamide, or paclitaxel) or the same chemotherapy plus trastuzumab. Patients treated with chemotherapy plus trastuzumab had an overall survival advantage compared with patients receiving chemotherapy alone (25.1 versus 20.3 months, p = 0.05) (Slamon et al., 2001). In a randomized study of patients with HER2-positive MBC, a three-drug regimen of trastuzumab, paclitaxel, and carboplatin when compared with trastuzumab plus paclitaxel produced an improved response rate (52% versus 36%) and longer time to progression (10.7 versus 7.1 months) (Robert et al., 2006). Patients tolerated the combination well.

**Side Effects and Administration Considerations**

Trastuzumab is well tolerated, and patients maintain a good quality of life (Vogel et al., 2002). Nursing considerations and patient education points associated with trastuzumab are shown in Figure 2. The most commonly reported (40% of patients) infusion-related adverse reactions are fever and chills. Other reported reactions include rash, rigors, nausea, vomiting, dizziness, dyspnea, and hypotension. The reactions decreased with subsequent trastuzumab infusions (Genentech, Inc., 2008). The sensation of pain at tumor sites during or a day or two after the first several trastuzumab infusions can be unsettling to women, particularly those who experience pain where no confirmation of tumor has been made.

Nurses must be aware that, although rare, severe or anaphylactic reactions can occur with trastuzumab (Gobel, 2007). Because trastuzumab is a humanized monoclonal antibody, true hypersensitivity reactions occurred in only about 1% of infusions during the monotherapy clinical trial for MBC (Moore & Cobleigh, 2007). Nevertheless, patients should be monitored closely for adverse effects during first and second infusions. Reactions, including anaphylaxis, urticaria, bronchospasm, angioedema, and hypotension, most commonly were reported in association with the initial infusion. Although symptoms generally occur during infusion, reports of symptom onset have been made as long as 24 hours later. The appearance of any such symptoms should alert nurses to the possibility of hypersensitivity reaction. The infusion must be stopped immediately and the institution’s protocol for management of hypersensitivity reactions initiated (Genentech, Inc., 2008).

Cardiac dysfunction is another side effect of trastuzumab. An overview of the trials of trastuzumab in the adjuvant setting showed symptomatic congestive heart failure in about 4% of patients and asymptomatic declines in left ventricular ejection fraction more than 10 points from baseline in about 30% of patients (Tell, Hunt, Carlson, & Guardino, 2007). In women with MBC, severe congestive heart failure was reported in about 2% of patients and a decline in ejection fraction in 6%–18% of patients (Ewer & O’Shaughnessy, 2007). Patients receiving trastuzumab should be monitored closely for signs of cardiac dysfunction. Before therapy is started, patients should undergo cardiac evaluation, including ejection fraction to determine baseline function, and a history of any cardiac problems or prior cardiotoxic chemotherapy should be recorded prominently in patients’ charts. At each subsequent visit, signs of cardiac dysfunction (such as shortness of breath, cough, and swelling of extremities) must be assessed prior to therapy.

Reports of congestive heart failure are higher when trastuzumab is combined with chemotherapy, especially the anthracyclines, compared with monotherapy (Piccart-Gebhart et al., 2005). However, the exact mechanism of action of trastuzumab is not fully understood. Trastuzumab does not cross the blood-brain barrier.

**Proprietary name:** Herceptin® (Genentech, Inc.)

**Indications:** first-line treatment of HER2-positive metastatic breast cancer alone or in combination with paclitaxel; for the adjuvant treatment of HER2-positive node-positive or node-negative breast cancer

**Pharmacology:** humanized DNA-derived humanized monoclonal antibody

**Dosage**

- Initial dose: 4 mg/kg IV infused for 90 minutes
- Maintenance dose: 2 mg/kg IV infused over 30 minutes

**Special concerns:** serious cardiomyopathy: risk of developing left ventricular dysfunction or congestive heart failure. A full evaluation of cardiovascular function should occur prior to the first dose, especially left ventricular function.

**Hypersensitivity reactions:** anaphylaxis, angioedema, or acute respiratory distress syndrome. May occur within 24 hours of administration. Most commonly seen with first dose

**Most common side effects:** headache, dizziness, diarrhea, nausea and vomiting, chills, rashes, fever, injection site pain, and peripheral edema

**Nursing considerations**

- Assess cardiac function prior to initiating therapy.
- Assess for fever, chills, and other infusion-associated symptoms during infusion. Side effects may be managed with acetaminophen.
- Prior to each infusion, assess for and immediately report any signs of left ventricular dysfunction (shortness of breath, cough, or swelling of extremities).
- Observe patient for one hour following completion of the initial loading dose and 30 minutes following completion of initial maintenance dose.

**Figure 2. Nursing Considerations and Patient Education Points for Trastuzumab**

*Note.* Based on information from Genentech, Inc., 2008; Sprotto & Woods, 2007; Wilkes & Barton-Burke, 2007.
2005; Seidman et al., 2002). Therefore, it is often given sequentially following doxorubicin. Dang et al. (2008) conducted a study in which 70 patients with left ventricular ejection fraction greater than 55% were enrolled to assess cardiac toxicity. No declines occurred in median left ventricular ejection fracture when trastuzumab was given sequentially. Based on those results, adriamycin and cyclophosphamide followed by paclitaxel and trastuzumab are considered safe.

Trastuzumab is administered via IV. The first dose usually takes about 90 minutes to administer. Patients are monitored closely for any adverse side effects, especially infusion reactions. Thereafter, smaller maintenance doses are given over a 30-minute period, either weekly or once every three weeks.

**Lapatinib**

**Mechanism of Action**

Clinical trials have demonstrated that many tumors eventually become resistant to trastuzumab, similar to what occurs with chemotherapy (Burris et al., 2005). Lapatinib is an oral anti-HER2 therapy with an FDA indication for patients who have become resistant to anthracycline, taxane, and trastuzumab therapy. Lapatinib inhibits the tyrosine kinase that initiates the downstream intracellular signaling of HER2 and EGFR (Burris et al.).

**Efficacy**

Lapatinib is approved in combination with capecitabine for advanced breast cancer or MBC who have received prior therapy, including trastuzumab, an anthracycline, and a taxane (GlaxoSmithKline, 2007). A nonblinded, randomized trial compared the combination of capecitabine and lapatinib to capecitabine alone in 324 patients with locally advanced or metastatic disease that progressed after treatments that included anthrancylines, taxanes, and trastuzumab (Geyer et al., 2006). At the updated analysis of the trial, time to progression (the primary end point of the study) was significantly longer in the combination arm than in the capcitabine-alone arm (median time to progression was 6.2 versus 4.3 months) (Geyer et al., 2007).

Lapatinib showed some promise as a single agent in patients with HER2-positive breast cancer who were heavily pretreated, with response rates of 4%–8% and stable disease rates of 8%–14% (Burris et al., 2005). It also has been studied as first-line, single-agent therapy in HER2-positive advanced breast cancer (Gomez et al., 2008). The overall response rate, defined as complete plus partial response, was 24%; an additional 51% of patients achieved stable disease. Response or stable disease was maintained for at least 24 weeks in 31% of patients.

About one-third of women with HER2-positive MBC develop brain metastases. It is hypothesized that the lapatinib molecule may be small enough to cross the blood-brain barrier, which may make it effective in treating brain metastasis (Lin et al., 2008).

**Side Effects and Administration Considerations**

Lapatinib is well tolerated; its most common side effects are diarrhea, rash, nausea, and fatigue. Diarrhea occurs in about 40%–60% of the patients receiving combination lapatinib and capecitabine, primarily grades 1 and 2 (Geyer et al., 2006).

Prompt management is critical. First, the patient should be evaluated for any signs of an infectious cause such as *Clostridium difficile*. If no infection is present, the patient can be advised to take loperamide 4 mg followed by 2 mg every four hours or after every diarrhea episode until it has stopped for at least 12 hours.

Rash occurs in about 30% of patients (Moore & Cobleigh, 2007). The rash is similar to that seen with other EGFR inhibitors such as cetuximab and erlotinib. It typically is pustular or popular, with skin that often is dry and red (Moore & Cobleigh). Patients should be examined at each visit for signs of secondary infection. They should be counseled to avoid the sun and to use sunscreen and mild cleansers as well as emollients. Acne medications should be avoided as they can irritate and worsen the rash. No optimal management has been established for the rash, although topical steroids, topical clindamycin, topical pimecrolimus, or oral doxycycline may help (Lynch et al., 2007). Nursing considerations and patient education points for patients receiving lapatinib are shown in Figure 3.

Cardiac toxicity rarely is seen with lapatinib. In a cardiac safety evaluation, lapatinib infrequently affected left ventricular ejection fraction (X decrease was 18.7%); it is estimated to occur in less than 2% of patients (Moy & Goss, 2007). The incidence in patients who have received prior cardiotoxic therapy may be higher, however. Therefore, left ventricular ejection fraction

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**Proprietary name:** Tykerb™ (GlaxoSmithKline)

**Indications:** treatment of metastatic breast cancer in HER2-positive tumors with capecitabine in patients who have received prior therapy including an anthracycline, a taxane, and trastuzumab

**Pharmacology:** kinase inhibitor of epidermal growth factor receptor and HER2

**Dosage:** 1,250 mg orally once a day on days 1–21 continuously in combination with capecitabine 2,000 mg/m² per day (administered orally in two doses approximately two hours apart) on days 1–14 in a repeating 21-day cycle

**Most common side effects:** diarrhea, nausea and vomiting, dyspepsia, palmar-plantar erythrodysthesia, rash, pain in extremity, insomnia, fatigue

**Nursing considerations**

- Be sure cardiac function is assessed prior to initiating therapy.
- Prior to each infusion, assess for and immediately report any signs of left ventricular dysfunction including shortness of breath, cough, or swelling of extremities.
- Assess for the following potential drug interactions: dexamethasone, phenytoin, rifampin, St. John’s Wort, ketoconazole (any CYP3A4 inhibitors or inducers). All should be discussed with a physician prior to administration.
- Should be taken one hour before or one hour after a meal. Dose should not be divided.
- Capecitabine should be taken with food or within 30 minutes of eating.
- No grapefruit, grapefruit juice, or any grapefruit product prior to treatment
- Assess for signs of hand-foot syndrome.
- Proactive management of diarrhea with antidiarrheal agents

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**Figure 3. Nursing Considerations and Patient Education Points for Lapatinib**

*Note.* Based on information from GlaxoSmithKline, 2007; Spratto & Woods, 2007; Wilkes & Barton-Burke, 2007.
Inset 1. Case Study

Mrs. P, a 43-year-old premenopausal woman, undergoes routine screening mammography as recommended for a woman of average risk. The mammogram shows nonspecific but suspicious changes in her left breast. Mrs. P is married and has two teenage daughters. She is employed as an elementary education teacher.

Menarche was at age 12. She denies the use of oral contraceptives or other hormonal manipulation. She had two uncomplicated pregnancies and deliveries. Menstrual periods are regular. She denies previous surgery. She takes a daily multivitamin and a 1,000 mg calcium supplement. Her family history includes a paternal aunt with breast cancer at age 52 and a paternal grandmother with breast cancer at age 57. She does not exercise regularly but states that her diet is reasonable.

On physical examination, a palpable nodule of approximately 1.5 cm is noted in her left breast. Blood pressure is 118/70 mmHg. Her last routine laboratory test, performed six months ago, was normal except for a borderline high total cholesterol level of 200 mg/dl. Her body mass index is 24.

Core biopsy confirms that Mrs. P has invasive carcinoma. She undergoes lumpectomy and sentinel lymph node biopsy. The histology report indicates invasive ductal carcinoma, measuring 1.9 cm, Bloom Richardson nuclear grade 2, mitotic rate 2, cellular differentiation grade 2. Multiple foci (three) of lymphovascular invasion (LVI) are noted. Neither of two identified sentinel lymph nodes contains metastatic cells. Immunohistochemistry (IHC) indicates that the tumor is estrogen receptor positive (moderate), progestosterone receptor negative, and HER2 positive.

What additional information would be needed before considering treatment options?

American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend HER2 testing for all cases of invasive breast cancer. HER2 positivity is defined as an IHC of 3+ (uniform intense membrane staining of > 30% of invasive tumor cells) or fluorescent in situ hybridization (FISH) amplification (HER2 to CEP17 ratio of > 2.2). HER2 positivity by either test warrants consideration of adjuvant trastuzumab. A 2+ result by IHC is considered indeterminate by ASCO guidelines and weakly positive by NCCN guidelines. Therefore, subsequent FISH testing was ordered and indicated HER2 gene amplification with a ratio of 2.1. NCCN guidelines recommend that all patients with a FISH score of 2.0 or higher be offered trastuzumab.

Mrs. P is concerned about a potential hereditary cause of her breast cancer, mainly out of concern for her daughters. What can you tell her?

Many women diagnosed with breast cancer are concerned about the genetic risk for breast cancer and potential hereditary risks to offspring. Mrs. P may have been at risk for a hereditary predisposition because of multiple family members with relatively early-onset breast cancer (Mahon, 2007). She should be referred to a genetics professional for counseling and education regarding testing for BRCA1 and BRCA2 to determine whether she has a germline mutation that puts her family at increased risk. Of course, the HER2 status of her breast cancer reflects a genetic change only in the tumor.

What are the implications of a node-negative, HER2-positive breast cancer for her prognosis?

The five-year recurrence rate among patients with T1–T2, node-negative, HER2-positive breast cancer is 15%–23% (Burstein, 2005). The presence of LVI increases the risk of recurrence and mortality related to breast cancer. Precise estimates of the impact of LVI are unclear, although one study suggests that LVI carries a risk approximating that of tumors with at least one positive axillary lymph node (Mohammed et al., 2007).

What are the therapeutic options for Mrs. P?

Node-negative HER2-positive disease carries an increased risk for disease progression; the risk reduction with trastuzumab is substantial enough to warrant treatment with it. The relative gains seen with trastuzumab are likely to outweigh those of chemotherapy alone (Hayes & Picard, 2006). Several prospective, randomized studies of adjuvant trastuzumab as treatment for node-negative and node-positive tumors have shown that it reduces risk of distant recurrence by 50% and reduces mortality by 33%.

What can you tell Mrs. P about what to expect from trastuzumab treatment? She wants to know the potential risks of the drug.

Risk of cardiotoxicity appears to be greatest when trastuzumab is given concurrently with anthracyclines, so it is recommended that it be given sequentially with anthracyclines (Telli, Hunt, Carlson, & Guardino, 2007). Patients receiving trastuzumab should be monitored via history, physical examination, and noninvasive imaging of ventricular function with a consistent form of cardiac imaging (Hayes & Picard, 2006).

Mrs. P underwent a course of doxorubicin and cyclophosphamide with paclitaxel followed by trastuzumab. She tolerated therapy well. She presented 15 months later with metastasis to the bone.

After the recurrence following the anthracycline and trastuzumab, what treatment options are available?

Lapatinib might be considered. Like trastuzumab, lapatinib is a HER2-specific drug. Approved by the U.S. Food and Drug Administration in 2007, lapatinib may be effective for HER2-positive breast cancer that does not respond to trastuzumab in this patient. It often is used in combination with capecitabine (Geyer et al., 2006).
Commentary 1: Individualization of Therapy

Suzanne M. Mahon, RN, DNsC, AOCN®, APNG: The goal of individualized treatment is to choose therapeutic plans that patients can reasonably tolerate and are as congruent as possible with their lifestyles and personal goals. The ultimate goal is to increase survival or have better disease control.

Frances M. Palmieri, RN, MSN, OCn®, CCRP: At our institution, we use a patient education brochure that explains in layman’s terms why certain things are measured. We have found it a great asset in discussions with patients about their pathology results.

Mahon: The American Society of Clinical Oncology recommends that, at minimum, patients have appropriate estrogen receptor (ER), progesterone receptor (PR), and HER2 testing and that Oncotype DX diagnostic testing is considered in the adjuvant setting. ER/PR testing and especially HER2 testing are open to interpretation, depending on the technique used and the laboratory that performs the testing. When transferring that information across institutions or across protocols, be sure that what the first person measures is the same as what the next person measures (e.g., being HER2 positive by immunohistochemistry [IHC] may not be equivalent to HER2 positivity by fluorescent in situ hybridization [FISH]).

Commentary 2: HER2 Measurement

Mahon: HER2 must be measured accurately. If a tumor is truly HER2 positive but is not measured properly and the testing comes back falsely negative, that patient will not receive trastuzumab, making her prognosis much poorer.

How HER2 is measured depends on the laboratory available in your institution. If IHC is done and the results show 0 or 1+, the results are truly negative. If the results are clearly 3+, then they are positive. However, for patients with an IHC of 2+, the question is “What should we do?” Such patients should have further evaluation with FISH to determine whether they have the gene amplification. Therefore, a series of steps must be taken before an answer is available. IHC is less expensive (base cost of IHC is $85; base cost of FISH is $381 [Elkin et al., 2004]); but many people believe that FISH is the gold standard. Despite the controversy, establishing whether a patient is HER2 positive is vital.

Debra K. Frye, RN, BSN, OCn®, CCRP: My patients often are upset when their tumors are HER2 positive because they know the prognosis is worse. However, I talk with them about targeted therapy available for their specific type of tumor. Sometimes, you must emphasize that although HER2 positivity signifies a more aggressive tumor type, effective therapies are available. This knowledge can give these patients hope.

Commentary 3: Nursing Considerations With Trastuzumab Therapy

Mahon: If trastuzumab is given to patients who are selected properly, overall survival increases. Patients tolerate it well. In fact, one of the biggest complaints from patients is that they have to keep coming back for treatment. We do not see a great deal of infusion reactions. That said, when infusion reactions occur, they’re impressive. The biggest issue is monitoring for cardiac toxicity. It can slip up quietly, and then all of a sudden, it is there. Patients need to understand the cardiac risk; if it occurs and is not managed well, it may have some impact on long-term quality of life. In the lay community, many people do not seem to think trastuzumab has any real side effects. That’s probably because it’s not associated with the more typical and apparent side effects of cancer treatment, such as alopecia. As a result, many patients overlook the side-effect profile.

Commentary 4: Nursing Considerations With Lapatinib Therapy

Mahon: Typically, lapatinib is given to patients who may have already received trastuzumab and is usually given with capcitabine. This brings about the important issue of compliance with oral medications. Giving patients pill boxes and having them count their pills at the beginning of the week and carry them with them are some suggestions to improve adherence. Patients may not mean to skip a dose, but one day rolls into the next. I used to think, “What is wrong with them? They should be able to keep track better.” But it can be very hard to remember, especially if they have to take pills at different times, with meals or on an empty stomach. They may have to take medications for comorbidities, as well.

If a patient starts to experience side effects, her desire to take the medication goes down. It is hard, too, if the patient is feeling pretty good and is busy with other parts of her life. Although this is obviously good, the patient may be less likely to focus on taking medications.

Rash and diarrhea can be significant with lapatinib. The side effects must be addressed promptly because they can be significant—in the case of diarrhea, almost to the point of becoming life threatening.

Frye: We were surprised at the significance of diarrhea. Some patients were hospitalized. We learned early that prevention of diarrhea and early intervention are important.

Mahon: We talk to people about dietary changes almost immediately because almost everyone has some degree of diarrhea. In some of the studies, the incidence was close to 70%.

Palmieri: Diarrhea is unpredictable and distressing. We tell patients to start loperamide if they notice an increase from their baseline stool count. Because most patients are used to being constipated from other treatments, they often do not believe they will get diarrhea. This highlights the need for education on the probability and potential severity of diarrhea. We are aggressive with dose reductions of lapatinib for grade 2 diarrhea. If patients don’t go back to baseline with the dose reduction, we hold the drug until they do. We then initiate lapatinib again, stay at the 20% reduction, and reduce or hold the dose further if needed. We discontinue lapatinib in patients with grade 3 who do not go down to grade 1 or less.

central to the process. Assessing adherence and reinforcing its necessity at every patient encounter are important nursing roles. Nursing challenges associated with trastuzumab and lapatinib therapy are illustrated in Inset 1.

Triple-Negative Breast Cancer

Breast cancer can be divided into several groups based on histopathologic features, which are included in the pathology report and will affect treatment decisions. Several major subtypes of breast cancer have been elucidated: hormone receptor positive (ER and PR positive), triple negative (HER2 negative and ER and PR negative), and HER2 positive (Burstein et al., 2006). Each subtype has different characteristics associated with different risk of recurrence, which impacts treatment choices. As discussed in this supplement, several treatment options are available for hormone receptor-positive and/or HER2-positive breast cancer. However, triple-negative breast cancer remains a clinical challenge.

An estimated 15% of breast cancer cases are classified as triple-negative disease (Hayes, 2008). Triple-negative disease is
most common in women younger than 40 years and in African Americans and Hispanics, despite the fact that breast cancer overall is less common in those ethnic groups (Morris et al., 2007). Studies have shown that triple-negative tumors can lead to poorer survival, regardless of the stage at diagnosis (Harris et al., 2007; Rakha, El-Sayed, Green, Lee, Robertson, & Ellis, 2007).

Triple-negative disease is an emerging area of targeted treatment research. A treatment challenge in patients with triple-negative breast cancer is the lack of targets, which makes hormone therapy and therapy with trastuzumab ineffective. Despite the poorer prognosis, this patient population can respond to chemotherapy (Harris et al., 2007; Rakha et al., 2007). The tumors often have features similar to those found in women with a BRCA1 mutation (Cleator, Heller, & Coombes, 2007). Triple-negative breast cancer may respond better to chemotherapy because of the high index of proliferation, indicated by high expression of Ki67 (a marker of cellular proliferation) (Kang, Martel, & Harris, 2008). Such cancers often are managed initially with standard chemotherapy of doxorubicin and cyclophosphamide, as well as platinum-based chemotherapy, which might be used in a woman with a BRCA1 mutation.

Research is evaluating potential targeted therapies for triple-negative breast cancer, including agents that inhibit EGFR signaling (Cleator et al., 2007). Platinum agents are thought to be more active in triple-negative breast cancers and are under investigation (Wasserman & Tan, 2008). Ixabepilone, a new chemotherapeutic agent with FDA approval for monotherapy or in combination with capcitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracyclene therapy is contraindicated, belonging to a new class called epothilones, has shown encouraging results in patients with triple-negative breast cancers. In a subset analysis of a phase III trial, ixabepilone added to capcitabine resulted in an increase in progression-free survival and response rates in patients with triple-negative breast cancers, compared with capcitabine alone (Rugo et al., 2007). Bevacizumab also shows promise for this patient population (Miller et al., 2007).

Conclusions

Breast cancer treatment is an ever-evolving process. Much of the success of current breast cancer treatment is based on previous research in which thousands of women with breast cancer participated in therapeutic studies. Breast cancer no longer is considered a homogeneous disease with one standard treatment. Pathology reports provide important information about the biologic features of breast cancer. Using that information is extremely helpful to selecting the most effective therapy for a specific tumor (see Inset 2). The success of targeted therapy is evident when considering the use of hormonal manipulation in ER/PR-positive tumors and trastuzumab and lapatinib in HER2-positive breast cancer. Current research is aimed at refining the therapeutic approaches and finding improved ways to provide more effective therapy for triple-negative breast cancer. Nurses play a key role in educating patients about their particular type of breast cancer and recommended treatments.

References


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