2007 Oncology Pharmacy Preparatory Review Course

Chapter 2

Breast Cancers, Parts 1 & II

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Breast Cancer

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Learning Objectives

After attending this session the participant shall be able to:

1. Outline the most appropriate screening and prevention strategy for breast cancer.

2. Describe the most appropriate patient-specific therapy and monitoring for a stage of disease.

3. Apply the clinical data underlying therapeutic treatment recommendations.

4. Explain expected outcomes to a given therapeutic modality in terms of response and toxicity or other endpoints (e.g., survival, clinical benefit, etc.).

5. Devise and communicate appropriate plans for preventing, monitoring and treating adverse reactions associated with treatment of breast cancers.

Self-Assessment Questions

1. TC is a 66 y.o. postmenopausal female with new onset left breast erythema, with a heavy, thick feeling in the breast. This came up over the last few weeks and is getting worse despite the antibiotics her local gynecologist gave her 2 weeks ago. She comes to the clinic for further work up. A mammogram is performed, indicating skin edema without a discrete mass. An ultrasound is performed, indicating similar findings, with negative lymph nodes. A core needle biopsy of the breast is performed indicating an invasive ductal carcinoma, involving the skin with extensive lymphatic invasion and a high Ki-67 (60%). This tumor was also ER/PR negative and HER2 status is pending. She is otherwise healthy. What would be the most appropriate therapy for this patient at this time?

    a. Modified radical mastectomy with axillary lymph node dissection followed by FAC x 6 cycles followed by radiation therapy.
    b. Lumpectomy with axillary lymph node dissection followed by FAC x 6 cycles followed by radiation therapy.
    c. FAC x 4 cycles followed by modified radical mastectomy with axillary lymph node dissection followed by radiation therapy.
    d. Anastrozole x 4 months followed by modified radical mastectomy with axillary lymph node dissection followed by radiation therapy.

2. JP is a 67 y.o. postmenopausal white female who presents to the clinic with a newly diagnosed right breast cancer, T2 N0 M0. Core biopsies of the right breast mass indicate an invasive ductal carcinoma, nuclear grade 2 (moderately differentiated), ER = 50%, PR = 60%, HER2 IHC = 2+, HER2 FISH = negative; Ki-67 = 20%. All other staging studies were negative for metastases. Based upon this information, what would be the *most appropriate* therapy for this patient at this time?

    a. Lumpectomy with surgical axillary staging followed by adjuvant tamoxifen for 5 years.
    b. Modified radical mastectomy with surgical axillary staging followed by FAC x 6 cycles.
    c. Modified radical mastectomy with surgical axillary staging followed by FAC x 6 cycles followed by anastrozole for 5 years.
    d. Lumpectomy with surgical axillary staging followed by adjuvant radiation therapy and tamoxifen for 5 years.

3. KJ is a 66 y.o. postmenopausal woman with newly diagnosed bone metastases. She was originally diagnosed 3 years ago with stage IIB right breast cancer (T2N1M0, invasive ductal carcinoma, ER/PR positive, HER2 negative by IHC and Ki-67 7%), underwent a modified radical mastectomy followed by adjuvant chemotherapy with AC for 4 cycles followed by Paclitaxel x 4 cycles. After her chemotherapy she was started on adjuvant tamoxifen therapy and continues on that therapy now. She is having new bone pain in her lower back, which is relieved with over the counter medications. A bone scan was performed that indicated suspicious areas of uptake in her lumbar spine, which were confirmed with x-rays of those areas to represent metastatic breast cancer. The rest of her staging studies demonstrated no other sites of metastases. What would be the most appropriate therapeutic option for KJ at this time?

    a. Paclitaxel protein-bound particles 260 mg/m2 IV over 30 minutes Q 3 weeks.
    b. Anastrozole 1 mg PO daily.
    c. Docetaxel 100 mg/m2 IV over 1 hour Q 3 weeks.
    d. Toremifene 60 mg PO daily.

4. JE is a 44 y.o. premenopausal woman with newly diagnosed lung metastases. She was originally diagnosed approximately 18 months ago with a stage IIIB left breast cancer (T3, N1, M0, invasive ductal carcinoma, ER/PR negative, HER2 negative by FISH, Ki-67 30%), underwent preoperative chemotherapy with weekly Paclitaxel for 12 weeks followed by FAC x 4 cycles followed by a segmental mastectomy with axillary lymph node dissection. She has done well since surgery, but now presents with a history of 4-6 weeks of persistent dry cough that has been treated with 2 rounds of antibiotics prescribed by her local primary care physician with little improvement. A chest x-ray was performed about 1 week ago and demonstrated new nodules in both lungs indicative of metastases. She is also not able to walk very far without becoming short of breath and coughing. What would be the most appropriate therapy for JE at this time?

    a. Goserelin 3.6 mg SQ Q 28 days plus tamoxifen 20 mg PO daily.
    b. Liposomal doxorubicin 50 mg/m^2 IV plus Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 Q 28 days.
    c. Goserelin 3.6 mg SQ Q 28 days plus anastrozole 1 mg PO daily.
    d. Docetaxel 100 mg/m^2 IV over 1 hour plus Capecitabine 2500 mg/m^2/day PO divided BID x 14 days Q 21 days.

5. TJ is a 35 y.o. premenopausal woman presenting with newly diagnosed left breast cancer. She has noticed a mass in her left breast for some time, but has neglected to have it checked out. She now comes in with dimpling of the skin of the breast, erythema, and palpable lymph nodes in the axilla and supraclavicular areas on the left. She undergoes biopsy of this mass and staging and is found to have an invasive ductal carcinoma, ER/PR-negative, HER2 positive by FISH, Ki-67 60% with axillary and supraclavicular involvement and also bone metastases and questionable lung metastases. What would be the most appropriate therapy for TJ at this time?

    a. Docetaxel 75 mg/m^2 IV over 1 hour plus Carboplatin AUC=6 over 30 minutes plus Trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly.
    b. Paclitaxel 175 mg/m^2 IV over 3 hours Q 21 days plus Trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly.
    c. Bevacizumab 10 mg/kg IV over 90 minutes Q 2 weeks plus Trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly.
    d. Capecitabine 2500 mg/m^2/day PO divided BID x 14 days Q 21 days plus Trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly.

BREAST CANCER

Overview of Disease & Management

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Patient case #1: JP is a 67 y.o. postmenopausal white female who presents to the clinic with a newly diagnosed right breast cancer found by the patient, confirmed with mammogram, ultrasound and core biopsy. A few weeks ago she noticed a mass while taking a shower and presented to her gynecologist for further evaluation. On physical exam she was noted to have a 2.4 x 3 cm mass at the 9 o'clock position of the right breast with some "shotty nodes" in the right axillary area. A mammogram was performed a few days later and noted 2.5 cm, irregular, equal density mass with spiculated margins in the nine o'clock position. A subsequent ultrasound was also performed and showed an abnormal appearing mass which was documented by FNA to represent cancer, measuring 2 x 2.5 x 1.3 cm. A lymph node was also biopsied (FNA) and found to be negative for malignancy in the right axilla. Core biopsies of the right breast mass indicate an invasive ductal carcinoma, nuclear grade 2 (moderately differentiated), ER = 50%, PR = 60%, HER2 IHC = 2+, HER2 FISH = negative; Ki-67 = 20%. All other staging studies were negative for metastases. Based upon this information, list the treatment options for this woman.

I. EPIDEMIOLOGY (American Cancer Society. *Cancer Facts & Figures 2007*. Atlanta: American Cancer Society;2007.)

A. Most common malignancy in women in the U.S (26%). An estimated 180,510 cases will be diagnosed in 2007 (178,480 women, 2030 men).

B. Second most common cause of cancer related death in women (15%). Estimated 40,910 people in U.S. will die of breast cancer in 2007.

C. The estimated incidence and mortality is down from the previous year. The decreased incidence is thought to be due to reduction in the prevalence of HRT since the WHI results were released. The reduction in mortality is thought to be due to improved treatments both in the adjuvant and metastatic setting, as well as effects of early diagnosis through screening efforts.

5-year survival		5-year survival	
All stages	89%	Regional	83%
Local	98%	Distant	26%

D. Lifetime risk (birth to death) of developing breast cancer in American women is approximately 1 in 8 (12.67%).

II. ETIOLOGY AND RISK FACTORS

A. Etiology is unknown (DeVita 2005, Chapter 33)

1. Genetics

a. Familial breast cancer represents 5-10% of all breast cancer cases.

1) BRCA1 and BRCA2 (tumor suppressor genes)

a) Increased incidence of breast and ovarian cancers (BRCA1) and female and male breast cancers and ovarian cancers (BRCA2); mutations found in other cancers also including pancreatic, prostate, fallopian tube, laryngeal, and adult leukemias and lymphomas.
b) Relatively rare in general population (1:500); estimated carrier frequency is 1:40 for Ashkenazi Jewish women.
c) Mutation carriers have 45-87% (BRCA1) and 26-84% (BRCA2) risk of breast cancer by age 70; 16-63% (BRCA1) and 10-27% (BRCA2) lifetime risk of ovarian cancer.
d) Prognostic significance of carrier status is disputed (mixed results from clinical trials).
e) More than 700 (BRCA1) and 300 (BRCA2) mutations identified; variable penetrance.
f) Individuals likely to benefit most from genetic counseling and testing are listed in TABLE 1.

TABLE 1: Characteristics Associated with an Increased Likelihood of BRCA1 or BRCA2 Mutations

Personal Characteristics	Family History Characteristics
Breast cancer at an early age	Two or more family members < 50 y.o. with breast cancer
Ovarian cancer	Both breast and ovarian cancer in family members
Bilateral breast cancer	Male breast cancer
Both breast and ovarian cancer	One or more family members < 50 y.o. with breast cancer and Ashkenazi Jewish ancestry

Adapted from Wood WC, Muss HB, Solin LJ, and Olopade OI. Malignant Tumors of the Breast, Chapter 33 Section 2. In: DeVita VT, Hellman S, and Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 7th Edition. Lippincott Williams & Wilkins, Philadelphia, PA; 2005:1415-77.

2) p53

a) Tumor suppressor gene ("guardian of the genome")
b) Associated with Li-Fraumeni syndrome of multiple hereditary cancers; less than 1% of breast cancers are associated with this syndrome.
c) Approximately 30% of breast cancers have mutation, inactivation, loss or down-regulated expression of p53; may be acquired or inherited?

b. Progression genes

1) HER2/*neu* (Human Epidermal Growth Factor Receptor-2, c-erbB-2) proto-oncogene

a) Encodes for human epidermal growth factor receptor-2 (protein, p185).

b) Amplification/overexpression generally imparts a poorer prognosis; chemotherapy resistance (controversial); endocrine therapy resistance (controversial).

c) Amplified/overexpressed in approximately 25-30% of all breast cancers.

d) Controversial as an independent prognostic factor.

e) Used primarily to select patients who will benefit from trastuzumab therapy.

f) Testing for HER2

i. Immunohistochemistry (IHC)

(a) Measures protein expression on cell surface.
(b) Scale: 0 = no expression; 1+ = minor membranous staining < 10% of cells; 2+ = > 10% of cells weakly positive; 3+ = > 10% of cells strongly positive.
(c) Subjective interpretation; image analysis being investigated to make this process more objective.

ii. Fluorescence in-situ hybridization (FISH)

(a) Identifies the presence of gene amplification; based on number of copies of gene present in the cells.
(b) Positive or negative; more objective than IHC, but not available in every center.
(c) Maybe more predictive of benefit with trastuzumab therapy.

2) Others (c-myc, cyclin D1, cyclin E, etc.)

2. Tumorigenesis

a. Malignant progression involves early changes in proliferation by systemic hormones (estrogen and progesterone) and local growth factors (such as TGF-α).
b. Continuum from atypical hyperplasia $\Rightarrow$ ductal carcinoma in situ (DCIS) $\Rightarrow$ invasive ductal carcinoma (IDC).
c. Involves many steps, some of which may be bypassed in familial forms or inflammatory breast cancers.

B. Risk Factors (>60% of breast cancer patients have no identifiable risk factors beyond female gender & aging)

1. Age – incidence of breast cancer increases with age; lifetime risk for all American women is 1 in 8, but more than half that risk occurs after the age of 60 years.

2. Family history of breast cancer - first and second-degree relatives impart an increased risk; early-onset breast cancer in a family member is suggestive of a hereditary predisposition (see TABLE 1).

3. Endogenous estrogen exposure

a. Early age of menarche ($\leq$ 12 y.o.)
b. Late age of natural menopause ($\geq$ 55 y.o.) or early induced menopause (BSO) before 40 y.o.
c. Age at birth of first child: $\geq$ 30 y.o.

4. Benign breast disease - proliferative breast disease without atypia (RR=1.5-2.0), atypical hyperplasia (RR=4.0-5.0).

5. Radiation exposure - atomic bomb (RR=3.0), radiotherapy for lymphoma or other cancer, historically other uses of radiation were common (e.g., acne, tinea capitus, Buster Brown Shoe sizer, etc.).

6. Obesity and BMI

    a. Complex association between BMI and obesity and breast cancer incidence; differs by age and menopausal status.
    b. Most studies in premenopausal women – no consistent association.
    c. Most studies in postmenopausal women – indicate an increased incidence of breast cancer with increasing weight.
    d. May also be related to distribution of fat and/or body composition.

7. Physical Activity

    a. Lower risks associated with greater physical activity; observed in both pre and postmenopausal women.
    b. Not clear whether adolescent activity, adult activity or lifetime activity provides the most benefit.

8. Exogenous estrogen exposure

    a. **Risks of postmenopausal ERT and oral contraceptives (OC) are controversial - for OC's most clinicians feel that the benefits for most women far outweigh the risks of developing breast cancer. For ERT, changing views based on current evidence.**

    b. **OC -** Current use (RR=1.5) vs past use (RR=1.0) vs never use (RR=1.0); risk may be higher in women diagnosed with breast cancer at a younger age (< 40 y.o.).

    c. **WHI - Estrogens alone vs Estrogen+progesterone combinations**

        1) WHI study *Prempro*® arm discontinued early; HR=1.26 (1.0-1.59) with 290 cases. (Women's Health Initiative Investigators. *JAMA* 2002;288(3):321-33.)
        2) WHI study *Premarin*® alone arm stopped after nearly 7 years mean follow-up, due to increased incidence of stroke. Breast cancer incidence not increased at the time of stopping. (Anderson, GL, et al. *JAMA* 2004;291(14):1701-12.)

    d. Prospective studies (WHI) appear to indicate little benefit related to cardiac events and questionable benefits for the bones (in terms of fracture rates and mortality), as well.

9. Alcohol

    - Risk increases with consumption in general, regardless of the beverage type or woman's menopausal status; causal relationship has not been proven; moderation is a sensible approach.

10. Breast Density and Mammographic Patterns

    a. Risk associated with certain mammographic patterns and appears to be genetically determined.
    b. Women with a greater proportion of the breast that are radiodense are at a higher risk compared to women with more radiolucent breast tissue.
    c. Different ways to measure breast density; many different studies have confirmed this association.

11. Gail Model risk assessment tool (Gail MH et al. J Nat Cancer Inst 1989;81(24):1879-86.)

    a. Useful for white women with a limited family history to assist with decisions regarding cancer prevention.

b. Mathematical model to determine relative risk (RR) % of developing breast cancer compared to an age-matched control at 5 years and during your lifetime.

1) Age
2) Number first-degree relatives
3) Nulliparity or age at first birth
4) Number breast biopsies
5) Atypical hyperplasia

c. Many assumptions; not validated with other races.

12. Breast cancer risk assessment tool used in prevention studies (http://bcra.nci.nih.gov/brc/)

a. Incorporates components of the Gail Model with data from the Breast Cancer Detection and Demonstration Project (a mammography screening project conducted in the 1970's).
b. Available on the web, this is the tool used in the NSABP prevention studies, P1 and STAR.
c. Many other tools also available.

III. ANATOMY & PATHOPHYSIOLOGY

A. The breast is comprised of ducts, lobules, fatty tissue, other connective tissues, and intramammary lymph nodes.

B. Regional lymph nodes include axillary and internal mammary lymph node chains. Level III axillary lymph nodes also referred to as infraclavicular. Supraclavicular also considered regional lymph nodes in new staging system.

C. Pathologic types of breast cancer

1. Ductal carcinoma in situ (DCIS) - premalignant lesion; hallmark clustered microcalcifications on mammogram; usually curable with resection alone; role of radiation and tamoxifen being studied (see management section for details).
2. Lobular carcinoma in situ (LCIS) - not a premalignant lesion; risk factor for breast cancer; both breasts are at equal risk; included in prevention studies with tamoxifen and raloxifene (see management section for details).
3. Invasive lobular carcinoma (ILC) - second most common type of breast cancer (15%); more likely to metastasize to serosal surfaces.
4. Invasive ductal carcinoma (IDC) - most common type of breast cancer (70%); worst prognosis of all types of breast cancer.
5. Others: tubular, mucinous, papillary, medullary generally have better prognosis compared to IDC (favorable histologies).
6. Also sarcomas, carcinosarcomas, sarcomatous carcinomas, squamous cell and others - rare variants with generally poor prognosis.

IV. SCREENING & PREVENTION

A. Screening

1. Breast self-examination (BSE)

a. Not generally recommended; little data supporting reduction in mortality when used alone. Shanghai study indicated that in the absence of mammography, BSE does not impact breast cancer mortality. (Thomas DB, et al. *J Natl Cancer Inst* 2002;94(19):1445-57.) May lead to high rates of unnecessary biopsies.

b. Many organizations endorse some type of screening guidelines with or with out BSE. ACS does still mention that women 20 years and older should be presented the risks and benefits of screening BSE.
c. Difficult to separate impact of different screening tools; all three should be viewed as complimentary modalities.
d. Monthly; week after menses.
e. Education is required to ensure careful examination and prompt reporting to a health care professional any abnormalities noted.

2. Clinical breast examination (CBE)

a. Not uniformly recommended. May be most beneficial with mammograms.
b. Difficult to separate impact of different screening tools; all three should be viewed as complimentary modalities.
c. ACS still recommends, at least every 3 years for women aged 20-39 and annually for women ≥ 40 years.
d. Training of qualified personnel is necessary to ensure quality of examination.

3. Mammography

a. AHCPR guidelines dictate the technical procedures for high-quality mammograms; ACR (American College of Radiology) MAP (Mammography Accreditation Program) established voluntary quality standards; ACR categories (I - V) are used to standardize the reading or analysis of the mammograms under these standards.

b. Definite evidence that annual screening mammography reduces the mortality from breast cancer in women over the age of 50 years.

c. Women ages 40-49 years:

1) Controversial; many randomized, controlled clinical trials assessing this question.

2) Studies had differing eligibility criteria; some allowed women with a known breast mass to be included in the screening population; other major problems with control groups.

3) Still under debate, but all major US recommendations include younger women.

4) Recommendations

TABLE 2: Screening Recommendations for Breast Cancer

	American Cancer Society[1]
BSE	Age ≥ 20 – risk/benefit discussion; prompt reporting of any changes
CBE	Age 20-39 – every 3 years; part of a periodic health examination
	Asymptomatic and age ≥ 40 – every year; part of a periodic health examination
Mammogram	Age ≥ 40 – every year

Abbreviations: BSE = breast self-exam; CBE = clinical breast exam.
[1] Smith RA, et al. American Cancer Society Guidelines for Early Detection of Cancer, 2006. *CA Cancer J Clin* 2006;56(1):11-25.

B. Prevention

1. Prophylactic mastectomies - not 100% preventive; but will decrease the risk.

2. Bilateral oophorectomies - decrease estrogen exposure; not 100%; but will decrease the risk.