Molecularly Targeted Therapies for Breast Cancer:
Expert Discussions of Nursing Practice Patterns

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Target Audience
This activity has been designed to meet the educational needs of oncology nurses and nurse practitioners treating patients with breast cancer.

Purpose
To educate nurses on the latest treatment and nursing management strategies for patients with breast cancer.

Program Overview
The constant evolution in breast cancer treatment requires oncology nurses to continually maintain an awareness of the evidence and the ability to apply the science of new treatments to patient care. In this newsletter, each of the major classes of biologic agents used in the treatment of early stage and metastatic breast cancer: human epidermal growth factor receptor 2 inhibitors, vascular endothelial growth factor inhibitors, and dual kinase inhibitors, will be discussed. Case-based presentations will be utilized to demonstrate challenges associated with using biologic therapies.

Learning Objectives
Upon completion of this program, participants should be better able to:

- Outline the mechanism of action of molecularly targeted agents being used in the treatment of adjuvant and metastatic breast cancer
- Interpret the latest research on molecularly targeted agents likely to influence breast cancer treatment in 2009
- Employ safe drug administration techniques for patients with breast cancer receiving molecularly targeted agents
- Utilize the latest nursing management strategies to minimize or alleviate side effects associated with targeted agents
- Counsel appropriately selected patients about ongoing clinical trials

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Biologic Therapies in Adjuvant and Metastatic Breast Cancer

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An estimated 194,280 new cases of breast cancer are expected to be diagnosed in the United States in 2009, and 40,610 are anticipated to die from the disease. It is the most common malignancy in the United States, accounting for 27% of all new cancer cases and is the second-leading cause of all cancer-related deaths in women (Jemal et al, 2009). Risk factors for breast cancer include female gender, increasing patient age, family history of breast cancer, early menarche, late menopause, prolonged hormone replacement therapy, and genetic mutations (National Comprehensive Cancer Network [NCCN], 2009). Although the incidence of breast cancer has increased steadily throughout the past several decades, mortality appears to be declining, suggesting a benefit from early detection and more effective treatment. Breast cancer treatment is twofold: it includes treating local disease with surgery, radiation therapy, or both, and treatment of systemic disease with chemotherapy, endocrine therapy, biologic therapy, or a combination of these (NCCN, 2009).

Increased understanding in extracellular and intracellular signaling processes, which are key in cell growth and survival, has led to the identification of therapeutic targets. Targeted agents, unlike cytotoxic chemotherapy, act on substances along the **signal transduction** pathway that are specific to cancer cell survival. Therefore, normal cells are spared the side effects of chemotherapy. The introduction of biologic agents such as human epidermal growth factor receptor 2 (HER2) inhibitors, **vascular endothelial growth factor** inhibitors, and dual kinase inhibitors has revolutionized the treatment of patients with breast cancer.

HER2-positive tumors overexpress the HER2/neu **oncogene**. They comprise approximately 25% to 30% of breast tumors and their presence typically conveys a poor response and prognosis (Slamon et al, 1987). However, the development of targeted therapies such as trastuzumab has significantly changed the prognosis and survival rate for patients with HER2-positive disease (Baselga et al, 2006). The determination of HER2 status through immunohistochemistry or fluorescent in situ hybridization is critical for therapeutic decision-making, as it determines which patients are likely to respond to HER2-directed therapy (Sauter et al, 2009).

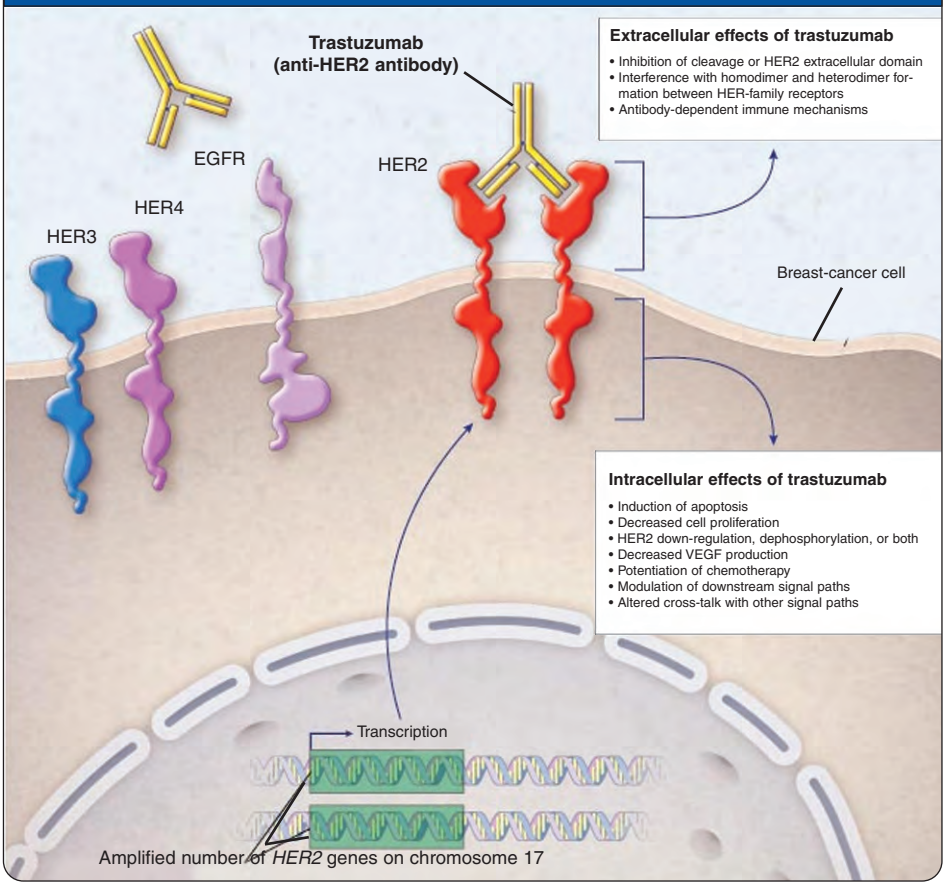
Trastuzumab is a humanized monoclonal antibody that binds with HER2 receptors to inhibit dimerization and kinase activity. It is believed to have multiple mechanisms by which it exerts antitumor effects, including inhibition of proliferation and angiogenesis, sensitization to chemotherapy, and recruitment of the immune system to kill tumor cells (Figure 1). It also potentiates the downstream effects of HER2-neu, interfering with cellular growth and ultimately causing cellular death (Burstein, 2005). Trastuzumab is highly effective as a single agent and in combination therapy for the treatment of HER2-positive disease (NCCN, 2009).

Clinical Research on HER2 Inhibitors in the Adjuvant and Metastatic Setting

Several large, phase III clinical trials of trastuzumab as adjuvant therapy in early breast cancer have been conducted. The Herceptin® Adjuvant, the National Surgical Adjuvant Breast and Bowel Project B-31, the North Central Cancer Treatment Group N9831, and the Breast Cancer International Research Group 006 involved more than 13,000 women with HER2-positive early breast cancer (Slamon et al, 2001; Joensuu et al, 2006; Perez et al, 2007; Robert 2007; Smith et al, 2007; Dowsett et al, 2009). Most patients received anthracycline and cyclophosphamide followed by paclitaxel or docetaxel alone, with trastuzumab or with trastuzumab and carboplatin. Overall, the trials showed that trastuzumab reduced the 3-year risk of recurrence, regardless of significant trial heterogeneity (Baselga et al, 2006).

As the Table shows, statistically significant increases in the disease-free survival (DFS)

FIGURE 1 Trastuzumab Mechanisms of Action



(Burstein, 2005)

Trastuzumab is believed to have multiple mechanisms by which it exerts antitumor effects. It is highly effective as a single agent and in combination therapy for the treatment of HER2-positive disease.

VEGF = vascular endothelial growth factor; EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor.

TABLE Adjuvant Trastuzumab Trials (Primary End Point Analysis: Recent Reports)

Trial	Events (median f/u)	3-Year DFS Control (%)	3-Year DFS Trastuzumab (%)	DFS HR (95% CI)	*p* Value
NSABP B-31/NCCTG-N9831 (Perez et al, 2007)	619 (2.9 years)	85.9 (at 4 years)	73.1 (at 4 years)	0.49 (0.41–0.58)	< .0001
BCIRG 006 AC/TH vs AC/T (Robert et al, 2007)	320 (36 months)	81	87	0.61 (0.48–0.76)	< .0001
BCIRG 006 TCH vs AC/T (Robert et al, 2007)	334 (36 months)	81	86	0.67 (0.54–0.83)	.0003
HERA (Dowsett et al, 2009)	539 (23.5 months)	74	81	0.63 (0.53–0.75)	< .0001
FinHer (Joensuu et al, 2006)	39 (3 years)	78	89	0.42 (0.21–0.83)	.01

Adjuvant trastuzumab produces statistically significant increases in disease-free survival rate.

AC = doxorubicin/cyclophosphamide; T = docexatel, H = trastuzumab; DFS = disease-free survival; HR = hazard ratio; CI = confidence interval; BCIRG = Breast Cancer International Research Group; HERA = Herceptin® Adjuvant; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCCTG = North Central Cancer Treatment Group; FinHer= Finland Herceptin®.

rate for the trastuzumab arms ranged from 33% to 51%. The higher DFS rate occurred in trials in which trastuzumab was combined with anthracycline, attesting to the greater efficacy of the anthracycline/trastuzumab combination.

Although trastuzumab is well tolerated, its use increases the risk of cardiovascular dysfunction in patients with metastatic disease who also receive anthracycline. This risk increases with age and in patients with lower cardiac ejection fractions (Rastogi et al, 2007).

TRASTUZUMAB IN THE NEOADJUVANT SETTING

In phase II trials evaluating trastuzumab in the neoadjuvant setting, most patients received an average of 3 to 4 months of a taxane-based chemotherapy combination prior to surgery. Between 30% to 50% of patients who received trastuzumab in addition to chemotherapy experienced a pathologically complete response rate (pCR), defined as no visible tumor during surgery, compared to the 10% to 15% pCR that typically occurs with chemotherapy alone (Bines et al, 2003; Burstein et al, 2003; Harris et al, 2003; Limentani et al, 2003; Gennari et al, 2004; Mohsin et al, 2005).

A phase III trial conducted at M. D. Anderson Cancer Center using the same protocol was halted early given the significant benefit seen in the trastuzumab arm. The trial resulted in pCR rates of 66.7% for combination therapy compared to 25% for chemotherapy only (p =.02; Buzdar et al, 2005).

FIRST-LINE THERAPY IN HER2-POSITIVE METASTATIC BREAST CANCER

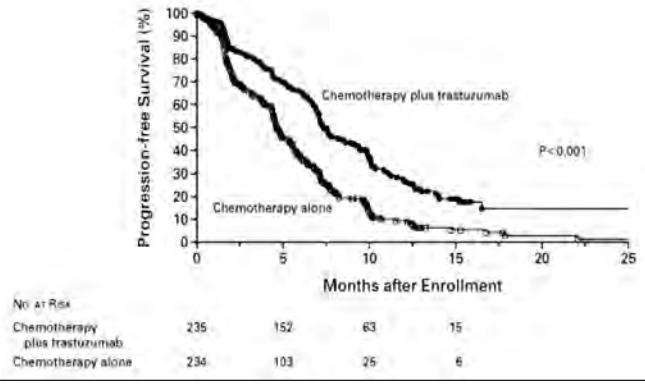
A trial evaluated the efficacy of anthracycline/cyclophosphamide in anthracycline-naive patients, or paclitaxel with or without trastuzumab, in metastatic breast cancer (MBC) patients with HER2-positive tumors. A significant improvement in DFS in the trastuzumab group was demonstrated, with a time to disease progression of 7.4 months compared to 4.6 months in the chemotherapy-only group (p < .001). Overall response in the combination group was also significantly higher (50% vs. 32%), as

was duration of response (median 9.1 vs. 6.1 months), and time to treatment failure (median 6.9 vs. 4.5 months; all $p < .001$; Slamon et al, 2001; Figures 2 and 3).

Clinical trial M77001 enrolled 186 patients with HER2-positive MBC to receive six cycles of docetaxel with or without trastuzumab every 3 weeks as first-line therapy. Patients in the docetaxel-only arm who experienced disease progression were allowed to cross over to trastuzumab. Patients who received the combination therapy initially demonstrated an overall response rate of 61% compared to 34% in the chemotherapy-only group ($p = .0002$). The combination group also experienced significantly better time to progression and overall survival (OS) rates compared to patients who received docetaxel alone or in whom trastuzumab was added after progression occurred (Marty et al, 2005). The majority of adverse events were mild to moderate with a slightly higher incidence of docetaxel-related adverse events in the combination arm. Slightly more patients in the combination arm experienced decreases in left ventricular ejection fraction than those in the docetaxel-only arm (Marty et al, 2005).

The phase III Breast Cancer International Research Group 007 trial randomly assigned patients to docetaxel/trastuzumab or docetaxel/trastuzumab/carboplatin, with chemotherapy given every 3 weeks for eight cycles and trastuzumab given weekly until progression in women with MBC (Pegram et al, 2007). There were no significant differences in any major outcomes, suggesting that using single-agent chemotherapy with trastuzumab could be just as effective as a double-agent approach.

Figure 2 Trastuzumab/Chemotherapy Combinations: PFS Analysis

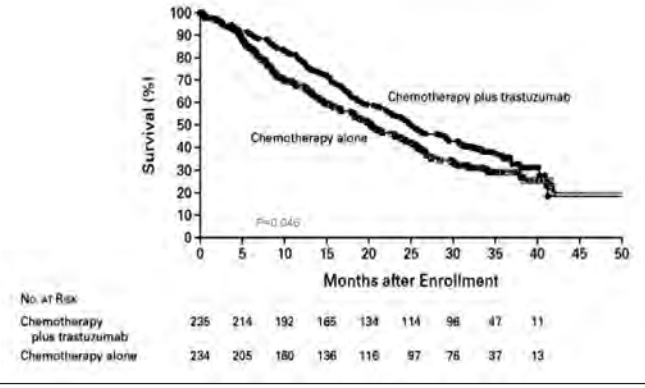


(Slamon et al, 2001)

The combination of chemotherapy and trastuzumab produced superior progression-free survival in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer.

PFS = progression-free survival.

Figure 3 Trastuzumab/Chemotherapy Combinations: Survival Analysis



(Slamon et al, 2001)

The combination of trastuzumab and chemotherapy produced a survival benefit in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer.

The Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer (Mackey et al, 2006) phase III trial evaluated the efficacy and safety of trastuzumab as first-line therapy for MBC with or without anastrozole.

The trastuzumab group experienced a doubling of time to progression (TTP; 4.8 months vs. 2.4 months; $p = .0016$), suggesting that the addition of trastuzumab could improve outcomes with hormone therapy. Although not statistically significant, there was also some evidence of gains in median OS (28.5 months vs. 23.9 months).

Trastuzumab-DM1

Trastuzumab-DM1 is a first-in-class compound that combines trastuzumab with the chemotherapy drug DM1. The drug is designed to bind to HER2 receptors and deliver the cytotoxic agent in a higher dosage than would otherwise be possible. Early data show markedly attenuated toxicities and substantial antitumor activity in patients who were trastuzumab resistant (Beeram et al, 2008).

Pertuzumab

Pertuzumab represents a new class of anti-HER2 agent that inhibits the dimerization of the HER2 protein itself. Phase II studies in HER2-positive patients showed pertuzumab was well tolerated with significant antitumor activity. Phase III studies are ongoing in patients with HER2-positive disease who have not received chemotherapy or biologic therapy (US National Institutes of Health 2007a).

Dual Kinase Inhibitors

Lapatinib is an oral small-molecule dual tyrosine kinase inhibitor associated with HER2 and epidermal growth factor receptor. It works intracellularly by binding reversibly to the cytoplasmic adenosine triphosphate binding site of the kinase, preventing receptor **phosphorylation** and activation (Figure 4; Reid et al, 2007).

A phase III study compared lapatinib/capecitabine with capecitabine alone in patients who were HER2-positive with refractory advanced or MBC previously treated with trastuzumab and in whom the disease had progressed (Geyer et al, 2006).

The trial was halted after the interim analysis demonstrated a 51% increase in TTP in the combination-therapy group (95% confidence interval: 0.34–0.71; $p < .001$). The median TTP was 8.4 months in the lapatinib group compared to 4.4 months in the monotherapy group, with no increase in serious adverse effects or cardiac dysfunction (Geyer et al, 2006). The drug has since been approved for use in women with MBC who had previously been treated with trastuzumab (Tykerb® prescribing information, 2008).

Lapatinib has also been evaluated in combination with paclitaxel as a first-line therapy for MBC in patients who were trastuzumab-naive. Patients in the combination group had a median TTP of 6.7 months compared to 5.3 months in the paclitaxel-only group ($p = .008$), and an OS of 22.8 months compared to 20 months ($p = .008$). Women whose tumors overexpressed HER2 had a much greater response, with a TTP of 8.1 months compared to 5.8 months in the paclitaxel-only group ($p = .27$; Di Leo et al, 2007). Sorafenib is also being evaluated in a phase III trial in combination with trastuzumab, to determine if total HER2-positive blockade improves clinical outcomes (O'Shaughnessy et al, 2008).

Sorafenib

Sorafenib is an oral multikinase inhibitor that targets numerous receptors and the Raf kinase. When evaluated as a monotherapy in phase II studies it demonstrated very low antitumor activity (Rini, & Small, 2005; Bianchi et al, 2007). However, it may improve outcomes when combined with other compounds. Current and recently completed phase II trials are evaluating its use as combination therapy with paclitaxel, capecitabine, gemcitabine, docetaxel, letrozole, and aromatase inhibitors (Cresta et al, 2004; Kellokumpu-Lehtinen et al, 2005; Modi et al, 2005; Perez, 2006; Gradishar et al, 2007; Arteaga et al, 2008; Memorial Sloan-Kettering Cancer Center, 2008).

Vascular Endothelial Growth Factor Inhibitors in Metastatic Breast Cancer

Bevacizumab is one of several agents that interferes with VEGF pathways, which are critical in cell proliferation, permeability, migration, and survival (Figure 5). The pivotal trial with bevacizumab randomly assigned women with HER2-negative MBC to paclitaxel with or without bevacizumab as a first-line therapy. Those receiving combination therapy exhibited a nearly doubling of progression-free survival compared to those receiving chemotherapy only (Miller, Wang, et al, 2007). Adverse effects included: hypertension, bleeding, thromboembolic events, and proteinuria. Patients who developed hypertension also exhibited greater antitumor activity, while those whose blood pressure remained normal had little benefit. There was no significant difference in health-related quality of life scores between either arm (Wagner, Wang, et al, 2006).

Other trials evaluated docetaxel with or without bevacizumab in women with locally recurrent breast cancer or MBC (Miles et al, 2008); albumin-bound paclitaxel with or without bevacizumab in patients with MBC (Link et al, 2006); and capecitabine with or without bevacizumab in patients with MBC (Sledge et al, 2007). Adverse effects including cardiotoxicity were negligible in all three trials, with each trial showing significant benefits in the bevacizumab arms.

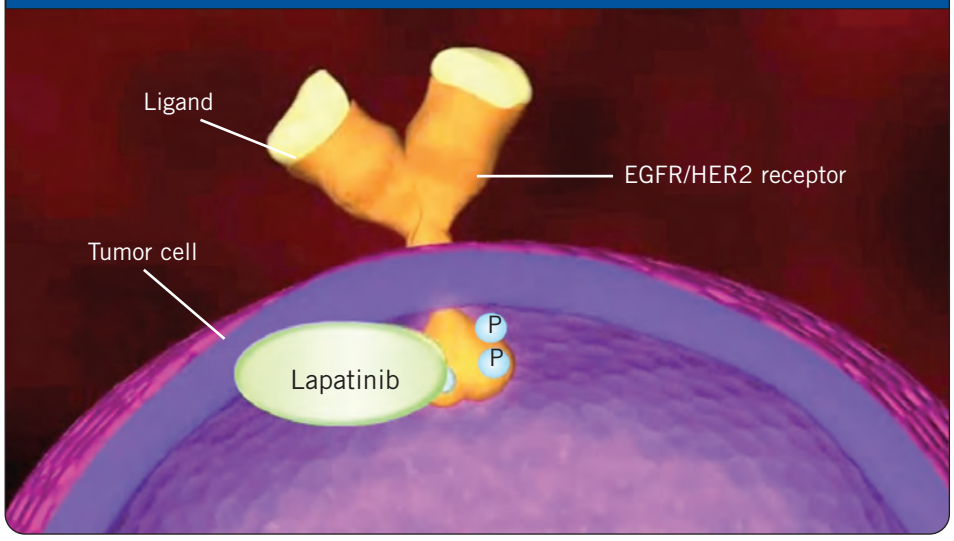
Bevacizumab is also being evaluated in the adjuvant setting with an ongoing trial involving doxorubicin/cyclophosphamide followed by paclitaxel plus placebo or bevacizumab (US National Institutes of Health, 2007b). Optimal duration of bevacizumab is being studied. Another adjuvant setting trial compared dose-dense doxorubicin/ cyclophosphamide followed by paclitaxel. All patients received bevacizumab every 2 weeks concurrently with doxorubicin or paclitaxel (Miller, O'Neil, et al, 2007). Toxicities of bevacizumab and chemotherapy combination were as expected, and, as with hypertension, may be predictive of response.

Combination of Biologic Agents

Preclinical data suggest that there is significant synergism between bevacizumab and trastuzumab (Scheuer, Friess, & Hasmann, 2006). Trials are ongoing evaluating various combination-targeted therapies. One such trial is National Surgical Adjuvant Breast and Bowel Project B-41 in women with palpable tumors that overexpress HER2. Patients are randomly assigned to either paclitaxel/trastuzumab, paclitaxel/lapatinib, or paclitaxel/ trastuzumab/ lapatinib, then surgically assessed for pCR, after which they receive postoperative trastuzumab (US National Institutes of Health 2007c).

In the Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation study, 8,000 women will be randomly

Figure 4 Lapatinib Mechanism of Action

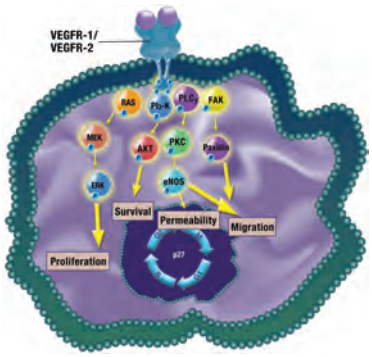


Lapatinib is an oral small-molecule dual inhibitor of HER2 and EGFR tyrosine kinases. It works intracellularly by binding reversibly to the cytoplasmic adenosine triphosphate binding site of the kinase, preventing receptor phosphorylation and activation.

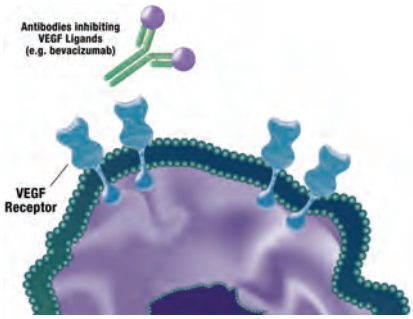
EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor; P = phosphorylation.

FIGURE 5 Mechanism of Action of VEGF Inhibitors

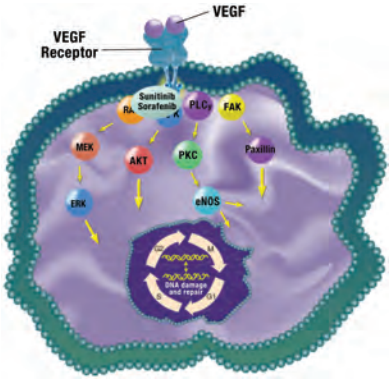
3a. VEGF Signal Transduction



3b. Blockage of Ligand-Receptor Binding



3c. Blockage of Activation of Receptors with Tyrosine Kinase Inhibitors



(Images courtesy of Bridget O'Brien, ND, APRN, FNP-BC, AOCNP®)

Bevacizumab is one of several agents that interferes with vascular endothelial growth factor pathways, which are critical in cell proliferation, permeability, migration, and survival.

VEGF = vascular endothelial growth factor.

assigned to either trastuzumab for 1 year; lapatinib for 1 year; trastuzumab for 3 months followed by lapatinib; or trastuzumab/lapatinib for 1 year (US National Institutes of Health 2007d). Meanwhile, a phase II trial combining bevacizumab and trastuzumab in patients with HER2-positive tumors suggested an increased response in the combination group (Pegram et al, 2006). In the Bevacizumab, Epirubicin, Docetaxel, Trastuzumab study, investigators are evaluating the addition of bevacizumab to chemotherapy and trastuzumab in patients with HER2-positive disease. Patients are randomly assigned to receive either six cycles of docetaxel/carboplatin and trastuzumab with or without bevacizumab, or three cycles of docetaxel and trastuzumab with or without bevacizumab followed by three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (US National Institutes of Health, 2008).

CONCLUSION

Advances in understanding of tumor biology have spurred the development of novel agents and treatment strategies that build upon progress already made. Several targeted agents have demonstrated great success against breast cancer, including trastuzumab, lapatinib, and bevacizumab. Current investigative efforts are aimed at optimizing their administration with other agents, and determining which patients are most likely to derive benefit. As we gain greater understanding of the molecular pathways involved in tumor development and progression, we come closer to truly individualizing patient care. New compounds, such as pertuzumab and trastuzumab DM1, are being studied and may one day continue to change the treatment landscape. ●

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CASE STUDY

MANAGING TOXICITIES ASSOCIATED WITH TRASTUZUMAB

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The use of trastuzumab and other biologic agents has revolutionized the care of women with human epidermal growth factor receptor 2 (HER2)-positive disease (Bartsch, Wenzel, & Steger, 2007). While traditional chemotherapy indiscriminately kills all rapidly dividing cells, biologic therapies selectively act on tumor cells and thus have fewer toxicities (Tigue et al, 2007). These novel agents are not without side effects, however. Along with the introduction of these agents has come the advent of novel toxicities that deserve careful nursing assessment and management.

CASE STUDY

Ms. L was a 65-year-old woman diagnosed with stage II estrogen receptor/progesterone receptor-positive breast cancer in 1985. She was initially treated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and tamoxifen (National Comprehensive Cancer Network [NCCN], 2009). After being disease-free for 8 years, she developed a local recurrence. Treatment ensued with doxorubicin and cyclophosphamide, and she achieved a complete response. Four years later, she presented to the clinic with low back pain. A bone scan revealed sacral and spinal metastases. The bony metastases were treated with bisphosphonate therapy (pamidronate and later zoledronic acid) and multiple hormonal agents including aromatase inhibitors and luteinizing hormone-releasing hormone antagonists, of which she became refractory (NCCN, 2009).

Most recently, Ms. L experienced difficulty with urination, a feeling of "fullness" in her vaginal area, and vaginal bleeding. Physical examination revealed a 6-cm lesion on the vaginal wall. The biopsy was positive for breast cancer with 2+ HER2 expression. It should be noted that HER2 testing was not available when Ms. L was initially diagnosed with breast cancer in 1985; therefore, her HER2 status prior to this relapse was unknown. Trastuzumab was recommended as the treatment of choice.

Prior to Ms. L receiving trastuzumab therapy, a baseline left ventricular ejection fraction (LVEF) was obtained via echocardiogram and reported at 55%. Trastuzumab therapy was initiated, and Ms. L experienced fever and chills early in the infusion. She was treated with acetaminophen and meperidine (Demerol® prescribing information, 2008). She was premedicated with acetaminophen for subsequent doses of trastuzumab and experienced no further transfusion reactions. Ms. L's pulmonary assessment revealed a dry cough that persisted throughout therapy. She also experienced shortness of breath upon exertion. Oxygen saturation, assessed at each outpatient visit, was 95% or higher. Ms. L received a total of 12 weeks of trastuzumab therapy and achieved a complete response. Vaginal bleeding ceased and there was complete disappearance of the vaginal tumor by physical examination. Cardiac and pulmonary assessments were also conducted at 12 weeks for surveillance. The echocardiogram revealed a drop in LVEF to 40%, but the chest radiograph was clear. While Ms. L was asymptomatic, trastuzumab was held due to a decrease in LVEF by 15 percentage points (Herceptin® prescribing information, 2009). The echocardiogram was repeated 8 weeks later and remained at 40%. Trastuzumab was discontinued at that time. She then developed a retroperitoneal tumor with spinal nerve compression. Treatment of choice would be trastuzumab, but this was no longer an option due to the low LVEF. Ms. L was treated with localized radiotherapy and achieved a partial response (NCCN, 2009). As of her last visit, she was alive and well. She reported some pain and fatigue but an overall "good quality of life." She was attending a weekly cancer support group and enjoyed quilting and playing cards.

Overview of Trastuzumab Therapy

Trastuzumab is a monoclonal antibody that targets the tyrosine kinase HER2. It is indicated for the adjuvant treatment of HER2-overexpressing breast cancer (Herceptin® prescribing information, 2009). It may be used as a combination agent with paclitaxel for the first-line treatment of HER2-overexpressing metastatic breast cancer or as a single agent in patients who have received one or more chemotherapy regimens for metastatic disease.

Trastuzumab-Induced Cardiotoxicity

Cardiotoxicity is defined as a reduction of LVEF from baseline > 5% to < 55% with accompanying signs and symptoms or > 10% when asymptomatic (Martin et al, 2009). The toxicity often presents as an asymptomatic decrease in LVEF. Unlike anthracycline-induced cardiotoxicity, trastuzumab does not appear to cause cardiac tissue cell death, no changes are detectable on muscle biopsy, cardiotoxicity is usually reversible, and is not associated with cumulative dose (Bria et al, 2008; Ewer & Ewer, 2008). The incidence of trastuzumab-induced cardiotoxicity is approximately 0% to 3.9% in the adjuvant setting (from five clinical trials; N > 10,000) but much higher in the metastatic setting (22%) when trastuzumab is given concurrently with chemotherapy. The percentage is even higher (28%), when it is administered with an anthracycline (Ewer & Ewer, 2008). Risks identified in assorted clinical trials include older age, diabetes, obesity, concurrent anthracycline administration, chest wall irradiation, and existing cardiac disease. A wealth of information exists regarding cardiac monitoring in patients receiving trastuzumab, but a lack of consistent guidelines has led to inconsistent practices. Initially, patients should undergo a baseline history, physical examination, and LVEF assessment by echocardiogram or multi-gated acquisition scan (Herceptin® prescribing information, 2009). Frequent monitoring should continue during and after trastuzumab therapy and more diligence should be given to those who develop significant LVEF dysfunction. Patients should be assessed for weight gain, shortness of breath, cough, chest pain, and fluid retention. Trastuzumab dose administration guidelines for an asymptomatic decrease in LVEF are outlined in the Table (Herceptin® prescribing information, 2009).

While no studies have examined the medical management of trastuzumab-induced cardiotoxicity, standard management of congestive heart failure should be employed. The American Heart Association and the American College of Cardiology recommend the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in patients with LVEF less than 40%. Additional measures include: diuretics for fluid overload,

Table Trastuzumab Administration for Asymptomatic Decreases in LVEF

	Absolute decrease from baseline (percentage points)		
Relationship of LVEF to LLN	< 10	10–15	≥ 16
Within normal limits	Continue	Continue	Hold for ≥ 4 weeks
Below LLN	Continue	Hold for ≥ 4 weeks	Hold for ≥ 4 weeks

- When trastuzumab is held, it may be resumed if, within 4–8 weeks:
  - The LVEF returns to normal limits and
  - The absolute decrease from baseline is ≤ 15 percentage points
- Trastuzumab should be permanently discontinued if:
  - Persistent (> 8 weeks) LVEF decline is observed or
  - Trastuzumab dosing is held on more than three occasions for cardiomyopathy

(Herceptin® prescribing information, 2009)

Asymptomatic decreases in LVEF may warrant treatment to be withheld or discontinued.

LLN = lower limits of normal; LVEF = left ventricular ejection fraction.

beta-blockers for class II – IV heart failure, and digoxin for symptomatic heart failure (Ewer & Ewer, 2008; Martin et al, 2009). Overall, cardiotoxicity is a potential adverse event with trastuzumab administration and close observation is crucial; however, most patients return to normal LVEF and are able to continue safely with trastuzumab therapy.

INFUSION REACTIONS

Trastuzumab contains 2% to 5% murine antibody. This may lead to reaction to the foreign protein (Gobel, 2007). While early clinical trials reported the anticipated mild reactions, cases of fatal anaphylaxis arose post-approval of the agent in 2000 (Herceptin® prescribing information, 2009). Most reactions from trastuzumab involve an initial infusion reaction characterized by fever and chills in 40% of patients. Other signs and symptoms include: nausea and vomiting, pain, rigors, headache, dizziness, hypotension, dyspnea, rash, and asthenia. The reaction usually occurs within 24 hours of administration and is most frequent with the first dose, decreasing thereafter. In rare instances, anaphylactic reactions can occur and cause respiratory failure, cardiovascular collapse, and gastrointestinal disturbances. Anaphylaxis is caused by exposure to the murine protein (antigen). The B-lymphocyte digests the antigen and displays fragments of the antigen. Immunoglobulin E antibodies that are specific to the foreign protein are released into the circulation. The immunoglobulin E then binds to mast cells and sensitizes them to the antigen, resulting in mast cell deregulation and the release of inflammatory mediators including histamine, serotonin, leukotrienes, prostaglandins, and platelet-activating factor (Figure; Gobel, 2005; 2007).

Prevention is the first line of defense in infusion reactions. An emergency plan and emergency equipment should be in place when administering any monoclonal antibody with potential for reaction (Lenz, 2007). For fever and chills, the infusion should be stopped and continued at a slower infusion rate only when resolved. Acetaminophen, diphenhydramine, and opioids may be administered for comfort (Gobel, 2007). Dyspnea and hypotension suggest a more serious reaction, and infusions should be interrupted until symptoms resolve (Lenz, 2007). Vital signs should be monitored every 2 to 5 minutes and then every 15 minutes when stable (Gobel, 2007). Pretreatment with acetaminophen, diphenhydramine, and/or steroids should be considered with subsequent treatments. Anaphylaxis, while rare, is an oncologic emergency. The emergency leads to airway and circulatory collapse due to the influx of inflammatory mediators. Patients often complain of a "sense of doom" prior to the reaction. An emergency drug kit, oxygen, and a defibrillator should be nearby for potential emergent reactions (Lenz, 2007; Gobel, 2007).

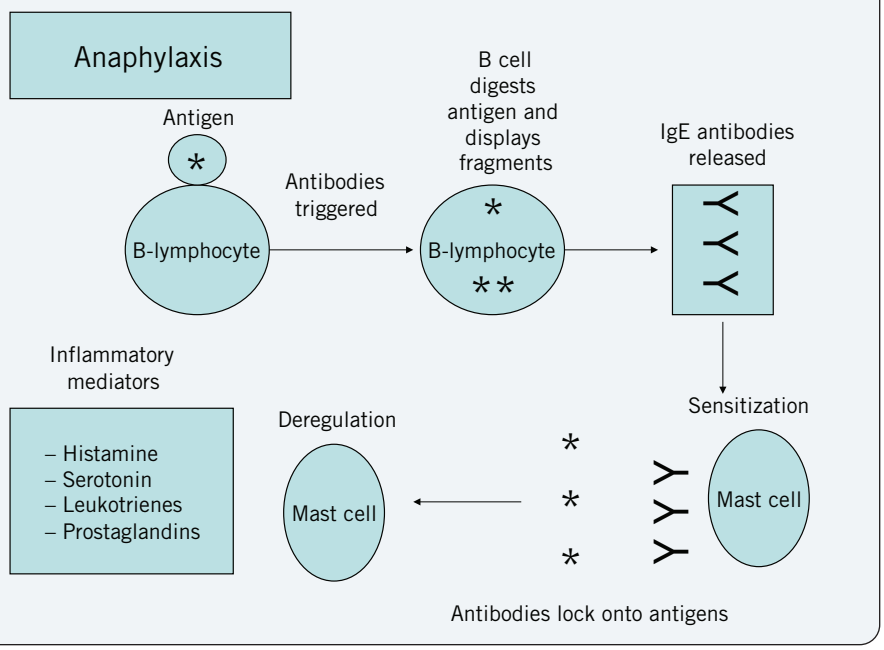
NEUTROPENIA

The incidence of neutropenia in patients receiving single-agent trastuzumab is rare (~3%), but incidence increases when given in combination with paclitaxel (24%) or with doxorubicin and cyclophosphamide (52%). As with any antineoplastic agent, a complete blood count should be monitored with ongoing administration. Patients should be educated about the signs and symptoms of febrile neutropenia and should be instructed to call their healthcare team for a fever > 38º C (Herceptin® prescribing information, 2009; Miceli et al, 2008).

PULMONARY TOXICITY

Pulmonary toxicities are additional adverse events associated with trastuzumab, but the mechanism of injury is unclear. The incidence is variable, depending on the type of toxicity induced: cough (26%), dyspnea (22%), rhinitis/pharyngitis (14% to 12%), sinusitis (9%), and interstitial pneumonitis (0.4% to 0.6%). Pepels and colleagues (2009) recently reported a case of interstitial pneumonitis in a patient who was receiving several months of trastuzumab therapy. The patient presented with pulmonary infiltrates, dyspnea, and pleural effusion. The pneumonitis improved following treatment with steroids (Pepels et al, 2009). If a patient develops pulmonary symptoms while on trastuzumab, recommendations include the following: (1) hold the infusion, (2) assess pulse oximetry, (3) conduct a pulmonary examination, (4) obtain a chest radiograph, (5) conduct pulmonary function tests, (6) order a computed tomography scan of the chest if interstitial pneumonitis is suspected, (7) consider steroid treatment, and (8) reevaluate the continuation of therapy. A computed tomography scan showing a ground glass appearance indicates interstitial pneumonia (Vahid & Marik, 2008; Vahid & Mehrota, 2006).

FIGURE **Anatomy of Anaphylaxis**



(Image courtesy of Jeannine Brant, PhD, APRN-CNS, AOCN®)
IgE = Immunoglobulin E.

Conclusion

Trastuzumab has a unique toxicity profile, and is associated with adverse events that should be monitored closely in women with metastatic breast cancer. The most serious of these events include cardiotoxicity, infusion reactions, neutropenia, and pulmonary toxicity. Oncology nurses should be knowledgeable of the unique challenges associated with this agent. Through optimal assessment, management, and prevention of side effects, oncology nurses can drastically improve a patient's quality of life and even improve the outcomes of patients with breast cancer. ●

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Case Study

Case Presentation/Nursing Practice Patterns: VEGF Inhibitors

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Targeted therapies are increasingly being used in the treatment of metastatic breast cancer. Each class of agent is associated with unique adverse effects that differ significantly from those that oncology nurses may be used to seeing in patients who receive traditional chemotherapy. Nurses play a critical role in managing side effects, which can have a direct impact on patient outcomes. Severity of effects determines if a dose should be reduced or if treatment should be temporarily or permanently discontinued.

VEGF Inhibitors

Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis. Inhibition of VEGF impairs angiogenesis, disrupts endothelial cell vascular integrity, and disturbs the interaction of endothelial cells with platelets and surrounding tissues (Chen & Cleck, 2009). VEGF inhibitors are increasingly being used as standard therapy across various therapeutic areas. Agents that target VEGF are associated with hypertension, arterial thromboembolic events (ATEs), proteinuria, wound-healing complications, hemorrhage, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome.

Bevacizumab Side-Effect Profile

Bevacizumab is a humanized monoclonal antibody that targets VEGF. Bevacizumab in combination with paclitaxel is indicated for the treatment of patients with metastatic breast cancer who have not received chemotherapy for metastatic human epidermal growth factor receptor 2-negative disease. It is administered as an intravenous infusion 10 mg/kg every 2 weeks (Avastin® prescribing information, 2009).

Adverse reactions from bevacizumab include hypertension, proteinuria, ATEs, venous thromboembolic events (VTEs), neutropenia, and infection (Table 1). Bevacizumab carries a boxed warning of gastrointestinal perforation (2.4% incidence in patients with colorectal cancer), pulmonary hemorrhage (31% incidence in squamous cell non-small cell lung cancer; 2.3% to 4% in other histologies; Avastin® prescribing information, 2009), and wound-healing complications (15%; Herbst, 2006).

Hemorrhage

Patients treated with bevacizumab are at increased risk of hemorrhage, both minor bleeding and serious hemorrhagic events (Chen & Cleck, 2009; Avastin® prescribing information, 2009). Across trials of bevacizumab, 20% to 40% of patients experienced mucocutaneous hemorrhage, typically mild **epistaxis** (Chen & Cleck, 2009). Patients should be advised to use humidifiers, saline sprays, and petroleum jelly, and to avoid harsh nose rubbing and blowing. In some cases, patients may require local cauterization of small nasal blood vessels. Severe or fatal hemorrhage (eg, hemoptysis, gastrointestinal bleeding, hematemesis, central nervous system hemorrhage) occurred up to 5-fold more frequently in patients receiving bevacizumab compared to those receiving only chemotherapy (Avastin® prescribing information, 2009). The incidence of ≥ grade 3 hemorrhagic events ranged from 1.2% to 4.6%. Nurses should educate patients about management of minor bleeding events such as applying pressure to minor nosebleeds and warning signs of major homorrhage. Any bleeding event should be reported. Bevacizumab should be discontinued if patients experience serious hemorrhage or recent hemoptysis (≥ ½ teaspoon of blood; Gobel, 2007).

Wound-Healing Complications and Elective Surgery

Because angiogenesis is critical in the wound-healing process, patients receiving antiangiogenic agents have a higher incidence of postoperative wound healing and bleeding complications. Patients receiving bevacizumab who undergo surgery have a 15% increased risk of wound complications (Avastin® prescribing information, 2009). There is no clear determination of the appropriate interval between the termination of bevacizumab and subsequent elective surgery. The half-life of bevacizumab is approximately 20 days (range 11–50 days; Chen & Cleck, 2009). Bevacizumab should be suspended at least 28 days prior to elective surgery. It should not be administered until at least 28 days postsurgery and until surgical wounds are fully healed (Avastin® prescribing information, 2009). Evidence from a large trial in patients with metastatic colon cancer who received bevacizumab plus chemotherapy showed a wound-healing complication rate of 1.6% in 324 patients who received a venous access device either 7 or 2 days prior to their first bevacizumab dose (Kretzschmar et al, 2005). This rate is similar to that seen in patients who do not take bevacizumab, suggesting that port implantation and other minor procedures prior to bevacizumab administration should be acceptable.

Venous Thromboembolic Events

Bevacizumab increases the risk of VTEs such as deep vein thrombosis and pulmonary embolism. In the E2100 trial, patients receiving bevacizumab plus paclitaxel experienced a higher incidence of cerebrovascular ischemia than patients receiving paclitaxel alone (1.9% vs. 0%; $p = .02$; Miller et al, 2007). Overall incidence of grade 3/4 VTEs occurred more frequently in patients with metastatic colorectal cancer or non-small cell lung cancer treated with bevacizumab versus those treated with chemotherapy alone (15.1% and 13.6%, respectively; Avastin® prescribing information, 2009). If patients have a grade 3 VTE, it is necessary to halt bevacizumab for 2 weeks and/or until full anticoagulation is established. Bevacizumab should be discontinued for grade 4 VTE events (Kabbinavar & Shah, 2008).

Arterial Thromboembolic Events

Serious and sometimes fatal ATEs occurred at a higher incidence in patients receiving bevacizumab than in those in control arms (grade ≥ 3 2.4% vs. 0.7%, respectively; Avastin® prescribing information, 2009). Such events include: cerebral infarction, transient ischemic attacks, myocardial infarction, and angina. Risk factors for ATEs include patients > 65 years of age and/or those with a previous history of ATE. Bevacizumab should be discontinued in patients who develop severe ATEs. The safety of resuming bevacizumab following resolution of an ATE has not been studied (Avastin® prescribing information, 2009).

Hypertension

There is some evidence indicating that VEGF increases levels of nitric oxide, a potent vasodilator. Thus, inhibiting VEGF with bevacizumab causes vasoconstriction and hypertension (Chen & Cleck, 2009). Overall, 22% to 32% of patients experience hypertension, which may persist after the drug is discontinued. The incidence of grade 3/4 hypertension ranged from 5% to 18% across clinical trials (Avastin® prescribing information, 2009). A rare complication is hypertensive encephalopathy, which is an emergency requiring immediate treatment (Tobelem, 2007; Osol et al, 2008).

Blood pressure should be monitored every 2 or 3 weeks during treatment with bevacizumab. Some patients may benefit from home blood pressure monitoring. Bevacizumab-induced hypertension may be controlled by angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, and calcium channel blockers (Chen & Cleck, 2009). Medications should be selected based on patient characteristics such as comorbidities and severity of symptoms. Two antihypertensives may be necessary in some cases. It is important that oncology nurses educate patients regarding the symptoms of a hypertensive crisis, including headache, dizziness, blurred vision, and changes in consciousness (Rosiak & Sadowski, 2005). Hypertensive crisis is an oncologic emergency requiring immediate intervention. In the rare occurrence of uncontrolled hypertension or hypertensive crisis, bevacizumab should be discontinued. Table 2 depicts management options for bevacizumab-related hypertension.

Proteinuria

Between 27% and 38% of patients receiving bevacizumab experience proteinuria, and 3% to 1% of patients experience grades 3 or 4 proteinuria, respectively (Miller et al, 2007). Nephrotic syndrome occurred in < 1% of patients receiving bevacizumab in clinical trials (Avastin® prescribing information, 2009). The link between bevacizumab and proteinuria may be related to the effect of VEGF on regulating glomerular vascular permeability and mediating glomerular endothelial repair (BC Cancer Agency, 2006). Urine protein should be assessed prior to each bevacizumab cycle with urine dipstick, 24-hour urine collection, or urine protein creatine (UPC). A spot UPC may be simpler to perform (Kashif et al, 2003).

Table 1 Incidence of Grade 3/4 Adverse Events With Bevacizumab in E2100 Study

	Paclitaxel (n = 354)		Paclitaxel + Bevacizumab (n = 368)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Hypertension[a]	0	0	15	< 1
Thromboembolic events	< 1	< 1	2	1
Bleeding[b]	0	0	1	0
Proteinuria[c]	0	0	3	1
Neuropathy	17	1	23	1
Fatigued	4.6	< 1	9	< 1
Neutropenia	0	0	1	< 1
Decreased LVEF	0	< 1	1	0

(Miller et al, 2007)

In the E2100 study, which compared paclitaxel with and without bevacizumab in the treatment of first-line metastatic breast cancer, adverse reactions from bevacizumab include hypertension, proteinuria, thromboembolic events, and bleeding.

LVEF = left ventricular ejection fraction.

[a]$p < .001$, [b]$p = .02$, [c]$p = .001$, [d]$p = .04$

Table 3 depicts 24-hour output ranges for proteinuria and albumin. Table 4 depicts the results of urine dipsticks. Bevacizumab should be temporarily discontinued in patients with moderate to severe proteinuria (Avastin® prescribing information, 2009). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been evaluated.

Table 2 Hypertension and Bevacizumab

Grade	Description	Recommended Intervention
1	Asymptomatic, transient (< 24 hours) increase by > 20 mm HG (diastolic) or to > 150/100 if previously normal	Continue bevacizumab and monitor blood pressure closely every 2 to 3 weeks
2	Recurrent or persistent or symptomatic increase by 20 mm Hg (diastolic) or to > 150/100 mm HG if previousy normal	Temporarily hold bevacizumab and begin antihypertensive therapy. Resume bevacizumab when blood pressure returns to baseline or grade 1 level.
3	Requiring more than one hypertensive agent or more intensive therapy than previously needed	Temporarily hold bevacizumab and begin antihypertensive therapy. Resume bevacizumab when blood pressure returns to baseline or grade 1 level.
4	Life-threatening consequence, such as hypertensive crisis > 180/110 mm HG	Discontinue bevacizumab and begin antihypertensive therapy

(BC Cancer Agency, 2006; Avastin® prescribing information, 2009; Kabbinavar & Shah, 2008)

Bevacizumab-induced hypertension may be controlled using standard antihypertensives. In the case of hypertensive crisis, bevacizumab should be discontinued.

Table 3 Protein and Albumin Excretion

Category	Value (mg/24 Hours)
Total protein excretion	
Normal value in adults	< 150
Proteinuria	≥ 150
Nephrotic-range preteinuria	> 3,500
Albumin excretion	
Normal albumin excretion	2–30
Microalbuminuria	30–300
Macroalbuminuria	> 300

(Kashif et al, 2003)

Proteinuria should be monitored closely since it is an indicator for renal damage and artherosclerotic disease.

Table 4 Proteinuria Grade by Dipstick and Bevacizumab

Proteinuria Dipstick Urinalysis Grade	Action
1	Give bevacizumab and continue to monitor
2	Give bevacizumab and collect 24-hour urine within 3 days before next cycle • When 24-hour proteinuria < 2 g: Give bevacizumab and follow with 24-hour urinary protein before each cycle; once it falls to < 1 g, resume monitoring by dipstick method • If 24-hour proteinuria > 2 g: Hold bevacizumab and repeat 24-hour urine collection for proteinuria before the next cycle. Once < 2 g, give bevacizumab and continue to check 24-hour protein before each cycle. Once < 1 g, resume monitoring with dipstick urinalysis. If not < 2 g after 3 months, discontinue bevacizumab
3	Hold bevacizumab and check 24-hour urinary protein • When < 2 g, restart bevacizumab • If > 2 g after 3 months, discontinue bevacizumab
4	Discontinue bevacizumab

(Avastin® prescribing information, 2009; BC Cancer Agency, 2006)

Bevacizumab should be suspended if ≥ 2 grams of proteinuria/24 hours and resumed when proteinuria is < 2 grams/24 hours. Bevacizumab should be discontinued in patients with nephrotic syndrome.

Gastrointestinal Perforations

Patients receiving bevacizumab are at increased risk of developing gastrointestinal perforations, which may be serious and sometimes fatal (Avastin® prescribing information, 2009). Presentation typically occurs within the first 50 days of therapy initiation. Symptoms include abdominal pain, nausea, fever, emesis, and constipation. Intra-abdominal abscess and fistula formation may complicate perforation. Bevacizumab should be discontinued in patients who develop gastrointestinal perforations. Patients should report any abdominal pain, which could indicate gastrointestinal perforations. This side effect has been rarely seen in patients with metastatic breast cancer (Saif, Elfiky, & Salem, 2007). Gastrointestinal perforations are most commonly seen in colon cancer patients following definitive surgery.

Case Study

Ms. S was a 50-year old with prior node-negative cancer in 2005, status post-lumpectomy, doxorubicin/cyclophosphamide. She had metastatic breast cancer that advanced to her bones and liver. Because she was taxane-naive, the first choice of treatment was paclitaxel plus bevacizumab. Ms. S was into her third month of treatment when her blood pressure rose from a baseline value of 125/80 mm Hg to 155/93 mm Hg. Ms. S began lisinopril with a dose escalation to 20 mg daily resulting in blood pressure normalization to baseline. After completing bevacizumab treatment, lisinopril was discontinued and her primary care physician monitored her blood pressure every 2 weeks.

Conclusion

Oncology nurses must be prepared to manage the adverse effects of today's newer, targeted agents, particularly as more such agents are used alone, with chemotherapy, or combined. Side effects may warrant treatment dose reduction or interruption. Although bevacizumab is generally well tolerated, nurses must be cognizant of its potential side effects and their respective treatments. Vigilant monitoring, patient education, and prompt intervention are keys to optimizing patient outcomes. ●

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Case Study

Managing Toxicities Associated With Lapatinib

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Ms. N was a 45-year-old woman with human epidermal growth factor receptor 2 (HER2)-positive stage IV metastatic breast cancer. Previous treatments included doxorubicin, cyclophosphamide, docetaxel, trastuzumab, and zoledronic acid (National Comprehensive Cancer Network [NCCN], 2009a). Recent computed tomography scans revealed progressive bony and visceral metastases. Following a discussion of treatment options and a review of insurance benefits, she was ready to begin oral lapatinib and capecitabine therapy (NCCN, 2009a).

The oncology clinic nurse provided Ms. N with information about the common side effects of lapatinib and capecitabine therapy. The education session included the dosing schedule, potential toxicities, and management strategies (Winklejohn, 2007). Ms. N was given a dosing calendar to track her daily dosages. She was instructed to call her oncology nurse with any concerns. The nurse informed Ms. N that she would receive a follow-up call in 1 week to assess tolerance of the new regimen.

During the follow-up phone call, Ms. N reported mild diarrhea (grade 1), nausea, and heartburn during the first week of treatment. The diarrhea was managed with fluids, diet modification, and occasional loperamide (Crown et al, 2008). The nausea and heartburn were effectively managed with a proton pump inhibitor (Delaney et al, 2008). Ms. N developed mild dermatologic toxicity. She reported mild facial pruritus on Day 3 of therapy and developed a mild rash by Day 8, managed effectively with hydrocortisone gel. Grade 1 palmar-plantar erythrodysesthesia (PPE) ensued on Day 10 of capecitabine but disappeared prior to the next cycle (Geyer et al, 2008). Ms. N received lapatinib and capecitabine therapy for more than 1 year. She continued to feel well with minimal side effects.

Overview of Lapatinib

Lapatinib, a dual kinase inhibitor of epidermal growth factor receptor (EGFR) and HER2, is approved for the treatment of metastatic breast cancer in combination with capecitabine for patients with overexpressing HER2 tumors and who have previously been treated with an anthracycline, taxane, and trastuzumab (Tykerb® prescribing information, 2009). Lapatinib is administered orally, once daily on an empty stomach for a 21-day cycle. Pharmacokinetic data reveal a low-fat meal can increase area under the curve (AUC) by 167%; a high-fat meal can increase AUC by 325%. Lapatinib is primarily metabolized by the cytochrome P450 3A4 isoenzyme, thus patients should avoid CYP3A4 inducers and inhibitors. Capecitabine is administered at 2,000 mg/m^2 daily divided in two doses about 12 hours apart for Days 1 to 14 of the 21-day cycle (Tykerb® prescribing information, 2009). Capecitabine should be administered with food (Medina & Goodin, 2008).

Adherence to Oral Regimens

Adherence to oral regimens poses a challenge for many patients. Studies show that adherence to tamoxifen drops to less than 80% long-term (Chlebowski & Geller, 2006). Other studies reveal that about 20% of patients were compliant with imatinib therapy (Marques & Pierin, 2008). Barriers to adherence include complexity of regimens and schedules, memory and comprehension, interaction with other medications and food, and fear of side effects (Moore et al, 2006). A complex regimen such as lapatinib and capecitabine poses distinct adherence barriers as one agent is administered on an empty stomach once daily while the other agent is administered with food twice daily (Tykerb® prescribing information, 2009). Several nursing interventions have been proposed to increase adherence (Table 1). Assessment of adherence at each ambulatory visit is a primary nursing responsibility. A diligent assessment can reveal con-

cerns about side effects or stressors associated with the scheduling of medications. In addition, educating patients about what side effects to expect can enhance self-care and increase adherence (Winkeljohn, 2007). Some of the common toxicities to address for lapatinib and capecitabine include diarrhea (65%), PPE (53%), nausea and vomiting (44%), and rash (28%; Tykerb® prescribing information, 2009). While not an expected toxicity, cardiotoxicity will also be discussed.

Cardiotoxicity

The pivotal phase III trial for lapatinib's FDA approval examined lapatinib and capecitabine versus capecitabine alone (N = 399) in women with metastatic breast cancer. Four patients receiving lapatinib and capecitabine experienced cardiac events, and all events were determined to be treatment related. Three patients experienced grade 2 heart failure and one patient had grade 3 (symptomatic) failure. All patients' left ventricular ejection fraction (LVEF) returned to normal following the discontinuation of lapatinib. These events prompt the need for cardiac monitoring in patients receiving lapatinib (Cameron et al, 2008). While no formal guidelines exist, some clinicians recommend a multi-gated acquisition scan at baseline, then every 6 weeks for 6 months, then every 12 weeks (Geyer et al, 2006). Patients should also be educated about the symptoms of congestive heart failure (eg, shortness of breath; swelling of the ankles, feet, or abdomen; nausea; abdominal pain) and the need to report them to their healthcare provider (Cameron et al, 2008; Tykerb® prescribing information, 2009). Lapatinib should be discontinued in patients with a decreased LVEF (grade 2 or higher as determined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]) or in patients whose LVEF falls below the institution's lower limits of normal (Tykerb® prescribing information, 2009). In the case of an asymptomatic patient, if the LVEF returns to normal, lapatinib may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks (Tykerb® prescribing information, 2009).

Table 1 Nursing Interventions to Increase Adherence

Nursing Intervention	Comments
Chemotherapy calendars	• Organizes chemotherapy regimen • Goal oriented • Include places to record daily dosages for tracking
Diaries to record adherence	• Daily log of medications taken • Can record side effects and other challenges to easily identify problems
Pill boxes	• Organizes pills in daily boxes to assist with memory of administration
Counting pills at each patient visit	• Most accurate method of tracking adherence to a regimen • Encourages dialogue between the nurse and the patient regarding therapy tolerance and adherence
Providing extensive contact information	• Allows for follow-up contact via phone or other mechanism • Encourages patient accountability
Patient education • Dosage information • Side effects • When to call the doctor or nurse	• Encourages self-care and autonomy • Allows patients to anticipate side effects; know what to expect • Education should include strategies to manage side effects

(Winklejohn, 2007)

Adherence to oral regimens poses a challenge for many patients. Assessment of adherence at each ambulatory visit is a primary nursing responsibility.

Diarrhea

Diarrhea is the most common side effect of lapatinib/capecitabine combination therapy (Cameron et al, 2008). Diarrhea, which is predominantly grade 1 or 2, usually presents early in the course of treatment and lasts about 5 days. It is not often dose limiting. Eighty five percent required no dose adjustment or interruption in lapatinib's pivotal trial (Crown et al, 2008). Nurses should assess the patient's bowel habits prior to initiation of therapy. Patients should be educated about the potential for diarrhea, the need to monitor the number of stools and the volume of diarrhea, and when to call their healthcare provider. Management of diarrhea includes fluid replacement, dietary modification, and pharmacologic interventions such as loperamide (Cameron et al, 2008; Crown et al, 2008). In the case of severe diarrhea, administration of oral or intravenous electrolytes and fluids may be required, as well as interruption or discontinuation of therapy (Tykerb® prescribing information, 2009).

Palmar-Plantar Erythrodysesthesia

PPE is a fairly common event associated with lapatinib/capecitabine therapy, but is primarily related to capecitabine (49% alone versus 53% with combination). Many etiologies have been proposed, but the cause remains unknown (Webster-Gandy, How, & Harrold, 2007). The syndrome presents with dysesthesias and erythema of the palms, fingers, soles of the feet, and other pressure surfaces for a 3–5 day period followed by progressive symptoms of burning pain, dryness, cracking, desquamation, ulcera-

tion, and edema. The palms are more commonly affected than other pressure surfaces (Webster-Gandy et al, 2007). The mainstay of treatment for PPE is dose modification via: (1) treatment interruption (2) lengthening the interval between treatments (3) dose reduction. Specific dosing guidelines are recommended to prevent more serious PPE. They include the following: (1) withhold capecitabine until PPE is resolved to grade 0–1, then restart the dose at 100% (2) with the second episode, withhold capecitabine until PPH resolves to grade 1–2, then resume dose at 75% (3) with the third episode, withhold capecitabine until resolution to grade 1–2, then resume dose at 50% (4) with the fourth episode, discontinue permanently (Xeloda® prescribing information, 2006).

Prevention of PPE is the first step in effective management. Patients should avoid excessive pressure or skin friction, avoid extreme temperatures, and use mild soaps and detergents to prevent irritation. Patients should be instructed to recognize symptoms early and know when to call the provider. Clinical trials are ongoing to investigate better management of PPE. Topical dimethyl sulfoxide was reported to be effective in two patients. Oral and topical steroids have shown inconsistent results. Oral pyridoxine may delay the onset, and pyridoxine cream may relieve the symptoms of PPE (n = 7; Webster-Gandy et al, 2007).

Rash

Rash is a common side effect of EGFR receptor antagonists. The rash typically develops within 1 to 14 days of initiating therapy and has an average duration of 29 days. NCI CTCAE grades 1 and 2 are most common. Occasionally, patients may develop grade 3 (Lacouture et al, 2009). Lynch and colleagues (2007) propose an alternative three-tier grading system for the assessment and management of EGFR rash (Table 2). Lynch's system uses mild, moderate, and severe grading with management recommendations according to each grade. EGFR rash also progresses through three phases of changes, initially with sensory changes (phase I) that begin soon after starting therapy. Next, the rash progresses to the papulopustular phase (phase II) approximately 7 to 10 days after the initiation of therapy and finally to the crusting phase (phase III) about a month after treatment. Table 3 provides an overview of the phases of EGFR rash and associated care strategies (Luu et al, 2007; Lynch et al, 2007). Recommendations for rash management are based on clinical expertise, and evidence-based data are lacking. One recent randomized, placebo controlled trial examined the use of tetracycline in the prevention of EGFR rash (Jatoi et al, 2008). While tetracycline was not found to prevent the rash, the severity was lessened. Additional research is needed to determine optimal strategies in the management of rash.

Table 2 Assessment and Management of EGFR Rash

Grade	Assessment	Management
Mild	• Localized papulopustular reaction • Minimally symptomatic	• No treatment • Gels: hydrocortisone or clindamycin
Moderate	• Generalized papulopustular reaction • Mild pruritus, tenderness, minimal impact on ADLs • No superinfection	• Gels: hydrocortisone, clindamycin • Doxycycline 100 mg po bid or minocycline
Severe	• Generalized papulopustular reaction • Severe pruritus, tenderness or pain, marked impact on ADLs • Potential for superinfection	• Interrupt dose of EGFR inhibitor • Gels: hydrocortisone, clindamycin • Doxycycline 100 mg po bid or minocylcine • Methylprednisolone dosepak

(Lynch et al, 2007)
Lynch's system uses mild, moderate, and severe grading with management recommendations according to each grade.
EGFR = epidermal growth factor receptor; po = by mouth; bid = twice a day; ADL = activities of daily living.

Nausea and Vomiting

While lapatinib is considered a minimal emetic risk and capecitabine low risk according to the NCCN (2009b), 44% of patients reported nausea in the early lapatinib/capecitabine trial (Ryan et al, 2008). Nausea can impact adherence and significantly diminish quality of life. No routine prophylaxis exists; however, management options are plentiful. Patients can try a bland diet, metoclopramide, prochloperazine, a H2 blocker, or a proton pump inhibitor (NCCN, 2009b). More aggressive antiemetics such as 5-HT3 antagonists can be tried as needed.

Lapatinib has a boxed warning regarding hepatotoxicity, which occurs in < 1% of patients. Liver function tests (ie, transaminases, bilirubin, alkaline phosphatase) should be monitored prior to initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated (Tykerb® prescribing information, 2009). It should be permanently discontinued in patients who experience severe changes in liver function tests.

Conclusion

Lapatinib is a targeted therapy that has demonstrated significant antitumor effects in women with HER2-positive breast cancer. While it is associated with some toxicity, diligent assessment of symptoms, surveillance of anticipated adverse events, and symptom management can promote therapy adherence and optimal quality of life. ●

TABLE 3 Phases of EGFR Rash and Associated Symptoms and Management

Phase	Initiation	Symptoms	Management
I	Soon after therapy initiates	• Burning on the face, upper trunk • Edema and erythema	• Topical anesthetic or pramoxine • Avoid sun, UV light • Mild soaps • Pyrithione zinc 1% shampoo may prevent dry scalp
II	• Seven to 10 days after initiation of therapy • Peak in 2 to 3 weeks	• Papulopustular rash • Vasodilation and edema • Concentration of rash in scalp, face, upper body, tissue around the nails	• See Table 2 for pharmacologic management according to severity • Sun protection • If infection suspected, culture and consider antibiotic therapy
III	• About a month after treatment	• Papulopustular lesions begin to dry • Crusting appearance	• Consider keratolytics, such as lactic or salicylic acid, creams containing urea • Sun protection • Mild soaps • Moisturizers to keep skin supple

(Wilkes, & Barton-Burke, 2008; Lacouture, 2006; Lynch et al, 2007; Van Cutsem, 2006; Luu et al, 2007)

Recommendations for rash management are based on clinical expertise, and evidence-based data are lacking.

EGFR = epidermal growth factor receptor; UV = ultraviolet.

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Glossary

epistaxis: hemorrhage originating from the nose

oncogene: a gene whose presence or activation can cause a normal cell to become cancerous

phosphorylation: the process of adding a phosphate group to a molecule. This often activates the molecule and allows it to participate in the transmission of an intracellular signal.

signal transduction: process by which a cell converts one kind of signal into another

vascular endothelial growth factor (VEGF): a protein that is a major factor in promoting the growth of new blood vessels

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Pharmaceutical Glossary

Generic Name	Trade Name
5-fluorouracil, 5-FU	Adrucil® Carc®
acetaminophen	Tylenol®
albumin-bound paclitaxel	Abraxane®
alemtuzumab	Campath®
anastrozole	Arimidex®
atropine	Lomotil® Lonox®
bevacizumab	Avastin®
bortezomib	Velcade®
carboplatin	Paraplatin®
capecitabine	Xeloda®
cetuximab	Erbitux®
clindamycin gel/lotion	Cleocin T® ClindaMax®
cyclophosphamide	Cytoxan® Neosar®
dexamethasone	Decadron® Dexameth Dexone® Hexadrol®
dimethyl sulfoxide (mucosal)	Rimso®-50
diphenhydramine	Benadryl®
docetaxel	Taxotere®
doxorubicin	Adriamycin® Rubex®
erlotinib	Tarceva®
epirubicin	Ellence®
exemestane	Aromasin®
gefitinib	Iressa®
gemcitabine	Gemzar®
hydralazine	Apresoline®
hydrocortisone topical	Corticaine® Cortizone 10® Lanacort® 10
imatinib mesylate	Gleevec®
ixabepilone	Ixempra™ labelatol Trandate®
letrozole	Femara®
lisinopril	Prinivil®
lorazepam	Ativan®
loperamide hydrochloride	Imodium®
meperidine	Demerol®
methotrexate	Rheumatrex® Trexall™
metoclopramide	Reglan®
lapatinib	Tykerb®
paclitaxel	Taxol®
pertuzumab	Omnitarg
pimecrolimus	Elidel®
prochlorperazine	Compazine®
rituximab	Rituxan® Mabthera®
sorafenib	Nexavar®
sunitinib malate	Sutent®
tamoxifen citrate	Nolvadex® Soltamox
tetracycline	Achromycin® Sumycin®
trastuzumab	Herceptin®
vinorelbine	Navelbine®
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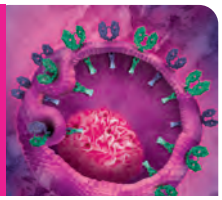

Posttest for Molecularly Targeted Therapies for Breast Cancer: Expert Discussions of Nursing Practice Patterns

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1. Which of the following statements regarding trastuzumab use for the treatment of metastatic breast cancer (MBC) is true?
   a. The addition of trastuzumab to chemotherapy as first-line therapy for MBC does not improve overall survival compared to chemotherapy alone
   b. Trastuzumab in combination with chemotherapy produces a high incidence of cardiac dysfunction
   c. The addition of trastuzumab to adjuvant chemotherapy does not reduce the rate of recurrence
   d. None of the above are true

2. Lapatinib, a dual kinase inhibitor of epidermal growth factor receptor and human epidermal growth factor receptor 2, is approved for the treatment of MBC.
   a. True
   b. False

3. Which of the following measures should be taken if a patient receiving bevacizumab has grade 2 proteinuria (protein level of 2 g/24 hours by dipstick or urinalysis)?
   a. Continue bevacizumab
   b. Continue bevacizumab but the patient should undergo further assessment by 24-hour urine collection prior to next dose
   c. Hold bevacizumab
   d. Discontinue bevacizumab

4. There are no formal cardiac guidelines for patients receiving lapatinib and capecitabine for MBC. Nurses must look to clinical trials for guidance about cardiac toxicities associated with this regimen.
   a. True
   b. False

5. Which of the following statements regarding diarrhea caused by lapatinib/capecitabine therapy is not true?
   a. Diarrhea is the most common side effect
   b. Diarrhea is predominantly grade 3 or higher and is dose limiting
   c. Eighty-five percent of patients do not require dose adjustment or interruption with lapatinib
   d. Management of diarrhea includes fluid replacement and dietary modification

6. When trastuzumab is held due to cardiac dysfunction, it may be resumed if:
   a. The left ventricular ejection fraction (LVEF) returns to normal limits within 4 to 8 weeks
   b. The absolute decrease from LVEF baseline is > 15 percentage points within 2 weeks
   c. The absolute decrease from LVEF baseline is < 15 percentage points within 3 weeks
   d. None of the above

7. Which intervention is recommended for resolving a grade 2/moderate rash caused by lapatinib therapy?
   a. Interrupt lapatinib until rash resolves
   b. Continue therapy and apply antiacne medication to affected areas
   c. Continue therapy and apply topical gels such as hydrocortisone, clindamycin, or pimecrolimus decrease from LVEF baseline is < 15 percentage points
   d. None of the above

Evaluation Form – Molecularly Targeted Therapies for Breast Cancer: Expert Discussions of Nursing Practice Patterns

IMER respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgement of participation for this activity.

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor

Extent to Which Program Activities Met the Identified Purpose

- To educate nurses on the latest treatment and nursing management strategies for patients with breast cancer. 5 4 3 2 1

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be able to:

- Outline the mechanism of action of molecularly targeted agents being used in the treatment of adjuvant and metastatic breast cancer 5 4 3 2 1
- Interpret the latest research on molecularly targeted agents likely to influence breast cancer treatment in 2009 5 4 3 2 1
- Employ safe drug administration techniques for patients with breast cancer receiving molecularly targeted agents 5 4 3 2 1
- Utilize the latest nursing management strategies to minimize or alleviate side effects associated with targeted agents 5 4 3 2 1
- Counsel appropriately selected patients about ongoing clinical trials 5 4 3 2 1

Overall Effectiveness of the Activity

- Was timely and will influence how I practice 5 4 3 2 1
- Will assist me in improving patient care 5 4 3 2 1
- Fulfilled my educational needs 5 4 3 2 1
- Avoided commercial bias or influence 5 4 3 2 1

Approximately what percentage of the program content was new to you?

☐ 0–20% ☐ 21–40% ☐ 41–60% ☐ 61–80% ☐ 81–100%

Impact of the Activity

Do you feel that the activity:

- Reinforced your current practice/treatment habits ☐ Yes ☐ No
- Will improve your practice/patient outcomes ☐ Yes ☐ No
- Enhanced your current knowledge base ☐ Yes ☐ No
- Will cause you to make changes in your practice? ☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity: _____

_____

How committed are you to making these changes?
(very committed) 5 4 3 2 1 (not committed)

Additional comments about this activity: _____

_____

Future Activities

Do you feel future activities on this subject matter are necessary and/or important to your practice? ☐ Yes ☐ No

Please list any other topics that would be of interest to you for future educational activities: _____

_____

Was there anything not covered that would have better helped meet the learning objectives? _____

_____

What prompted you to participate in this educational activity? _____

_____

What are your perceived barriers to implementing the information presented in this activity? _____

_____

Is there a gap between the information provided in this activity and your practice habits? _____

☐ Yes ☐ No

If yes, please describe: _____

_____

Would you recommend this activity to a colleague? ☐ Yes ☐ No

If you wish to receive acknowledgement of participation for this activity, please fill out your contact information.
Mail or fax this test and evaluation form to receive your certification of completion.

Institute for Medical Education & Research
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Signature _____ Date _____

This newsletter can be viewed on our Web site, www.IMERonline.com. On the homepage, click on the CE/CME tab, select On-Demand Education, and select **Molecularly Targeted Therapies for Breast Cancer: Expert Discussions of Nursing Practice Patterns**

Posttest Answer Key (448)

1	2	3	4	5	6	7

☐ **Please send me FREE IMER CE programs and invitations to IMER's FREE CE symposia.**

I'm also interested in these other types of cancers:

☐ **lung** ☐ **breast** ☐ **lymphoma** ☐ **leukemia**
☐ **colorectal** ☐ **prostate** ☐ **ovarian** ☐ **head & neck**
☐ **other**
(please describe) _____

While we strive not to send duplicates, we hope that you will share yours with a friend if you receive more than one copy.

The following items do not need to be completed to receive acknowledgement of participation for this activity.

Follow-up

Years in practice:
- ☐ < 2 years
- ☐ 2–5 years
- ☐ 6–10 years
- ☐ >10 years

Educational background (highest degree):
- ☐ Associate/Diploma
- ☐ BSN
- ☐ MSN
- ☐ PhD
- ☐ Other _____

Primary functional area:
- ☐ Patient care
- ☐ Education
- ☐ Administration
- ☐ Research
- ☐ Other _____

Primary specialty:
- ☐ Chemotherapy/biotherapy
- ☐ GI oncology
- ☐ Pediatric oncology
- ☐ Thoracic oncology
- ☐ Prevention/detection
- ☐ Other _____
- ☐ Breast oncology
- ☐ Hematology/BMT
- ☐ Radiation oncology
- ☐ Patient education
- ☐ Palliative care

Primary position:
- ☐ Academic educator
- ☐ Clinical trials nurse
- ☐ Clinical nurse specialist
- ☐ Director/asst. director/VP
- ☐ Nurse manager/coordinator
- ☐ Nurse practitioner

Do you prefer educational CE seminars or mail CE programs?
- ☐ Seminars
- ☐ Mail

I most prefer CE programs that are:
- ☐ On a Web site that I can visit
- ☐ Audio CDs
- ☐ Print materials
- ☐ Teleconferences
- ☐ CD-ROMs (audio plus slideshow)

I least prefer CE programs that are:
- ☐ On a Web site that I can visit
- ☐ Audio CDs
- ☐ Print materials
- ☐ Teleconferences
- ☐ CD-ROMs (audio plus slideshow)

As part of our ongoing quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:
- ☐ Yes, I would be interested in participating in a follow-up survey
- ☐ No, I'm not interested in participating in a follow-up survey

Privacy Policy

When you participate in an educational activity provided by the Institute for Medical Education & Research ("IMER" or "we"), we ask you for your name, degree, affiliation, street address, telephone number, fax number, and e-mail address (the "Information"). We use that Information in the following ways:
We use the Information to grade your posttest and to send you a certificate of completion of the educational activity. If we use a third-party company to grade your posttest and issue certificates of completion, we will give the Information to that company for that purpose only.
For each educational activity that you take, you must complete an evaluation questionnaire. That questionnaire asks if you are willing to participate in a follow-up survey. If you answer yes, we will use your name and contact information to send you the survey.
We may use the Information to invite you to participate in other educational activities that IMER or its affiliates may offer.
On occasion, the commercial supporter of an educational activity will ask us for a list of the people who participated in that activity, so that it may document the first level of outcomes-based evaluation in the educational activity (i.e., who attended, which medical specialties/practices were represented, how this compares to the target audience, and whether the activity needs to be repeated because significant numbers of the target audience did not attend). In that event, we will provide the supporter with your name, title and affiliation, but we will request in writing that the supporter not contact you directly for any purpose.
If our company is acquired or merged into another company, we may make the Information available to the new owner/entity to use in the ways described above, to enable it to continue our business.
Any changes to our privacy policy will be posted here immediately.