The Pharmacist’s Role in Breast Cancer Awareness and Treatment

James A. Trovato, Pharm.D., BCOP
Associate Professor
University of Maryland School of Pharmacy

This program has been supported by an educational grant from Genentech & Pfizer Pharmaceuticals

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
The Pharmacist’s Role in Breast Cancer Awareness and Treatment

Speaker: James A. Trovato, PharmD, BCOP, is Associate Professor in the Department of Pharmacy Practice and Science, and Oncology Residency Director at the University of Maryland School of Pharmacy. He received his B.S. in pharmacy from Massachusetts College of Pharmacy; Pharm.D. from Purdue University, and completed an ASHP Accredited Oncology Pharmacy Residency at The University of Texas, Health Sciences Center at San Antonio. He has an active clinical practice in medical oncology at the University of Maryland Marlene and Stewart Greenebaum Cancer Center.

Speaker Disclosure: Dr. Trovato has no actual or potential conflicts of interest in relation to this program.

This program has been supported by an educational grant from Genentech & Pfizer Pharmaceuticals

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education

Legal Disclaimer: The material presented here does not necessarily reflect the views of Pharmaceutical Education Consultants (PharmCon) or the companies that support educational programming. A qualified healthcare professional should always be consulted before using any therapeutic product discussed. Participants should verify all information and data before treating patients or employing any therapies described in this educational activity.
The Pharmacist’s Role in Breast Cancer Awareness and Treatment

**Accreditation:**  
Pharmacists 798-000-08-048-L01-P  
Pharmacy Technicians 798-000-08-048-L01-T

**Target Audience:** Pharmacists & Technicians

**CE Credits:**  
1.0 Continuing Education or 0.1 CEU for pharmacists/technicians

**Expiration Date:** 05/1/2011

**Program Overview:** This program will assist pharmacists to better understand breast cancer, enhance their knowledge of currently available treatment options and the adherence challenges with treatment. The program includes information on pharmacologic treatments, patient counseling and a question/answer period.

**Objectives:**
1. Describe the risk factors for breast cancer.
2. Identify the current screening guidelines of the American Cancer Society.
3. Outline the pharmacological treatments for metastatic breast cancer with respect to their mechanisms of action, efficacy, safety, and toxicologic effects.
4. Describe the role pharmacists can play in breast cancer awareness, pharmacological treatment, and adherence to medication.

This program has been supported by an educational grant from Genentech & Pfizer Pharmaceuticals
Educational Objectives

• Describe the risk factors for breast cancer.
• Identify the current screening guidelines of the American Cancer Society.
• Outline the pharmacological treatments for metastatic breast cancer with respect to their mechanisms of action, efficacy, and toxicities.
• Describe the role pharmacists can play in breast cancer awareness, pharmacological treatment, and adherence to medication.
Breast Cancer Statistics - 2008

- 1 in 8 women will develop breast cancer during her lifetime.

- Estimated 182,460 new cases in women will be diagnosed in U.S.

- Estimated 40,480 women in U.S. will die of breast cancer.

Source: American Cancer Society, Cancer Facts & Figures 2008
Breast Cancer Risk Factors

- Female Gender
- Age (> 60 years)
- Family history – first and second degree relatives
- Benign breast disease – atypical hyperplasia
- Early age of menarche (< 14 years old)
- Late age of menopause (> 55 years old)
- Age at birth of first child (> 30 years old)
- Mutations in genes BRCA, TP53, PTEN
- Exogenous estrogen exposure
- Obesity and low physical activity
## ACS Breast Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>20 years</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>20 to 39</td>
<td>every 3 years</td>
</tr>
<tr>
<td></td>
<td>40 +</td>
<td>Annual</td>
</tr>
<tr>
<td>Mammography</td>
<td>40 +</td>
<td>Annual</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines for Breast Screening with MRI

Recommend Annual MRI Screening as Adjunct to Mammography for the following:

- BRCA mutation
- First-degree relative of BRCA carrier
- Lifetime risk of about 20-25% or greater
- Radiation to chest between age 10 and 30 years
- Carry or have a first-degree relative who carries a genetic mutation in the TP53 or PTEN genes

Role of the Pharmacist in Breast Cancer Awareness

• Educate patient about risks associate with a increased risk of breast cancer.
• Advise patients to speak with physician about available screening methods.
• Discuss the importance of self awareness and reporting breast changes to physician.
• Discuss risks and benefits of tamoxifen or raloxifene for breast cancer risk reduction.
Metastatic Breast Cancer

• 6% of newly diagnosed cases

• Develops in 30% of those diagnosed initially with early stage disease

• Median survival of 24-30 months

• Response to treatment varies:
  – ≥ 30% in previously untreated patients
  – Significantly less response rates in previously treated patients

Treatment Guidelines for Metastatic Breast Cancer

ER/PR (+)
Bone/Soft Tissue
Asymptomatic visceral

Endocrine Therapy

ER/PR (-)
Symptomatic visceral

HER2 (+)
Trastuzumab ± Chemotherapy

HER2 (-)
Chemotherapy

NCCN Guidelines, v1.2008
## Endocrine Therapy for Metastatic Breast Cancer

### Aromatase inhibitors

**Oral non-steroidal**
- Anastrozole (Arimidex®)
- Letrozole (Femara®)

**Oral steroidal**
- Exemestane (Aromasin®)

### Antiestrogens

**Selective estrogen receptor modulators**
- Tamoxifen (Nolvadex®)
- Toremifene (Fareston®)

**Selective estrogen receptor down regulators**
- Fulvestrant (Faslodex®)
## Endocrine Therapy Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>hot flashes, mild nausea, fatigue, endometrial hyperplasia, thromboembolic events and endometrial cancer (long term use).</td>
</tr>
<tr>
<td>Toremifene</td>
<td>Similar to tamoxifen</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Nausea, vomiting, constipation, diarrhea, abdominal pain, headache, back pain, hot flashes, and pharyngitis</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Asthenia, myalgias/arthralgias, headaches, diarrhea, hot flashes, mild nausea, vaginal dryness, possible bone loss</td>
</tr>
<tr>
<td>Letrozole</td>
<td>hot flashes, mild nausea, headache, fatigue, arthralgias, possible bone loss</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Fatigue, hot flashes, nausea, dyspnea, anxiety, insomnia, pain at tumor site</td>
</tr>
</tbody>
</table>
# Chemotherapy for Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Single Agent Therapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Cyclophosphamide/Doxorubicin/5-FU (CAF)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>5-FU/Epirubicin/cyclophosphamide (FEC)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Doxorubicin/cyclophosphamide (AC)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Epirubicin/cyclophosphamide (EC)</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>Doxorubicin/Paclitaxel (AT)</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Cyclophosphamide/Methotrexate/5-FU (CMF)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Docetaxel/capecitabine</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Gemcitabine/paclitaxel (GT)</td>
</tr>
</tbody>
</table>

NCCN Guidelines, v1.2008
Pharmacist’s Role
Myelosuppression

• Neutropenia
• Risk of febrile neutropenia
  – doxorubicin-docetaxel
  – dose dense AC followed by paclitaxel
  – doxorubicin +paclitaxel (AT)
  – Docetaxel, Doxorubicin, cyclophosphamide(TAC)
  – Use of hematopoietic growth factors
• Anemia
  – Educate patient on symptoms
  – Use of erythropoietic stimulating agents
  – Iron therapy
Pharmacist’s Role
Nausea and Vomiting

- Identify highly emetogenic chemotherapy regimens
  - Doxorubicin or epirubicin plus cyclophosphamide
- Prophylactic use of antiemetic agents
  - Selective 5-HT₃ antagonists
  - Dexamethasone
  - Aprepitant
- Identify patient specific risk factors
  - Female
  - Younger age
  - Minimal history of alcohol exposure
Pharmacist’s Role
Peripheral Neuropathy

• Chemotherapy agents associated with high risk
  – Vinca alkaloids
  – Taxanes
  – Platinum agents
  – Epothilones

• Medications to manage neuropathy
  – Tricyclic antidepressants
  – Anticonvulsants
  – Gabapentin
  – Pregabalin
Capecitabine (Xeloda®)

- An oral fluoropyrimidine carbamate prodrug which is metabolized to 5-Fluorouracil.
- Treatment of metastatic breast cancer resistant to paclitaxel and an anthracycline.
- In combination with docetaxel for patients with metastatic breast cancer after anthracycline failure.
Capecitabine Phase III Clinical Trial

- 511 women with advanced or metastatic disease
- Randomized to docetaxel plus capecitabine or docetaxel alone
- Objective tumor response: 42% vs. 30%
- Median survival: 14.5 months vs. 11.5 months
- Median time to progression: 6.1 months vs. 4.2 months

Capecitabine: Dosing and Administration

- Approved dosing: 2,500 mg/m²/day orally in 2 divided doses for 14 days followed by 7 days of rest in 21 day cycle
- A 25% reduction of the starting dose (to 950 mg/m² twice daily) is required for patients with a calculated creatinine clearance of 30 to 50 mL/min.
- Contraindicated in patients with creatinine clearance <30 mL/min.
Capecitabine: Drug–Drug Interactions

- Warfarin: Altered coagulation parameters and/or bleeding
- Phenytoin: Elevated phenytoin levels. The dose of phenytoin may need to be decreased.
- Leucovorin: The concentration of 5-Fluorouracil is increased and its toxicity may be enhanced.
- Antacids: Small increase in plasma concentrations of capecitabine.
Capecitabine Side Effects

- Diarrhea
- Nausea and vomiting
- Stomatitis
- Rash, Dry, Itchy Skin
- Myelosuppression
- Hand-foot syndrome
## Hand-Foot Syndrome Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Domain</th>
<th>Functional Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Numbness, tingling, paresthesia, painless swelling, or erythema</td>
<td>Discomfort that does not disrupt normal activities</td>
</tr>
<tr>
<td>II</td>
<td>Painful erythema with swelling</td>
<td>Discomfort that affects activities of daily living</td>
</tr>
<tr>
<td>III</td>
<td>Moist desquamation, ulceration, blistering, or severe pain</td>
<td>Severe discomfort, unable to work/perform ADL</td>
</tr>
</tbody>
</table>
TRASTUZUMAB (Herceptin®)

• FDA Approved September 1998

• Humanized monoclonal antibody against the extracellular domain of HER-2 positive breast cancer
HER2/neu Proto-oncogene

• C-erb B2 is a proto-oncogene that encodes for the HER-2 receptor protein
• See up-regulation of HER2 protein
• Over-expression seen in 20-25% of cases
Trastuzumab and HER2

Trastuzumab (anti-HER2 antibody)

Extracellular effects of trastuzumab
- Inhibition of cleavage of HER2 extracellular domain
- Interference with homodimer and heterodimer formation between HER family receptors
- Antibody-dependent immune mechanisms

Intracellular effects of trastuzumab
- Induction of apoptosis
- Decreased cell proliferation
- HER2 downregulation, dephosphorylation, or both
- Decreased VEGF production
- Reactivation of chemotherapy
- Modulation of downstream signal paths
- Altered cross-talk with other signal paths

Interactions between Trastuzumab and Tumor Cells:
HER2 serves as a coreceptor with related members of the HER family of tyrosine kinase-associated growth factors. Acquired amplification of the HER2/new gene on chromosome 17 in HER2-positive breast cancer leads to marked overexpression of HER2 on the cell surface, which alters normal signaling function. Trastuzumab is a humanized monoclonal antibody that binds to HER2 and inhibits tumor-cell growth through a variety of intracellular, and possibly extracellular, mechanisms.

Burstein HJ. NEJM. 2005;353;16;1653.
Trastuzumab for First-line Treatment in HER2 (+) Metastatic Disease

- Phase III, Randomized Multicenter Study
- 466 women with metastatic disease
- Doxorubicin plus cyclophosphamide (AC) plus trastuzumab versus AC alone
- Paclitaxel plus trastuzumab versus paclitaxel alone
- Overall response rate 50% vs. 32%
- Overall survival 25.1 months vs. 20.3 months
- Time to disease progression 7.4 months vs. 4.6 months

Trastuzumab - FDA Approved Indication and Dosing

- Single agent for patients having received one or more chemotherapy regimens
- Combination therapy with paclitaxel for first line treatment
- 4 mg/kg IV over 90 min on day 1 followed by 2 mg/kg IV over 30 min weekly
- Alternative dosing
  - 8 mg/kg IV over 90 min followed by 6 mg/kg IV over 90 min every 3 weeks

Trastuzumab Adverse Effects

- Infusion related - fever and/or chills
- Cardiotoxicity - development of ventricular dysfunction and congestive heart failure.
- Pain (especially at tumor sites)
- Nausea and Vomiting
- Skin rash
- Headache, Dyspnea, Hypotension
Lapatinib (Tykerb®)

- Orally active small molecule tyrosine kinase inhibitor of HER1 and HER2

- FDA Approval March 14, 2007

HER = Human Epidermal growth factor Receptor
Lapatinib: mode of action

**EGFR-TKI** = Epidermal Growth Factor Receptor – Tyrosine kinase Inhibitor
Phase III study of Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

- HER2(+) locally advanced or metastatic disease progressing after treatment with regimens that included an anthracycline, taxane, or trastuzumab

- Patients were randomized to capecitabine plus lapatinib versus capecitabine alone

*N Eng J Med* 2006;533;26:2733-2743.
### Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lapatinib plus Capecitabine (N=163)</th>
<th>Capecitabine (N=161)</th>
<th>Hazard Ratio (95% CI) (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP (months)</td>
<td>8.4</td>
<td>4.4</td>
<td>0.49 (0.34-0.71) (P&lt;0.001)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>8.4</td>
<td>4.1</td>
<td>0.47 (0.33-0.67) (P&lt;0.001)</td>
</tr>
<tr>
<td>Overall Response (%)</td>
<td>22</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Death (%)</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

Lapatinib (Tykerb®)

• Indicated in combination with capecitabine for HER2(+) metastatic breast cancer after treatment failure with anthracycline, taxane, and trastuzumab

• Dose: 1250 mg orally once daily

• Adverse events: diarrhea, rash, nausea, anorexia

• Metabolized in liver via CYP3A4
Management of Skin Toxicities Associated with EGFR Inhibitors

- Best described as a pustular/papular eruption with an acne like distribution.
- Systemic and topical retinoids not recommended.
- Rash tends to improve over time.
- If suspect infection; start systemic antibiotics.
- Treat dry skin with emollients.
- Make-up use okay; use water-based products.

Pharmacist’s Role
Adherence to Oral Chemotherapy

Influenced by several factors
– Patients do not understand reason for medication
– Patient beliefs about medications
– Receive conflicting information on medication use
– Patient is taking multiple medications
– Complex chemotherapy regimens
Ixabepilone (Ixempra®)

- Semi-synthetic analog of epothilone B
- Microtubule inhibitor
- Antitumor activity in several taxane-resistant cell lines
- Combination therapy with capecitabine after failure of an anthracycline and a taxane.
- Monotherapy after failure of an anthracycline, a taxane, and capecitabine.

Ixabepilone
Dose and Administration

- Dose is 40 mg/m² intravenously over 3 hours
- Bilirubin 1.5-3 x ULN - initial dose 20 mg/m²
- Bilirubin > 3 – do not give
- Do not give with capecitabine if AST or ALT >2.5 x ULN or bilirubin >1 x ULN
- Hypersensitivity reactions: Premedicate with an H₁ and H₂ antagonist
- Inhibitors of CYP3A4 may increase plasma concentrations
- Inducers of CYP3A4 may decrease plasma concentrations
Phase III Study of Ixabepilone Plus Capecitabine

• 752 patients with anthracycline pretreated or resistant and taxane resistant locally advanced or metastatic disease

• All patients received capecitabine and were randomized to additional treatment with ixabepilone 40 mg/m²

Phase III Results

Ixabepilone
Common Adverse Effects

- Myelosuppression (neutropenia)
- Peripheral sensory neuropathy
- Fatigue/asthenia
- Myalgia/arthralgia
- Alopecia
- Nausea, vomiting,
- Stomatitis/mucositis, diarrhea
- Musculoskeletal pain
Conclusions

• The role of new targeted therapies is increasing in patients with metastatic breast cancer.

• Pharmacists play a role in raising public awareness of breast cancer risk factors, screening methods, and available treatment options.

• Pharmacists play a role in the management of toxicities associated with the treatment of metastatic breast cancer.

• Pharmacists play a role in identifying barriers to patient adherence to oral chemotherapy.