Chapter 60: Breast Cancer

INTRODUCTION

- *Breast cancer* is a malignancy originating from breast tissue. Disease confined to a localized breast lesion is referred to as *early, primary, localized*, or *curable*. Disease detected clinically or radiologically in sites distant from the breast is referred to as *advanced* or *metastatic breast cancer* (MBC), which is usually incurable.

EPIDEMIOLOGY

- Two variables most strongly associated with occurrence of breast cancer are gender and age. Additional risk factors include endocrine factors (eg, early menarche, nulliparity, late age at first birth, and hormone replacement therapy), genetic factors (eg, personal and family history, mutations of tumor suppresser genes [*BRCA1* and *BRCA2*]), and environmental and lifestyle factors (eg, radiation exposure, weight, height, and alcohol use).
- Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastatic disease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain.

PREVENTION OF BREAST CANCER

- Selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) are being studied for pharmacologic risk reduction of breast cancer.
- The most clinical information is available for the SERMs, **tamoxifen** and **raloxifene**, which reduce the rates of invasive breast cancer in women at high risk for developing the disease. Tamoxifen increased incidence of endometrial cancer and both agents increased thromboembolic events.
- **Exemestane** and **anastrozole** taken for 5 years significantly reduced the rates of invasive breast cancers in postmenopausal women with tolerable adverse events.
- Risk reduction strategies include mastectomy, oophorectomy, and pharmacologic agents. Clinical guidelines recommend the use of tamoxifen, raloxifene, anastrozole, or exemestane for postmenopausal women at high risk.

CLINICAL PRESENTATION

- A painless, palpable lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. Nipple changes are less commonly seen. More advanced cases present with prominent skin edema, redness, warmth, and induration.
- Symptoms of MBC depend on the site of metastases but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, and mental status changes.
- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.

DIAGNOSIS

- Initial workup should include a careful history, physical examination of the breast, three-dimensional mammography, and, possibly, other breast

imaging techniques, such as ultrasound and magnetic resonance imaging (MRI).

- Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

Staging

- Stage (anatomical extent of disease) is based on primary tumor extent and size ($T_{1–4}$), presence and extent of lymph node involvement ($N_{1–3}$), and presence or absence of distant metastases ($M_{0–1}$). The staging system determines prognosis and assists with treatment decisions. Simplistically stated, these stages may be represented as follows:

  ✔ *Early breast cancer*

  - Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane
  - Stage I: Small primary invasive tumor without lymph node involvement
  - Stage II: Involvement of regional lymph nodes

  ✔ *Locally advanced breast cancer*

  - Stage III: Usually a large tumor with extensive nodal involvement in which the node or tumor is fixed to the chest wall

  ✔ *Advanced or metastatic breast cancer*

  - Stage IV: Metastases in organs distant from the primary tumor

- Staging for breast cancer is separated into clinical and pathologic staging. Clinical stage is assigned before surgery and is based on physical examination (assessment of tumor size and presence of axillary lymph nodes), imaging (eg, mammography, ultrasonography), and pathologic examination of tissues (eg, biopsy results). Pathologic staging occurs after surgery and adds data from surgical exploration and resection.

Pathologic Evaluation

- Development of malignancy is a multistep process involving preinvasive (or noninvasive) and invasive phases. The goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease.
- Pathologic evaluation of breast lesions establishes the histologic diagnosis and confirms the presence or absence of prognostic factors.
- Most breast carcinomas are adenocarcinomas and are classified as ductal or lobular.

Prognostic Factors

- The ability to predict prognosis is used to design personalized treatment recommendations.
- Age at diagnosis and ethnicity can affect prognosis.
- Tumor size and presence and number of involved axillary lymph nodes are independent factors that influence the risk for breast cancer recurrence and subsequent metastatic disease. Other disease characteristics that provide prognostic information are histologic subtype, nuclear or histologic grade, lymphatic and vascular invasion, and proliferation indices.
- Hormone receptors (estrogen [ER] and progesterone [PR]) are not strong prognostic markers but are used clinically to predict response to endocrine therapy.
- *HER2* overexpression occurs in about 20%–30% of breast cancers and is associated with increased tumor aggressiveness, increased rates of recurrence, and increased rates of mortality.
- Genetic profiling tools provide additional prognostic information to aid in treatment decisions for subgroups of patients with otherwise favorable

prognostic features.

TREATMENT

- Goals of Treatment: Adjuvant therapy for early and locally advanced breast cancer is administered with curative intent. Neoadjuvant therapy is given to eradicate micrometastatic disease, determine prognosis, and potentially conserve breast tissue for a better cosmetic result. Palliation is the desired therapeutic outcome in the treatment of MBC.
- Treatment is rapidly evolving. Specific information regarding the most promising interventions can be found only in the primary literature.
- Treatment can cause substantial toxicity, which differs depending on the individual agent, administration method, and combination regimen. A comprehensive review of toxicities is beyond the scope of this chapter; consult appropriate references.

Early Breast Cancer (Stage I and II)

Local-Regional Therapy

- Surgery alone can cure most patients with in situ cancers, 70%–80% of stage I cancers, and approximately one-half of those with stage II cancers.
- Breast-conserving therapy (BCT) is an appropriate primary therapy for most women with stages I and II disease and is preferable because it provides survival rates equivalent to modified radical mastectomy. BCT includes removal of part of the breast, surgical evaluation of axillary lymph nodes, and radiation therapy (RT) to prevent local recurrence.
- RT is administered to the entire breast over 3–5 weeks to eradicate residual disease after BCT. Reddening and erythema of the breast tissue with subsequent shrinkage of total breast mass are minor complications associated with RT.
- Multiple sites of cancer within the breast and the inability to attain negative pathologic margins on the excised breast specimen are indications for mastectomy.
- Axillary lymph nodes should be sampled for staging and prognostic information. Lymphatic mapping with sentinel lymph node biopsy is a less invasive alternative to axillary dissection.

Systemic Adjuvant Therapy

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. The goal of such therapy is cure.
- Administration of chemotherapy, endocrine therapy, targeted therapy, or some combination of these agents results in improved disease-free survival (DFS) and/or overall survival (OS) for high-risk patients in specific prognostic subgroups.
- The National Comprehensive Cancer Network (NCCN) practice guidelines are updated at least annually and should be consulted for treatment recommendations.
- Several multigene expression assays are commercially available as decision-support tools for adjuvant chemotherapy.

Adjuvant Chemotherapy

- Early administration of effective combination chemotherapy at a time of low tumor burden should increase the likelihood of cure and minimize emergence of drug-resistant tumor cell clones. Combination regimens have historically been more effective than single-agent chemotherapy (**Table 60-1**).
- Anthracycline-containing regimens (eg, **doxorubicin** and **epirubicin**) reduce the rate of recurrence and death as compared with regimens that contain **cyclophosphamide**, **methotrexate**, and **fluorouracil**.

- The addition of taxanes, **docetaxel** and **paclitaxel**, to adjuvant regimens comprised of the drugs listed above resulted in reduced risk of distant recurrence, any recurrence, and breast cancer mortality compared with a nontaxane regimen in node-positive breast cancer patients. The use of taxane-containing regimens in node-negative patients remains controversial.
- Initiate chemotherapy within 12 weeks of surgical removal of the primary tumor. Optimal duration of adjuvant treatment is unknown but appears to be 12–24 weeks, depending on the regimen used.
- *Dose intensity* refers to the amount of drug administered per unit of time, which can be achieved by increasing dose, decreasing time between doses, or both. *Dose density* is one way of achieving dose intensity by decreasing time between treatment cycles.
- Dose-dense adjuvant regimens for node-positive breast cancer resulted in prolonged DFS and OS. No benefit in DFS or OS was shown for sequential versus concurrent chemotherapy, but sequential therapy appears to be less toxic.
- Concomitant or sequential administration of a taxane with an anthracycline-based regimen is standard of care in node-positive breast cancer.
- Dose increases in standard regimens appear to not be beneficial and may be harmful.
- Avoid dose reductions in standard regimens unless necessitated by severe toxicity.
- Short-term toxicities of adjuvant chemotherapy are generally well tolerated, especially with the availability of serotonin-antagonist and substance P/neurokinin 1–antagonist antiemetics and myeloid growth factors.
- Survival benefit for adjuvant chemotherapy in stage I and II breast cancer is modest. The absolute reduction in mortality at 10 years is 5% in node-negative and 10% in node-positive disease.

TABLE 60-1

Selected Neo/Adjuvant Chemotherapy Regimens for Breast Cancer

Dose-Dense AC → Paclitaxel[a]	**AC → Paclitaxel**
Doxorubicin 60 mg/m^2 IV bolus, day 1 Cyclophosphamide 600 mg/m^2 IV, day 1 Repeat cycles every 14 days for 4 cycles (must be given with growth factor support) Followed by paclitaxel 80 mg/m^2 IV weekly Repeat cycles every 7 days for 12 cycles **TC**[a] Docetaxel 75 mg/m^2 IV, day 1 Cyclophosphamide 600 mg/m^2 IV, day 1 Repeat cycles every 21 days for 4 cycles **Dose-Dense AC → Dose-Dense Paclitaxel**[a] Doxorubicin 60 mg/m^2 IV bolus, day 1 Cyclophosphamide 600 mg/m^2 IV, day 1 Repeat cycles every 14 days for 4 cycles (must be given with growth factor support) Followed by paclitaxel 175 mg/m^2 IV over 3 hours Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	Doxorubicin 60 mg/m^2 IV, day 1 Cyclophosphamide 600 mg/m^2 IV, day 1 Repeat cycles every 21 days for 4 cycles Followed by paclitaxel 80 mg/m^2 IV weekly Repeat cycles every 7 days for 12 cycles **TAC** Docetaxel 75 mg/m^2 IV, day 1 Doxorubicin 50 mg/m^2 IV bolus, day 1 Cyclophosphamide 500 mg/m^2 IV, day 1 (doxorubicin should be given first) Repeat cycles every 21 days for 6 cycles (must be given with growth factor support) **CMF** Cyclophosphamide 100 mg/m^2 per day orally, days 1–14 Methotrexate 40 mg/m^2 IV, days 1 and 8 5-fluorouracil 600 mg/m^2 IV, days 1 and 8 Repeat cycles every 28 days for 6 cycles

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); CMF, cyclophosphamide, methotrexate, 5-fluorouracil; TAC, Taxotere (docetaxel), Adriamycin (doxorubicin), cyclophosphamide; TC, Taxotere (docetaxel), cyclophosphamide.

Adjuvant Biologic or Targeted Therapy

- **Trastuzumab** in combination with or sequentially after adjuvant chemotherapy is indicated in patients with early stage, *HER2*-positive breast cancer. The risk of recurrence was reduced up to 50% in clinical trials.
- Unanswered questions with the use of adjuvant trastuzumab include optimal concurrent chemotherapy, optimal dose, schedule and duration of therapy, and use of other concurrent therapeutic modalities.

Adjuvant Endocrine Therapy

- Tamoxifen, **toremifene**, oophorectomy, ovarian irradiation, luteinizing hormone–releasing hormone (LHRH) agonists, and AIs are hormonal therapies used in the treatment of primary or early-stage breast cancer. Tamoxifen was the gold standard adjuvant hormonal therapy for three decades and is generally considered the adjuvant hormonal therapy of choice for premenopausal women. It has both estrogenic and antiestrogenic properties, depending on the tissue and gene in question.
- Tamoxifen 20 mg daily, beginning soon after completing chemotherapy and continuing for 5 years, reduces the risk of recurrence and mortality. It is usually well tolerated; however, symptoms of estrogen withdrawal (hot flashes and vaginal bleeding) may occur but decrease in frequency and intensity over time. Tamoxifen reduces the risk of hip radius and spine fractures. It increases the risks of stroke, pulmonary embolism, deep vein

thrombosis, and endometrial cancer, particularly in women age 50 years or older. Administration of tamoxifen for 10 years in patients with a higher risk of recurrence is supported by recent studies.

- Premenopausal women benefit from ovarian ablation with LHRH agonists (eg, **goserelin**) in the adjuvant setting, either with or without concurrent tamoxifen. Trials are ongoing to further define the role of LHRH agonists.
- Guidelines recommend incorporation of AIs into adjuvant hormonal therapy for postmenopausal, hormone-sensitive breast cancer. Experts believe that **anastrozole**, **letrozole**, and **exemestane** have similar antitumor efficacy and toxicity profiles. Adverse effects with AIs include bone loss/osteoporosis, hot flashes, myalgia/arthralgia, vaginal dryness/atrophy, mild headaches, and diarrhea.
- The optimal drug, dose, sequence, and duration of administration of AIs in the adjuvant setting are not known.

Locally Advanced Breast Cancer (Stage III)

- Neoadjuvant or primary chemotherapy is the initial treatment of choice. Benefits include rendering inoperable tumors resectable and increasing the rate of BCT.
- Primary chemotherapy with an anthracycline- and taxane-containing regimen is recommended. The use of trastuzumab and **pertuzumab** with chemotherapy is appropriate for patients with *HER2*-positive tumors.
- Surgery followed by chemotherapy and adjuvant RT should be administered to minimize local recurrence.
- Cure is the primary goal of therapy for most patients with stage III disease.

Metastatic Breast Cancer (Stage IV)

- Treatment of MBC with cytotoxic, endocrine, or targeted therapy often results in regression of disease, improvements in quality of life, and improved OS with the addition of some biologic or targeted therapies.
- The choice of therapy for MBC is based on the extent of disease involvement and the presence or absence of certain tumor or patient characteristics, as described below.
- The most important predictive factors are the presence of *HER2*, ER, and PR receptors in the primary or metastatic tumor tissue.
- Consider adding bone-modifying agents (eg, **pamidronate**, **zoledronic acid**, or **denosumab**) to treat breast cancer patients with metastases to the bone to decrease rates of skeletal-related events, such as fractures, spinal cord compression, and pain, and the need for radiation to the bones or surgery.

Biologic or Targeted Therapy

- Fifteen percent to 20% of patients with MBC overexpress *HER2*. Five anti-*HER2* agents are available in the United States: trastuzumab, **lapatinib**, **pertuzumab**, **ado-trastuzumab emtansine**, and **neratinib**.
- First-line therapy with a pertuzumab-trastuzumab-taxane combination is the preferred option for *HER2*-overexpressing MBC in patients who have not received pertuzumab in the neoadjuvant or adjuvant setting. Second-line *HER2*-targeted therapy for MBC depends on the specific agent given as first-line therapy. Subsequent therapy (third-line) for *HER2*-positive MBC is controversial.
- Consider combination endocrine plus *HER2*-directed therapy when chemotherapy is not tolerated or after achieving maximal response with chemotherapy-*HER2* therapy approach.
- All *HER2*-targeted therapies are cardiotoxic with the type of toxicity differing among agents. The incidence of heart failure is ~5% with single-agent trastuzumab and unacceptably high in combination with an anthracycline.
- *HER2*-targeted regimens for MBC are summarized in **Table 60-2**.

- Other targeted agents including mTOR inhibitors (eg, **everolimus**) and cyclin-dependent kinases (CDK) (eg, **abemaciclib**, **palbociclib**, and **ribociclib**) are used in combination with endocrine agents to improve outcomes. To date, CDK inhibitors have improved progression-free survival in combination with AIs (as first-line therapy), fulvestrant (as first- and second-line therapy), and tamoxifen (as first-line therapy) (see **Table 60-3**).

TABLE 60-2

Selected Regimens for *HER2*-Positive Metastatic Breast Cancer

Select Chemotherapy/Biologic Therapy Regimens	
Docetaxel + Trastuzumab + Pertuzumab Docetaxel 75 mg/m^2 IV day 1 Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV Pertuzumab 840 mg IV day 1 followed 21 days later by 420 mg IV Repeat cycle every 21 days **Paclitaxel + Trastuzumab + Pertuzumab** Paclitaxel 80 mg/m^2 IV days 1, 8, 15 Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV Pertuzumab 840 mg IV day 1 followed 21 days later by 420 mg IV Repeat cycle every 21 days	**Ado-Trastuzumab Emtansine (T-DM1)** Ado-Trastuzumab Emtansine 3.6 mg/kg IV day 1 Repeat cycle every 21 days **Trastuzumab + Chemotherapy** Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV day 1 Repeat cycle every 21 days (for every 21 day chemotherapy) **OR** Trastuzumab 4 mg/kg IV day 1 followed 7 days later by 2 mg/kg IV day 1 Repeat cycle weekly (for weekly chemotherapy) Chemotherapy may include any one of the following: Paclitaxel, docetaxel, protein-bound paclitaxel, capecitabine, vinorelbine, gemcitabine
Select Endocrine Therapy/Biologic Therapy Regimens	
Trastuzumab + Lapatinib (± Aromatase Inhibitor) Lapatinib 1000 mg orally daily continuously Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV Repeat cycle every 21 days (*aromatase inhibitor dosed per Table 60-3*)	**Trastuzumab (± Aromatase Inhibitor or Fulvestrant or Tamoxifen)** Trastuzumab 8 mg/kg IV day 1 followed 21 days later by 6 mg/kg IV day 1 Repeat cycle every 21 days (*aromatase inhibitor, fulvestrant, and tamoxifen dosed per Table 60-3*)
Lapatinib + Capecitabine Lapatinib 1250 mg orally daily continuously Capecitabine 1000 mg/m^2 twice daily × 14 days Repeat cycle every 21 days	**Lapatinib + Aromatase Inhibitor** Lapatinib 1500 mg orally daily continuously (*aromatase inhibitor dosed daily continuously per Table 60-3*)

Endocrine Therapy

- Consider endocrine therapy in combination with a targeted agent when feasible although this increases the risk of adverse events that require supportive management strategies. The choice of endocrine therapy is based on the menopausal status of the patient, prior therapies and previous response, duration of response, or disease-free interval.
- Endocrine therapy is the treatment of choice for patients who have hormone receptor-positive metastases in soft tissue, bone, pleura, or, if asymptomatic, viscera. Compared with chemotherapy, endocrine therapy has an equal probability of response and a better safety profile.
- Patients are sequentially treated with endocrine therapy until their tumors cease to respond, at which time chemotherapy can be given.

- No one endocrine therapy has clearly superior survival benefit. Choice of agent is based primarily on mechanism of action, toxicity, and patient preference (**Table 60-3**).
- AIs are generally first-line therapy in postmenopausal women. AIs reduce circulating and target organ estrogens by blocking peripheral conversion from an androgenic precursor, the primary source of estrogens in postmenopausal women. The third-generation AIs anastrozole, letrozole, and exemestane are more selective and have an improved toxicity profile. When compared with tamoxifen, patients receiving AIs had similar response rates as well as lower incidence of thromboembolic events and vaginal bleeding.
- Tamoxifen, an estrogen agonist/antagonist, is the preferred initial agent when metastases are present in premenopausal women except when metastases occur within 1 year of adjuvant tamoxifen. In addition to the side effects described for adjuvant therapy, tumor flare or hypercalcemia occurs in approximately 5% of patients with MBC.
- **Toremifene**, also an estrogen agonist/antagonist, has similar efficacy and tolerability as tamoxifen and is an alternative to tamoxifen in postmenopausal patients. **Fulvestrant** is a second-line intramuscular agent with similar efficacy and safety when compared with anastrozole or exemestane in patients who progressed on tamoxifen.
- Surgical or chemical ovarian ablation is considered by some experts to be the endocrine therapy of choice in premenopausal women and produces similar overall response rates as tamoxifen. Medical castration with an LHRH analogue (**goserelin**, **leuprolide**, or **triptorelin**) is a reversible alternative to surgery.
- Progestins are generally reserved for third-line therapy. They cause weight gain, fluid retention, and thromboembolic events.

TABLE 60-3

Therapies Used for Hormone Receptor–Positive Metastatic Breast Cancer

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Aromatase Inhibitors: Nonsteroidal					
Anastrozole	Arimidex, generic	1 mg orally daily			
Letrozole	Femara, generic	2.5 mg orally daily		Caution in severe liver impairment[a]	
Aromatas Inhibitor: Steroidal					
Exemestane	Aromasin, generic	25 mg orally daily			Take after meals
Estrogen Agonists/Antagonists					
Tamoxifen	Nolvadex, generic	20 mg orally daily		See text regarding *CYP2D6*	
Toremifene	Fareston	60 mg orally daily			
Antiestrogen: SERD					
Fulvestrant	Faslodex	500 mg IM every	250–500 mg	Moderate liver impairment[a] administer 250 mg IM	

		28 days (after loading days 1, 15, 29)	(see text for details)	every 28 days (after loading days 1, 15, 29)	
LHRH Agonists					
Goserelin	Zoladex	3.6 mg SC every 28 days		Premenopausal women only	
Leuprolide	Lupron (IM), generic	3.75 mg IM every 28 days	Other formulations and doses are not used for breast cancer	Premenopausal women only	Not FDA approved for breast cancer; other formulations are administered differently
Triptorelin	Trelstar	3.75 mg IM every 28 days		Premenopausal women only	Not FDA-approved for breast cancer
Progestins					
Megestrol acetate	Megace, generic	40 mg orally 4 times a day	80 mg twice daily also appropriate		Absorption may be increased when taken with food
Medroxyprogesterone	DepoProvera, generic	400 mg IM every week	400–1000 mg IM every week	May need to decrease dose in severe liver impairment[a]	
Androgens					
Fluoxymesterone	Androxy, generic	10 mg orally twice a day	10–20/day in divided doses	Avoid in severe renal or liver impairment[a]	
Estrogens					
Ethinyl estradiol	Multiple generics	1 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or “marked” liver disease	Take with food
Conjugated estrogens	Premarin	2.5 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or “marked” liver disease	Take with food
Biologic/Targeted Therapies					
Abemaciclib (± Letrozole or Fulvestrant)	Verzenio	Single agent 200 mg orally twice a day continuously OR	50–200 mg twice a day	Adjust dose for diarrhea, myelosuppression, and/or severe hepatic impairment. Monitor for hepatotoxicity and thromboembolism. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets
		Combination			

		150 mg orally twice a day continuously			
Palbociclib (+ Letrozole or Fulvestrant)	Ibrance	125 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	75–125 mg daily	Adjust dose for myelosuppression and severe hepatic impairment. Monitor for nausea, diarrhea, and hepatotoxicity. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not open capsules
Ribociclib (+ Letrozole or Fulvestrant)	Kisqali	600 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	200–600 mg daily	Adjust dose for myelosuppression and/or severe hepatic or renal impairment. Monitor for hepatotoxicity and QT prolongation. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets
Everolimus (+ Exemestane or Fulvestrant or Tamoxifen)	Afinitor	10 mg orally daily	2.5–10 mg daily	Adjust dose in mild, moderate, and severe liver impairment; also monitor for myelosuppression, hyperglycemia, dyslipidemia, renal dysfunction. May need to adjust dose with concomitant CYP3A4 inhibitors/inducers	Do not split tablets

[a]Severe liver impairment: Child–Pugh class C; moderate liver impairment: Child–Pugh class B; minor liver impairment: Child–Pugh class A.

IM, intramuscular; LHRH, luteinizing hormone-releasing hormone; SC, subcutaneous; SERD, selective estrogen receptor downregulator.

Chemotherapy

- Chemotherapy is used as initial therapy for women with hormone receptor-negative tumors, with triple negative tumors, and after failure of endocrine/targeted therapy regimens.
- Chemotherapy is chosen based on overall efficacy, the risk of toxicity, performance status and presence of comorbidities in the patient, aggressiveness of disease (eg, indolent vs. visceral crisis), and patient preferences related to chemotherapy schedules, dosing route (eg, oral vs. intravenous), and frequency (eg, weekly vs. every 3 weeks).
- Response rates are high with combination chemotherapy, but sequential use of single agents is an effective strategy and may be preferred due to decreased rates of adverse events. In the palliative setting, when efficacy is similar, the least toxic approach is preferred (**Table 60-4**).
- Treatment with sequential single agents is recommended over combination regimens unless the patient has rapidly progressive disease, life-threatening visceral disease, or the need for rapid symptom control.
- Most patients experience partial responses to chemotherapy, but complete disappearance of disease occurs in less than 10% of patients. The median duration of response is highly variable, ranging from 5–18 months; the median OS is 14–33 months. A specific chemotherapy regimen is continued until there is unequivocal evidence of progressive disease or intolerable side effects.
- **Anthracyclines** and **taxanes** produce response rates of 50% to 60% when used as first-line therapy for MBC. Single-agent **capecitabine**, **vinorelbine**, and **gemcitabine** have response rates of 20% to 25% when used after an anthracycline and a taxane.
- **Ixabepilone**, a microtubule stabilizing agent, is indicated as monotherapy or in combination with capecitabine. **Eribulin** is a second

antimicrotubule agent approved as monotherapy in patients who have received at least two prior chemotherapy regimens for MBC.

TABLE 60-4

Select Chemotherapy Regimens for *HER2*-Negative Metastatic Breast Cancer

Single-Agent Chemotherapy	
Paclitaxel Paclitaxel 175 mg/m^2 IV over 3 hours Repeat cycles every 21 days ***or*** Paclitaxel 80 mg/m^2/week IV over 1 hour Repeat dose every 7 days	**Vinorelbine** Vinorelbine 25 mg/m^2/week IV Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)
Docetaxel Docetaxel 60–100 mg/m^2 IV over 1 hour Repeat cycles every 21 days	**Gemcitabine** Gemcitabine 800–1200 mg/m^2/week IV, days 1, 8, and 15 Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)
Protein-Bound Paclitaxel Protein-Bound Paclitaxel 260 mg/m^2 IV over 30 minutes Repeat cycles every 21 days *or* Protein-Bound Paclitaxel 100–125 mg/m^2 IV over 30 minutes on days 1, 8, and 15 Repeat cycle every 28 days	**Ixabepilone** Ixabepilone 40 mg/m^2 IV over 3 hours Repeat cycles every 21 days **Eribulin** Eribulin 1.4 mg/m^2/dose IV over 2–5 minutes on days 1 and 8 Repeat dose every 21 days
Capecitabine Capecitabine 1000–1250 mg/m^2 orally twice daily for 14 days Repeat cycles every 21 days	**Liposomal Doxorubicin** Liposomal Doxorubicin 50 mg/m^2 IV over variable duration Repeat cycles every 28 days
Olaparib Olaparib tablet 300 mg orally twice daily Repeat cycles every 28 days	**Talazoparib** Talazoparib tablet 1 mg orally daily Repeat cycles every 28 days
Combination Chemotherapy Regimens	
Gemcitabine + Carboplatin Gemcitabine 1000 mg/m^2 IV, days 1 and 8 Carboplatin AUC 2 IV, days 1 and 8 Repeat cycles every 21 days	**Paclitaxel + Gemcitabine** Paclitaxel 175 mg/m^2 IV over 3 hours, day 1 Gemcitabine 1250 mg/m^2 IV days 1 and 8 Repeat cycles every 21 days
Docetaxel + Capecitabine Docetaxel 75 mg/m^2 IV over 1 hour, day 1 Capecitabine 950 mg/m^2 orally twice daily for 14 days Repeat cycles every 21 days	**Paclitaxel + Bevacizumab** Paclitaxel 90 mg/m^2 IV over 1 hour, days 1, 8, and 15 Bevacizumab 10 mg/kg IV over 30–90 minutes, days 1 and 15 Repeat cycles every 28 days

Adapted from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer V.3.2019. National Comprehensive Cancer Network, Inc. Accessed September 20, 2019.

Radiation Therapy

- Commonly used to treat painful bone metastases or other localized sites of disease, including brain and spinal cord lesions. Pain relief is seen in approximately 90% of patients who receive RT for painful bone metastases.

EVALUATION OF THERAPEUTIC OUTCOMES

Early Breast Cancer

- The goal of adjuvant therapy, chemotherapy, biologic or targeted therapy, and endocrine therapy, in early-stage disease is cure. Adjuvant therapy is intended to eradicate micrometastases and thus cure the patient of breast cancer, which cannot be fully evaluated for years after initial diagnosis and treatment. In addition, because disease cannot be detected at the time adjuvant therapy is started, an assessment of disease response is not possible.
- Adjuvant chemotherapy can cause significant toxicity. Optimize supportive care measures such as antiemetics and growth factors to maintain dose intensity.

Locally Advanced Breast Cancer

- The goal of neoadjuvant chemotherapy in locally advanced breast cancer is cure. Complete pathologic response, determined at the time of surgery, is the desired end point.

Metastatic Breast Cancer

- Palliation is the therapeutic end point in the treatment of MBC. Optimizing quality of life is an important therapeutic end point. Valid and reliable tools are available for objective assessment of quality of life in patients with breast cancer.
- The least toxic therapies are used initially, with increasingly aggressive therapies applied in a sequential manner that does not significantly compromise quality of life.
- Tumor response is measured by changes in laboratory tests, diagnostic imaging, or physical signs or symptoms.

See Chapter 145, Breast Cancer, authored by Bonnie Lin Boster, Neelam K. Patel, and Laura Boehnke Michaud, for a more detailed discussion of this topic.