

EARLY AND LOCALLY ADVANCED BREAST CANCER

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Learning Objectives

1. Distinguish between women at various risks of breast cancer recurrence and apply differences to management strategies accordingly.
2. Develop evidence-based treatment plans for the management of early and locally advanced breast cancer.
3. Assess the role of neoadjuvant and adjuvant chemotherapy in early and locally advanced breast cancer.
4. Apply pharmacokinetic and pharmacodynamic principles and analyze clinical controversies in the management of specific patient populations with early and locally advanced breast cancer.
5. Analyze clinical data for the use of tamoxifen and aromatase inhibitors as nonadjuvant and adjuvant treatments of early and locally advanced breast cancer.
6. Contrast the adverse effects and indications of chemotherapy and hormonal agents in the management of women with early and locally advanced breast cancer.
7. Devise management strategies for adverse events associated with adjuvant chemotherapy and hormonal therapy for women with early and locally advanced breast cancer.

Introduction

Breast cancer is the most often diagnosed cancer in women (excluding skin cancers) and is the second most common cause of cancer death in women. It is estimated that 182,460 new cases of invasive breast cancer and 67,770 new cases of noninvasive breast cancers (lobular and ductal carcinomas in situ) will occur in 2008. An estimated 40,930 deaths will result.

Increased public awareness and screening programs have shifted the stage at which women receive the diagnosis. About 75% of newly diagnosed cases are classified as early breast cancer (EBC). Despite this, locally advanced breast

cancer (LABC) remains a major clinical problem. This heterogeneous group of breast cancer, typically defined by bulky primary chest wall tumors with or without extensive lymph node (LN) involvement, represents up to 10% of all breast cancers.

Despite overall reductions in breast cancer-related mortality, significant proportions of women with EBC and LABC relapse at distant sites and ultimately die of recurrence-related complications. The 5-year survival for EBC and LABC is about 87% and 50%, respectively. The goal in EBC is to cure, whereas the goal in LABC is to minimize recurrence rates and increase long-term survival. The ability to identify patients at risk of recurrence and then to tailor treatment accordingly is crucial and may offer life-saving benefits.

Diagnosis and Staging

Initial Examinations and Biopsy

A thorough patient history and physical examination should be performed, followed by diagnostic mammography and possibly an ultrasound examination of the breast and LN basins. Suspicious breast areas, detected by either palpation or radiologic criteria, should be monitored by biopsy (excisional biopsy, fine-needle aspiration, or core needle biopsy). These tests are sufficient for the diagnosis of EBC. In LABC, the chance of distant metastasis is considerably higher, and additional systemic staging is indicated to rule out widely metastatic disease. Additional examinations include a full-body bone scan and computerized tomography scans of the chest, abdomen, and pelvis.

Axillary LN Evaluation

The evaluation of LN status is performed primarily through surgical resection and histopathologic examination. Traditionally, a complete axillary LN dissection was performed in all patients; however, this practice resulted in anatomic disruption producing lymphedema, nerve injury, shoulder dysfunction, and other complications. The sentinel LN biopsy technique has advantages compared with the complete axillary LN dissection. Because breast cancer

Abbreviations in This Chapter

AC	Doxorubicin and cyclophosphamide
AI	Aromatase inhibitor
BCS	Breast conservation surgery
CMF	Cyclophosphamide, methotrexate, and fluorouracil
DFS	Disease-free survival
EBC	Early breast cancer
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
LABC	Locally advanced breast cancer
LN	Lymph node
OS	Overall survival
TAC	Docetaxel, doxorubicin, and cyclophosphamide
TC	Docetaxel and cyclophosphamide

typically spreads sequentially through the nodal chain, an evaluation of the first affected LNs, sentinel LNs, may be performed first. If no disease is identified, the need for an additional axillary LN evaluation by a complete dissection is eliminated, thereby minimizing surgical morbidity. Long-term data are not available to assess the effects of the sentinel LN biopsy on survival. However, women eligible for breast conservation surgery (BCS) can be considered for sentinel LN biopsy to guide the need for a complete axillary dissection, whereas women who require mastectomy should receive a complete axillary LN dissection.

Prognostic and Predictive Factors

Several tumor characteristics have been associated with disease recurrence. A prognostic factor is a measurement available at the time of surgery that correlates with disease-free survival (DFS) or overall survival (OS). The presence of these prognostic factors can provide guidance in treating individual patients. Among these factors associated with recurrence are stage, primary tumor size, presence of nodal involvement, hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, histologic grade and proliferative rate, vascular invasion, and response to primary therapy. With the exception of response to primary therapy, these factors are independent of the influence of systemic adjuvant therapy and correlate with the natural history of the disease. Furthermore, some factors such as HR status and HER2 status are both prognostic and predictive. These factors not only determine patient populations at risk of recurrence (prognostic) but also can identify patients who may benefit from certain types of systemic therapy (predictive). The goal in every patient is to prevent later

systemic disease without causing unnecessary adverse effects from treatment.

Primary Tumor Size

Other than stage (Table 1-1), primary tumor size and LN status are among the most powerful prognostic factors in women with breast cancer. Primary tumor size is the single most important prognostic factor among women without LN disease. Studies demonstrate that with increasing tumor size, recurrence of breast cancer at distant sites is more common and OS is reduced. Women with primary tumors smaller than 1 cm have a 20-year recurrence-free survival rate of almost 88%, compared with 77% in women with tumors between 1.1 cm and 3 cm, and 59% for women with tumors between 3.1 cm and 5 cm.

LN Status

In women with positive LNs, there is a direct correlation between the number of LNs affected and the risk of distant recurrence. Data derived subsets of this continuous variable show that the 5-year survival rate is 82.8% for women without positive LNs compared with 73% for women with 1–3 positive LNs; 45.7% in women with 4–12 positive LNs; and 28.4% in women with more than 13 positive LNs. For simplicity, not because compelling evidence supports that the recurrence or survival curves change at these break points, women are placed in one of four nodal categories: negative LNs, 1–3 positive LNs, 4–9 positive LNs, or 10 or more positive LNs.

Pathologic Tumor Characteristics

The pathologic characteristics of the tumor, such as tumor type and grade, can also serve to estimate a woman's risk of recurrence. Tubular, mucinous, and medullary subtypes of breast cancer have a more favorable prognosis compared with ductal, lobular, mixed, metaplastic, and unknown types. All invasive breast cancers should also be graded (except medullary carcinomas). Histologic grading systems such as the Nottingham combined histologic grading system can provide useful information in determining recurrence. The grade of a tumor is determined by assessing the mitotic index, differentiation, and pleomorphism of cancer cells and is used to determine the aggressiveness of tumors. Tumors are assigned values from 1 (favorable) to 3 (unfavorable). Studies evaluating this approach have shown that women with well-differentiated tumors (grade 1) have a significantly improved prognosis compared with women who have less-differentiated (grades 2 and 3) tumor cells.

HR Status

The presence of HRs on invasive breast cancer cells is both prognostic and predictive, although it seems to be more predictive. Some data suggest that within 5 years of diagnosis, the presence of these receptors confers a reduced risk of disease recurrence and death. However, these receptors may not have long-term prognostic significance. The presence of HRs is also predictive of response to adjuvant endocrine therapy. Women with HR-positive breast cancer experience significant reductions in the risk of disease recurrence with endocrine therapy, whereas women with HR-negative disease benefit little from endocrine therapy. Subdividing HR status into estrogen receptor (ER)-positive and progesterone-

Table 1-1. American Joint Committee on Cancer TNM Staging System for Breast Cancer

Breast Cancer Category	Stage	T	N	M
Noninvasive breast cancers (LCIS, DCIS)	0	Tis	N0	M–
Early breast cancer	I	T1 ^a	N0	M–
		T0	N1	M–
		T1 ^a	N1	M–
	IIA	T2	N0	M–
		T2	N1	M–
		T3	N0	M–
	IIIA	T0	N2	M–
		T1 ^a	N2	M–
		T2	N2	M–
Locally advanced breast cancer	IIIB	T3	N1	M–
		T3	N2	M–
		T4	N0	M–
	IIIC	T4	N1	M–
		T4	N2	M–
		Any T	N2	M–
Metastatic breast cancer	IV	Any T	Any N	M+

^aIncludes tumors with a microinvasion of 0.1 cm or less in greatest dimension.

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; M = metastasis; M– = no distant metastasis; M+ = distant metastasis present; N = number of lymph nodes; T = primary tumor size; Tis = carcinoma in situ; T1 = tumor 2 cm or less in greatest dimension; T2 = tumor more than 2 cm but no more than 5 cm in greatest dimension; T3 = tumor more than 5 cm in greatest dimension; T4 = tumor of any size with direct extension into the chest wall and/or skin.

Information from the National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology. In Practice Guidelines in Oncology v.1.2009. Available at www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed February 25, 2009.

positive subgroups further predicts response to endocrine therapy. When given endocrine therapy with tamoxifen, patients with ER-positive and progesterone-positive tumors have a lower recurrence rate than those with ER-positive and progesterone-negative tumors.

HER2 Status

The overexpression of the proto-oncogene HER2 on breast cancer cells (20% to 25% of cases) is associated with increased tumor aggressiveness, recurrence rates, and mortality, especially in women with LN-positive disease. Retrospective data suggest the presence of this overexpression has several predictive clinical applications. Women with HER2 overexpression are relatively resistant to endocrine therapy alone. These tumors appear to respond better to an aromatase inhibitor (AI) compared with tamoxifen; are relatively resistant to certain chemotherapy regimens (e.g., cyclophosphamide, methotrexate, and fluorouracil [CMF]); and respond better to anthracycline and taxane-based chemotherapy regimens. These tumors also respond well to trastuzumab therapy, which is targeted against the extracellular domain of this human epidermal growth factor receptor.

Proliferation Markers

Several proliferation markers have also been investigated. The concentration of cyclins, which are involved in molecular control mechanisms of the cell cycle, correlate with disease-specific survival in some studies. Women with high concentrations of cyclin E, in particular, have reduced 5-year DFS and OS rates. Increased expression of another proliferation marker, Ki-67, may also correlate with decreased OS and DFS. Currently, there are mixed results regarding the importance of the cyclins and Ki-67 in determining patient prognosis. Their routine assessment in clinical practice is not supported; however, this information may be helpful in predicting recurrence in women with borderline tumor sizes and LN-negative disease.

Response to Systemic Therapy

Response to systemic chemotherapy is correlated with outcomes. Women who attain clinical and pathologic responses with preoperative systemic therapy have improved DFS and 5-year recurrence-free survival rates. Complete clinical and pathologic responses are associated with better outcomes than partial or no responses. In addition, patients with cancers that attain both complete clinical and pathologic responses have better DFS than those with tumors that attain a complete clinical response but show residual invasive cells on pathologic examination. The association of clinical and pathologic responses with OS is less clear. However, there is a clear indication that local tumor response correlates with subsequent patient outcome and that these indications should be considered in clinical practice.

Treatment of EBC and LABC

The treatment of EBC and LABC involves a multifaceted approach. A combination of surgery, radiation, endocrine therapy, and chemotherapy may be used depending on the individual patient. In EBC, surgery is typically followed by several cycles of adjuvant chemotherapy, radiation, and endocrine therapy. For other patients with EBC and those with LABC, chemotherapy may be given first (neoadjuvant), followed by surgery; then radiation and endocrine therapy. Patients with LABC deemed inoperable after preoperative chemotherapy undergo palliative radiation and additional systemic adjuvant chemotherapy.

The timing of surgery and chemotherapy depends on the surgical candidacy of the patient and the stage of the breast cancer. The timing of radiation depends primarily on the chemotherapy regimen given. In patients receiving chemotherapy regimens that may potentiate cardiovascular toxicities or radiation recall, radiation therapy commences about 4 weeks after the completion of chemotherapy. Endocrine therapy begins before surgery (neoadjuvant) or concurrently with radiation because it does not increase radiation toxicities.

Surgery

Mastectomy

The primary goal of surgery is to minimize the risk of locoregional recurrence. The surgical modalities used in breast cancer include mastectomy and BCS. Mastectomy

had been the primary surgical strategy for all women with EBC and remains a major treatment component of patients with LABC. Over time, different types of mastectomy procedures have evolved including total mastectomy; skin-sparing mastectomy; and, most recently, nipple-sparing mastectomy. Overall, when used with other regional strategies, mastectomy maintains durable OS and DFS rates.

Breast Conservation Surgery

In appropriately selected women, BCS by quadrantectomy, segmentectomy, or lumpectomy, with axillary LN evaluation and adjuvant radiation therapy, yields results similar to mastectomy. This approach produces DFS and OS rates as high as 54% and 63%, respectively, at 18 years of follow-up. Breast conservation surgery has now become a well-defined alternative to mastectomy for appropriate candidates.

Most women with stage 0–II breast cancer and those with T3N0 breast cancer are candidates for BCS. A portion of women with LABC who respond to preoperative systemic therapy are also candidates. Various factors must be considered when evaluating a woman's candidacy for BCS. First, contraindications to BCS must be considered. The presence of two or more primary tumors in separate areas of the breast, a history of therapeutic radiation to the breast (which eliminates full breast radiation for the present condition), and pregnancy are among some of the contraindications to BCS. Second, relative contraindications are considered. Cancer involving more than one breast quadrant or the presence of inflammatory carcinoma or systemic collagen vascular disease typically precludes BCS and is a relative contraindication. Furthermore, patients with diffuse, malignant-appearing microcalcifications may be best managed with mastectomy because this condition is a surrogate for a higher tumor burden and decreases the ability to obtain clear surgical margins. An extensive intraductal component, which is found in 25% to 40% of breast cancer cases, may require mastectomy if negative margins are not obtained on re-excision. The presence of persistently positive margins after repeated attempts at surgical excision is another relative contraindication to BCS because the incidence of recurrence is higher among patients with smaller negative margins or those with focally or diffusely positive margins. Finally, a high tumor-to-breast ratio is a relative contraindication to BCS because the feasibility of the procedure depends on the ability to remove the tumor without compromising surgical margins and cosmetic outcomes.

Neoadjuvant Therapy

Preoperative or neoadjuvant systemic therapy can offer women with breast cancer several advantages. By decreasing primary tumor size, down-staging nodal involvement, and providing pathologic complete responses, it can allow the use of mastectomy and BCS in more patients. For instance, women with EBC who fulfill the requirements for BCS except for a high tumor-to-breast ratio are able to undergo BCS after neoadjuvant therapy; about 80% of women with LABC who are inoperable at presentation become operable; and almost 25% of women with operable LABC (mastectomy candidates) can undergo BCS. Initial investigations of neoadjuvant chemotherapy found that

this approach decreases morbidity, improves body image, and provides locoregional control of disease and OS rates equivalent to those noted with mastectomy followed by adjuvant chemotherapy. This approach has become a standard of care for appropriate women with EBC and for all women with LABC.

Noncomparative trials demonstrate that endocrine therapy can provide clinical response rates between 36% and 55% and enable up to 45% of patients with ER-positive breast cancer to undergo BCS. Several questions exist regarding the selection of patients who will benefit from this approach, the optimal treatment duration, and the best method to evaluate treatment response. However, study data show encouraging results that support the use of neoadjuvant endocrine therapy, especially in frail patients who may not tolerate the adverse effects associated with chemotherapy.

Radiation

The primary goal of radiation therapy is to eliminate undetected disease deposits that may remain within the residual breast tissue, scar area, chest wall, or regional LNs after surgery. When used after BCS, radiation reduces the risk of recurrence by 20% and overall mortality by 5%.

When adjuvant radiation is used after mastectomy, radiation therapy reduces the risk of locoregional recurrence by almost two-thirds. This benefit continues for 20 years after radiation therapy. Major trials and groups of trials have demonstrated a moderate but significant reduction in breast cancer mortality. This reduction is significant, primarily for the first 2 years after treatment is begun. Thereafter, the annual breast cancer death rate is reduced by 13.2%. The effect on OS has been more difficult to determine. Historically, radiation therapy after mastectomy has increased cardiovascular-related mortality and offset the significance of reductions seen in breast cancer–related mortality. Therefore, the risks of cardiovascular-related mortality were weighed against the risk of the recurrence of locoregional breast cancer in a particular patient, given the individual's risk factors. Since then, improvements in technology and knowledge in radiation therapy have minimized exposure to the heart and lungs, decreasing risks of cardiovascular and pulmonary toxicities and making radiation therapy after surgery a standard of care.

Adjuvant Therapy

A significant proportion of women with EBC and LABC experience relapse at distant sites with locoregional therapy alone. In the absence of systemic therapy, the estimated risk of relapse 15 years after diagnosis in women with LN-positive or LN-negative disease is 70% and 40%, respectively. These relapses have led to the understanding that undetected deposits of disease, or micrometastases, may remain locally or at distant sites after locoregional treatment. Eliminating micrometastases by giving postoperative or adjuvant hormonal therapy, chemotherapy, or both has proved highly effective in preventing both local and distant relapses and is essential in optimizing the chance for cure.

Systemic adjuvant therapy can result in significant adverse effects; therefore, treatment decisions regarding adjuvant therapy are made by estimating an individual's risk of recurrence and his or her expected benefit of therapy. Prognostic factors such as HR status, nodal status, tumor

size, number of involved axillary LNs, and histologic tumor grade help indicate an individual's risk of recurrence; these factors, in addition to age and comorbidity, should be considered when weighing the benefits and risks of adjuvant therapy in a particular patient (Figure 1-1).

Patients with small tumors (0.5 cm or less) and node-negative disease have such favorable outcomes that adjuvant chemotherapy is of minimal benefit. Women with larger tumors (0.6–1 cm) and node-negative disease can be placed in two categories: those with a low risk of recurrence; and those with negative prognostic factors that might benefit from adjuvant therapy. In general, the presence of LN-positive disease or tumors greater than 1 cm warrants adjuvant therapy.

Assessment Tools

Tools such as Adjuvant Online (www.adjuvantonline.com) are available to aid clinicians in objectively estimating patient outcomes with systemic treatment. Information regarding individual patients and their disease is entered in this statistical database and is used to estimate the risk of cancer-related mortality, the risk of relapse without

systemic adjuvant therapy, the reduction of these risks afforded by therapy, and the risks of adverse effects from adjuvant treatment. Results are then displayed in graphic and text format and can be used in conjunction with clinical judgment to determine the best treatment approach for an individual patient.

Analysis of a panel of 21 genes (a test available in a product called Oncotype DX) is another assessment tool. Results are used to calculate a recurrence risk score in patients with node-negative, ER-positive breast cancer. It has been suggested that patients treated with tamoxifen and with good estimated prognosis (i.e., low recurrence risk score according to this tool) may be spared adjuvant chemotherapy. Women with higher recurrence risk scores appear to have higher proportional benefits from adjuvant chemotherapy, specifically CMF. Although this tool has several limitations, and it is still unclear whether the results can be extrapolated to endocrine agents other than tamoxifen or chemotherapy regimens other than CMF, it may provide helpful information in clinical practice.

Tumor Characteristics			Recommended Adjuvant Approach
T1, T2, or T3; and	pN0 and • Tumor ≤ 0.5 cm • Microinvasive	HR+	No therapy
		HR–	No therapy
		HER2+	No therapy
	pN1mi and • Tumor ≤ 0.5 cm • Microinvasive • Well-differentiated, 0.6- to 1-cm tumor without unfavorable features ^a	HR+	± Endocrine therapy
		HR–	± Chemotherapy
		HER2+	± Trastuzumab
	pN0 or pN1mi and 0.6-1 cm and • Moderate/poor differentiation • Unfavorable features ^a	HR+	+ Endocrine therapy ± Chemotherapy
		HR–	± Chemotherapy
		HER2+	± Trastuzumab
Any T; and	pN0 or pN1mi and • Tumor > 1 cm • Node positive ^b	HR+	+ Endocrine therapy + Chemotherapy
		HR–	+ Chemotherapy
		HER2+	+ Trastuzumab

Figure 1-1. Systemic adjuvant treatment recommendations stratified according to tumor characteristics.

^aUnfavorable features include angiolymphatic invasion, high nuclear grade, or high histologic grade.

^bOne or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes.

± = respective therapies may or may not provide additional outcome benefits. The decision to use these therapies must balance the known toxicities of the regimens and be individualized with consideration of patient-specific characteristics such as age and comorbidity. HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor–positive tumors; HR– = for hormone receptor–negative tumors; pN0 = no regional lymph node metastasis, histologically; pN1mi = micrometastasis (greater than 0.2 mm, none greater than 2 mm); T1 = tumor 2 cm or less in greatest dimension; T2 = tumor more than 2 cm but no more than 5 cm in greatest dimension; T3 = tumor more than 5 cm in greatest dimension.

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Endocrine Surgery

Adjuvant treatment of breast cancer by hormonal manipulation, such as ovarian ablation and suppression and, more recently, selective ER modification or aromatase inhibition, improves OS, decreases annual recurrence rates, and decreases cancer mortality in women with HR-positive breast cancer, irrespective of age or nodal status.

Luteinizing Hormone–Releasing Hormone Analogs

The luteinizing hormone–releasing hormone analogs goserelin and leuprolide down-regulate the secretion of luteinizing hormone and follicle-stimulating hormone, resulting in suppressed ovarian function and decreased estrogen production in premenopausal women. These agents yield results similar to surgical castration but have the benefit of being reversible.

The use of ovarian suppression in breast cancer has been studied alone, compared with chemotherapy, in addition to tamoxifen, and in combination with chemotherapy. Compared with no therapy, ovarian suppression improves DFS and OS in women younger than 50 years. Compared with chemotherapy, ovarian suppression by a luteinizing hormone–releasing hormone analog provides similar outcomes for premenopausal women with node-positive or node-negative, HR-positive breast cancer. Combining a luteinizing hormone–releasing hormone analog with tamoxifen produces variable results. Some data show improvements in DFS when the two modalities are combined, whereas other data show that the addition of a luteinizing hormone–releasing hormone analog does not offer additional benefit. In contrast, combining a luteinizing hormone–releasing hormone analog with chemotherapy appears to prolong DFS compared with chemotherapy alone.

Many questions remain regarding the role of goserelin and leuprolide in the adjuvant treatment of breast cancer, such as the optimal duration of ovarian suppression, the value of combining ovarian suppression with other endocrine therapies, and the ways in which newer chemotherapy regimens compare with these endocrine agents. However, there may be a benefit of luteinizing hormone–releasing hormone analogs, at least when used in combination with other systemic therapies in premenopausal women with HR-positive disease.

Selective ER Modulators

Tamoxifen, a selective estrogen receptor modulator, blocks the interaction between estrogen and ERs at the cellular level and therefore produces its therapeutic effect independently of the source of estrogen. Tamoxifen undergoes extensive hepatic oxidation by the cytochrome P450 (CYP) isoform 2D6, which results in several metabolites. The 4-hydroxytamoxifen and endoxifen metabolites have a greater affinity for ERs, are more than 30-fold more potent than the parent form, and are present in significant concentrations. These characteristics result in effective antagonism of ERs in the ovaries.

Tamoxifen is the most established adjuvant endocrine agent for both premenopausal and postmenopausal women. In women with HR-positive breast cancer, 1–2 years of tamoxifen reduces recurrence rates and breast cancer deaths. This benefit is even greater with 5 years of tamoxifen,

providing relative reductions in the annual risk of relapse and death of 41% and 34%, respectively. The benefits of endocrine therapy are maintained 15 years later, with a 12% reduction in the likelihood of recurrence and a 9% reduction in breast cancer–related death.

Aromatase Inhibitors

Anastrozole and letrozole are nonsteroidal AIs, and exemestane is a steroidal-selective AI. In postmenopausal women, estrogen production results from an enzymatic conversion of adrenal androgens in peripheral tissues to estrogen. Aromatase inhibitors prevent the formation of estrone and estradiol by inhibiting the CYP aromatase enzyme responsible for this conversion in the periphery.

The AIs may offer advantages compared with tamoxifen in both the neoadjuvant and adjuvant settings. Compared with tamoxifen, the use of anastrozole, letrozole, and exemestane in the neoadjuvant setting increases the number of women with operable ER-positive breast cancer who are able to undergo BCS by 13%, 10%, and 17%, respectively. In the adjuvant setting, anastrozole and letrozole significantly increase DFS by 17% and 19%, respectively, and provide a greater reduction in the incidence of distant metastasis compared with tamoxifen. Furthermore, these effects appear to be independent of progesterone receptor positivity, unlike tamoxifen. Results of studies comparing exemestane and tamoxifen, as well as those investigating differences among the AIs, are still being evaluated.

Combining an AI and tamoxifen does not offer benefits compared with monotherapy with either agent, but studies investigating sequencing strategies of tamoxifen and AIs reveal that postmenopausal women with ER-positive disease have several adjuvant endocrine options. Sequencing strategies have included the use of an AI (anastrozole or letrozole) administered for 2 years, followed by 3 years of tamoxifen; tamoxifen used for 2–3 years, followed by an AI (anastrozole, letrozole, or exemestane) to complete 5 years of endocrine therapy; and tamoxifen for 5 years, followed by an AI (anastrozole or letrozole) for an additional 5 years to provide 10 years of adjuvant therapy. Switching from tamoxifen to an AI (particularly anastrozole) is associated with an increase in DFS. This benefit occurs irrespective of nodal status, age, progesterone receptor positivity, and tumor grading.

In contrast, the effect of sequential endocrine administration on OS is less clear. Some data show an improvement in survival in patients who have switched to an AI, whereas other data demonstrate no significant difference between women who switch and those who remain on tamoxifen. The lack of clarity could be secondary to the short duration of follow-up in these studies. Furthermore, trials investigating sequential endocrine administration involve several strategies, and direct comparisons are lacking. It is therefore difficult to discern the best sequence of agents. In summary, the use of an AI at some time in the adjuvant setting provides women with ER-positive breast cancer with an improved chance of DFS.

Endocrine Therapy Summary

In summary, most women with ER-positive breast cancer should receive either tamoxifen or an AI as adjuvant endocrine therapy (Figure 1-2). Currently, premenopausal

Pre-MP ^a	Tamoxifen × 2–3 years ± Leuprolide, goserelin or ovarian ablation	Reassess MP status	Pre-MP	Complete 5 years of tamoxifen	Reassess MP status	Pre-MP	Stop treatment	
			Post-MP	Complete 5 years of tamoxifen			Post-MP	Letrozole OR Anastrozole × 5 years
				Letrozole OR Anastrozole × 2–3 years (Complete 5 years of hormonal therapy) Exemestane				
Post-MP	Anastrozole OR Letrozole × 5 years							
	Tamoxifen × 5 years ^a							
	Tamoxifen × 2–3 years		followed by	Anastrozole OR Letrozole × 5 years				
	Tamoxifen × 4.5–6 years		followed by	Anastrozole OR Letrozole × 5 years				

Figure 1-2. Systemic adjuvant endocrine therapy recommendations stratified according to menopausal status. Definitions of menopause include (1) prior bilateral oophorectomy, (2) age ≥ 60 years, (3) age < 60 years, and follicle-stimulating hormone and plasma estradiol levels within the postmenopausal range.

^aConsider for patients who are intolerant, have contraindications, or decline aromatase inhibitors

MP = menopause.

Information from the National Comprehensive Cancer Network. In: Clinical Practice Guidelines in Oncology, v.1.2009. Available at www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed February 25, 2009.

women are limited to treatment with tamoxifen with or without ovarian suppression (with goserelin or leuprolide) or ablation; other agents and strategies have not been investigated and pharmacologically lack the ability to block the primary source of estrogen. Postmenopausal women have several treatment options. The inclusion of an AI at some point in adjuvant treatment is preferred. Tamoxifen, an AI, or sequential use of both for a total of 5 years of treatment is optimal. Selection of an endocrine regimen should depend on patient characteristics and the types and risks of adverse effects associated with each endocrine agent.

Chemotherapy

The use of chemotherapy has been an integral part of treatment for women with breast cancer. Meta-analyses of randomized trials reveal several concepts. Combination chemotherapy regimens are superior to single-agent regimens and significantly reduce the annual hazard ratio for recurrence and death by 23.5% and 15.3%, respectively. Women of all ages benefit from combination chemotherapy; however, the benefit appears to be greatest among women younger than 50 compared with those aged 50–69. The relationship between age and prognosis is confounded by several factors (e.g., younger women typically present with HR-negative disease, limited data are available for women older than 70). Finally, combination regimens appear to produce proportional reductions in the risks of recurrence and death for women with node-positive and -negative disease and for those with HR-positive and -negative disease, although women with LN-positive and HR-negative

disease experience a proportionally larger benefit from chemotherapy.

Anthracycline-Based Regimens

Since it was established that combination chemotherapy is more effective than single chemotherapy agent regimens, various combination regimens have been investigated. First, 12 cycles of CMF significantly improves relapse-free survival and OS in the adjuvant setting. Used preoperatively, CMF increases BCS rates by 7%. Subsequent trials investigating the use of a regimen consisting of an anthracycline agent (e.g., doxorubicin, epirubicin) in combination with cyclophosphamide and fluorouracil for six cycles produced a moderate, but significant, survival advantage compared with CMF. Ten-year probabilities of recurrence, breast cancer mortality, and overall mortality are each reduced by about 3% at 5 years and 4% at 10 years. Another anthracycline-based regimen, doxorubicin and cyclophosphamide (AC), was found to be as effective as CMF with the advantage of a shorter treatment duration (four vs. six cycles). In the preoperative setting, AC is also effective, providing objective clinical response rates in about 80% of women and complete pathologic response rates in 36%, as well as converting 27% to BCS.

Taxane-Based Regimens

The taxanes have shown great antitumor activity in breast cancer, even in anthracycline-resistant disease. Their preserved activity in previously treated breast cancer has

generated hope that these agents may improve survival in patients who will not benefit from anthracycline therapy.

Adding a taxane (docetaxel or paclitaxel) to an anthracycline-based regimen increases long-term benefits for women with high-risk breast cancer. Docetaxel in combination with doxorubicin and cyclophosphamide (TAC) is superior in 5-year DFS and OS compared with regimens combining fluorouracil, doxorubicin, and cyclophosphamide. A meta-analysis of several taxane-based combinations used in the adjuvant setting confirms this finding. Taxanes were given concurrently with an anthracycline and concurrently with AC, as well as sequentially before, in between, and after combination anthracycline or CMF chemotherapy in women with LN-positive breast cancer. Adding a taxane resulted in an absolute 5-year risk reduction of 5% for DFS and 3% for OS, independent of HR status, degree of nodal involvement, administration schedule, and taxane used. In the neoadjuvant setting, administering docetaxel sequentially after standard AC increases the complete clinical response rate by 24% and the complete pathologic response rate by almost 12% compared with using preoperative AC alone. Trial results regarding DFS and OS are anticipated.

Combination regimens may increase toxicity and result in dose reductions. Conversely, sequential regimens may permit optimal dosing, thereby increasing response rates. In the neoadjuvant setting, giving AC followed by docetaxel provides higher complete clinical and pathologic response rates compared with giving the taxane concurrently with doxorubicin. Another study investigating the use of neoadjuvant epirubicin in combination with paclitaxel versus epirubicin followed by paclitaxel demonstrated that both BCS rates and complete pathologic response rates were higher in the sequential regimen. These findings are also supported in the adjuvant setting. In a meta-analysis of studies of postoperative taxane combinations, sequential regimens provided a statistically significant improvement of DFS and OS, whereas concurrent regimens only trended toward an improvement in OS. These data should be used with caution because the meta-analysis was not designed to compare these chemotherapy administration approaches.

Replacing an anthracycline with a taxane may also provide acceptable outcomes in some patient populations, particularly those at risk of cardiovascular events. One trial compared docetaxel plus cyclophosphamide (TC) with AC in women with LN-positive or -negative operable breast cancer. Results revealed that TC provided significantly superior DFS rates and similar OS rates at 5 years.

Unfortunately, the diversity of trials limits the ability to form absolute conclusions regarding the best approach to taxane therapy in the adjuvant and neoadjuvant settings. Despite this limitation, it is well demonstrated that taxanes offer additional benefits for women with high-risk breast cancer.

Dose Intensification Strategies

Total dose and dose intensity have been postulated to be important variables in the outcome of patients with breast cancer. In studies of animal tumors, chemotherapeutic agents have displayed steep dose-response curves. Initial clinical trials evaluating this concept in women with breast cancer compared escalated doses of combination anthracycline regimens given for a standard-cycle duration with moderate-

and low-dose strategies. Results of these trials vary. Trials comparing epirubicin 50 mg/m² with epirubicin 100 mg/m² (in combination with fluorouracil and cyclophosphamide) have shown significant improvements in 5-year DFS and OS favoring the higher-dose epirubicin regimens, whereas other studies investigating escalated doses of doxorubicin reveal no benefits compared with standard dose regimens. In some cases, outcomes are worse in patients receiving higher doses of anthracyclines; this may have resulted from hematologic toxicity, subsequent dose reductions, and administration delays. Giving chemotherapy for a longer duration (more than three to six cycles) does not offer additional benefit. One trial demonstrated this by randomizing women who received four cycles of a doxorubicin-based regimen to either four cycles of docetaxel or four more cycles of the initial regimen. Women achieved an 18% higher complete pathologic response rate when changed to docetaxel compared with continuing the same regimen for four additional cycles.

Since the completion of initial dose intensity trials, it has been recognized that breast cancer cells grow according to a Gompertzian kinetic model, multiplying exponentially initially and then showing some growth retardation as the tumor enlarges. More frequent administration of cytotoxic therapy may be more effective in minimizing residual tumor burden than dose escalation because the former limits the opportunity for cancer cell regrowth between cycles. This approach has been termed *dose-dense therapy*.

The use of bone marrow-stimulating factors has made dose-dense therapy possible. In women with EBC, administering AC every 2 weeks with growth factor support, rather than the standard every-3-week administration schedule, improves DFS by 4% and OS by 3% at 4 years; this has become a standard of care for women with EBC at high risk of recurrence. In LABC, the efficacy of dose-dense therapy is less established. One study that evaluated neoadjuvant dose-dense epirubicin and cyclophosphamide did not demonstrate a benefit in DFS or OS compared with the standard combination of cyclophosphamide, epirubicin, and fluorouracil. In another trial, which compared the use of weekly paclitaxel to paclitaxel given every 3 weeks, more frequent administration of paclitaxel dosed at a cumulatively higher dose (than the total dose given in the every-3-week regimen) significantly improved the pathologic complete response rate (28% vs. 15%). This has been postulated to be consistent with the schedule-dependent activity of paclitaxel on tumor cells.

Summary

Various chemotherapy regimens have been investigated in the EBC and LABC settings (Table 1-2). Currently, direct comparisons among regimens are lacking. Many questions remain regarding the best regimen and schedule; however, some conclusions can be extrapolated. For high-risk patients such as those with larger tumor size, positive LNs, or less-differentiated tumors, the following concepts are accepted in clinical practice. Anthracycline-based regimens are preferred to CMF; adding a taxane to chemotherapy regimens offers additional benefits; dose-dense anthracycline regimens may optimize survival outcomes; replacing an anthracycline with a taxane may be acceptable for patients with cardiovascular comorbidities; and the use of CMF should be limited to

Table 1-2. Chemotherapy Regimens for Early and Locally Advanced Breast Cancer

Regimen	Agents	Doses	Route	Days administered	Length of cycle (days)	No. of Cycles/Duration of Therapy
Combination Chemotherapy Regimens						
AC	Doxorubicin	60 mg/m ²	IV	1	q21	4
	Cyclophosphamide	600 mg/m ²	IV	1		
EC	Epirubicin	100 mg/m ²	IV	1	q21	8
	Cyclophosphamide	830 mg/m ²	IV	1		
TC	Docetaxel	75 mg/m ²	IV	1	q21	4
	Cyclophosphamide	600 mg/m ²	IV	1		
CMF	Cyclophosphamide	100 mg/m ²	PO	1–14	q28	6
	Methotrexate	40 mg/m ²	IV	1, 8		
	Fluorouracil	600 mg/m ²	IV	1, 8		
FAC	Fluorouracil	500 mg/m ²	IV	1, 8 or 1, 4	q21	6
	Doxorubicin	50 mg/m ²	IV	1		
TAC ^a	Cyclophosphamide	500 mg/m ²	IV	1		
	Docetaxel	75 mg/m ²	IV	1	q21	6
	Doxorubicin	50 mg/m ²	IV	1		
DD-AC ^{a,b}	Cyclophosphamide	500 mg/m ²	IV	1		
	Doxorubicin	60 mg/m ²	IV	1	q14	4
	Cyclophosphamide	600 mg/m ²	IV	1		
Sequential Chemotherapy Regimens						
AC or DD-AC	Doxorubicin	60 mg/m ²	IV	1	q21 or q14 ^{a,b}	4
↓	Cyclophosphamide	600 mg/m ²	IV	1		↓
T	Paclitaxel	175 mg/m ²	IV	1	q21 or q14 ^a	4
A	Doxorubicin	75 mg/m ²	IV	1	q21	4
↓						↓
CMF	Cyclophosphamide	600 mg/m ²	IV	1		
	Methotrexate	40 mg/m ²	IV	1	q21	8
	Fluorouracil	600 mg/m ²	IV	1		
FEC	Fluorouracil	500 mg/m ²	IV	1	q21	3
	Epirubicin	100 mg/m ²	IV	1		
	Cyclophosphamide	500 mg/m ²	IV	1		
↓						↓
T	Docetaxel	100 mg/m ²	IV	1	q21	3
Chemotherapy Regimens Specific for HER 2-Positive Tumors						
----	Trastuzumab ^c	4 mg/kg	IV	Cycle 1	Once	1 year of therapy
		2 mg/kg	IV	1,8, 15, 22	q28	
----	Trastuzumab ^c	8 mg/kg	IV	Cycle 1	Once	1 year of therapy
		6 mg/kg	IV	1	q21	
TCH	Docetaxel	75 mg/m ²	IV	1	q21	6
	Carboplatin	AUC 6	IV	1		
	Trastuzumab	4 mg/kg	IV	Cycle 1	Once	Once
		2 mg/kg	IV	1,8, 15, 22	q28	17 weeks
	OR Trastuzumab	6 mg/kg	IV	1	q21	Complete 1 year

AUC = area under the curve; HER2 = human epidermal growth factor receptor 2; IV = intravenous; PO = oral; q = every. ^aAll cycles should be given with colony-stimulating factor support. ^bDD-AC = dose dense AC regimen. ^cAdminister trastuzumab after approved adjuvant chemotherapy regimens for at least four cycles. Information from the National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology: In: Practice Guidelines in Oncology, v.1.2009. Available at www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed February 25, 2009.

women with cardiovascular comorbidities who have a very low risk of recurrence.

Targeted Therapy

Trastuzumab is a humanized, monoclonal antibody targeted at the extracellular domain of the HER2. Historically, HER2 overexpression conferred a worse prognosis compared with non-overexpressing HER2 cohorts. These HER2-overexpressing breast cancers are relatively resistant to both chemotherapy and endocrine therapy. However, data evaluating the use of HER2-targeted therapy in the adjuvant setting showed that 1 year of HER2-targeted treatment after or in combination with adjuvant chemotherapy significantly improves DFS and OS in patients with HER2-positive disease who have LN-positive or high-risk LN-negative breast cancer, regardless of the chemotherapy regimen given (AC followed by docetaxel, AC followed by paclitaxel, or docetaxel plus carboplatin).

In the neoadjuvant setting, data regarding the use of trastuzumab are limited. Only two trials have been reported to date. The first study compared the use of paclitaxel, followed by fluorouracil, epirubicin, and cyclophosphamide, with the same regimen combined with 24 weeks of concurrent trastuzumab. After 42 patients were enrolled, the trial was modified to allow patients in the chemotherapy arm to receive trastuzumab. Results of the analysis, although underpowered, demonstrated that trastuzumab increases complete pathologic response rates and the percentage of disease-free patients. In a second trial, HER2-positive patients were randomized to receive pre- and postoperative trastuzumab, given concurrently with docetaxel and carboplatin; or pre- and postoperative docetaxel and carboplatin with only postoperative trastuzumab. Preliminary results demonstrated that patients receiving trastuzumab preoperatively had higher complete pathologic response rates compared with women receiving neoadjuvant chemotherapy alone (36.6% vs. 9%).

Adverse Effects of Breast Cancer Therapy

Systemic therapy can improve DFS and OS in patients with breast cancer. Many of these therapies are associated with substantial toxicities that can compromise the ability to receive treatment and subsequently affect long-term outcomes. Therefore, proactive management of adverse events is crucial.

Vasomotor Symptoms

Hot flashes and night sweats are well-known consequences of estrogen deprivation. This adverse effect has been observed in all clinical trials of adjuvant endocrine therapies, including treatment with tamoxifen, an AI, and placebo. Comparative trials evaluating the use of endocrine therapy in the adjuvant setting suggest that AIs cause a lower incidence of hot flashes compared with tamoxifen. Hot flashes still occur in 35% of women treated with an AI, but this compares favorably with tamoxifen, in which the incidence is almost 40%.

In postmenopausal women, estrogen replacement therapy is the most effective management strategy. In patients with a history of breast cancer, however, hormone replacement therapy results in an increased risk of new breast cancer events. Investigations of other steroid treatment modalities (e.g., progestins, dehydroepiandrosterone) can reduce the incidence of hot flashes by up to 90%. Conclusions regarding the long-term safety of these agents in women with a history of breast cancer are limited. Clonidine and gabapentin have also been investigated but with minimal success.

The use of agents that inhibit the reuptake of neurotransmitters involved in thermoregulation has been investigated in women with a history of breast cancer. Venlafaxine, which inhibits norepinephrine and serotonin reuptake, can reduce hot flashes by 55%. Of note, venlafaxine and other serotonin reuptake inhibitors are CYP2D6 inhibitors. The potential for interaction between these types of agents and tamoxifen should be considered because they may alter the effectiveness of tamoxifen therapy.

Genitourinary Complications

Vaginal dryness and loss of libido are common complaints related to low estrogen concentrations. In clinical trials, the incidence of vaginal dryness and loss of libido has been reported with higher frequency among women treated with an AI compared with women treated with tamoxifen, but this demonstrates that this adverse effect is problematic in both populations.

For most patients, the use of nonhormonal local lubricants may provide temporary relief from vaginal dryness; other patients may seek additional relief. Using topical vaginal estrogen preparations that restore the vaginal epithelium from an atrophic state improves symptoms. However, one investigator reported that a vaginal tablet significantly increased serum estradiol concentrations and may therefore be contraindicated in women with ER-positive disease. In healthy women, transdermal testosterone may increase libido, but data in women with a history of breast cancer are lacking. New investigations have evaluated the effects of serotonin reuptake inhibitors. Compared with placebo, women with a history of breast cancer who took venlafaxine, a serotonin and norepinephrine reuptake inhibitor, had a reduction in the number and severity of hot flashes. In many reports, antidepressants have been associated with sexual dysfunction; however, one trial showed that venlafaxine improves libido in breast cancer survivors.

The estrogenic activity of tamoxifen on the genitourinary tract can result in other unwanted gynecologic problems such as vaginal bleeding, vaginal discharge, and endometrial cancer. In breast cancer prevention trials, tamoxifen increased the risk of endometrial cancer by 2.5-fold compared with placebo. Data from trials comparing the use of AI and tamoxifen suggest that these gynecologic adverse effects are less problematic in patients receiving AI than in those receiving tamoxifen.

Arthralgia

As a class, the AIs cause significantly more arthralgia than tamoxifen; however, the mechanism of action and the best way to manage this symptom have not been determined. Nonpharmacologic treatment strategies such as physiotherapy, massage, physical therapy, and weight

loss have been tried, but results have been less than satisfactory. Pharmacologic agents such as nonsteroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, and opioid analgesics have been used, but long-term safety data and other adverse effects limit their use.

Women receiving AI therapy who are troubled by arthralgias and myalgias may benefit from a switch to tamoxifen. In most cases, muscle and joint pain are rarely severe enough to necessitate treatment discontinuation of the AI, and symptoms usually improve with time. Because AIs are more effective than tamoxifen in the adjuvant setting, nonpharmacologic and pharmacologic management strategies for symptom relief should be tried before making the change to tamoxifen.

Bone Loss

Bone loss is another problematic adverse effect of estrogen deprivation. Tamoxifen exhibits selective estrogen agonistic activity on bones and is protective. However, AIs lack this effect, making bone loss a major concern. The American Society of Clinical Oncology recommends that all women at high risk of osteoporosis, including those taking AIs, receive baseline assessment of bone mineral density and regular follow-up during therapy. Patients should also begin calcium and vitamin D supplementation and consider lifestyle changes such as exercise to improve bone health.

In two large trials, the use of intravenous bisphosphonates (mainly zoledronic acid) given every 6 months in postmenopausal women receiving AI therapy prevented bone loss, especially when initiated at the start of AI therapy. In one trial, baseline lumbar spine and total hip bone mineral density T-scores increased by 5.7% and 3.6%, respectively, in women who began immediate bisphosphonate therapy. This approach resulted in more favorable outcomes (mineral density scores) compared with women who delayed therapy until bone mineral density T-scores decreased by at least 2 standard deviations or when a fracture had occurred. Although these data did not demonstrate a difference in fracture rates because of the short-term follow-up of the trial, they do suggest that beginning bisphosphonate therapy at the initiation of AI therapy is an effective treatment to prevent bone loss.

Thromboembolic Events

The incidence of venous thromboembolic events can be 2 or 3 times higher in women receiving tamoxifen compared with placebo, especially in women older than 50. Although warfarin has been studied as a primary prevention therapy in women receiving treatment for breast cancer, there are no data to support its use specifically with tamoxifen therapy. Therefore, it is important to counsel patients regarding the signs and symptoms of venous thromboembolic disease and to encourage them to ambulate regularly. In some cases, it may be appropriate to consider an AI rather than tamoxifen to avoid the risk of this adverse event. Trials comparing the use of tamoxifen and AIs in the adjuvant setting noted that the incidence of deep venous thromboembolic complications was significantly less in women receiving an AI (1.6%) than in those receiving tamoxifen (2.4%).

Cardiac Dysfunction

Anthracyclines

The anthracyclines are among the most active chemotherapy agents used in breast cancer. Unfortunately, these agents have a well-known cardiotoxic profile. Dose-limitation strategies, cardioprotective agents, and liposomal formulations have been attempted to minimize this complication, yet it remains a limitation of breast cancer treatment.

The American Heart Association, American College of Cardiology, American Society of Echocardiography, and American Society of Nuclear Cardiology have developed guidelines for anthracycline-induced cardiotoxicity. Despite these recommendations, there is still much variation in the monitoring strategies used in clinical practice, especially when a patient has had an abnormal test.

Current recommendations advise that patients undergo baseline echocardiography with or without radionuclide angiocardiology. In patients who have received cumulative doxorubicin dose equivalents of less than 300 mg/m², echocardiography should be performed before every other course of chemotherapy; echocardiography should be performed before every course in patients who have reached cumulative doses of 300 mg/m² or more. Radionuclide angiocardiology should be added in patients who have received more than 400 mg/m². At the completion of therapy, echocardiography and electrocardiography should be performed at 3–6 months, at 12 months, and then every 2–3 years. Radionuclide angiocardiology should be performed at 12 months and then every 5 years after anthracycline completion.

In patients with baseline cardiac dysfunction, non-anthracycline-based chemotherapy combinations should be considered. The combination regimen CMF can be considered in patients with a low risk of recurrence; TC in women with higher risk of recurrence; and docetaxel, carboplatin, and trastuzumab in women with HER2-positive disease.

Taxanes

The addition of taxanes to anthracycline therapy has further escalated the risks of cardiomyopathy. In early trials, the combination of paclitaxel and doxorubicin had impressive response rates but with an increased incidence of congestive heart failure. The enhanced cardiotoxicity of this combination results from a pharmacokinetic interaction between these agents. Paclitaxel causes a nonlinear displacement of doxorubicin, increasing plasma concentrations of doxorubicin by 30% or more. Doxorubicin clearance is also reduced when paclitaxel is administered before doxorubicin. Administration of paclitaxel at least 30 minutes after completion of doxorubicin and limiting the cumulative dose of doxorubicin to 360 mg/m² minimizes this complication. Most studies have limited the addition of paclitaxel to anthracycline-based therapy to sequential regimen strategies.

Trastuzumab

Trastuzumab is another agent highly effective in breast cancer treatment that carries cardiotoxic risks. When used concurrently or sequentially with an anthracycline, trastuzumab increases the incidence of heart failure as

much as 22%, compared with 5% in patients who receive an anthracycline alone. Risk factors for trastuzumab-related cardiotoxicity include older age, higher body mass index, antihypertensive therapy, and concurrent anthracycline therapy. Compared with anthracycline-induced cardiotoxicity, the effect of trastuzumab on cardiac function is not dose related; also, trastuzumab does not cause anthracycline-like pathologic changes, and cardiotoxicity is usually reversible. In clinical practice, trastuzumab therapy commences after the completion of anthracycline therapy to minimize cardiotoxic risks to the patient. In addition, a left ventricular ejection fraction should be taken at baseline, every 3 months during therapy, at the conclusion of therapy, and then every 6 months for at least 2 years after the completion of therapy.

Peripheral Neuropathies

Although paclitaxel and docetaxel are associated with several adverse effects, peripheral neuropathy may cause the most concern. This adverse effect is more common with paclitaxel and, in most cases, can be managed with dose reduction. In some cases, patients fail to report this effect because of concerns of treatment delays or omitted doses, thereby resulting in decreased efficacy of their adjuvant treatment. Therefore, it is important to encourage communication regarding this adverse effect, which can substantially decrease ambulation and quality of life. Although data regarding the use of agents such as gabapentin and pregabalin for chemotherapy-induced neuropathies are lacking, these agents have been used in clinical practice to help manage symptoms.

The Role of the Pharmacist

In women with HR-positive breast cancer, long-term adjuvant endocrine therapy provides substantial benefits; however, adverse effects associated with long-term therapies may decrease quality of life. Because these agents are most effective when used for several years, the management of adverse events becomes critical to ensure patient adherence.

Pharmacists can play a crucial role in educating patients regarding the importance of drug adherence. In the ambulatory setting, pharmacists should counsel patients regarding the adverse effects of endocrine therapy and discuss strategies that can be used to help manage them. Pharmacists are also equipped to monitor adherence by evaluating prescription pickup times. Compassionately approaching patients who demonstrate signs of nonadherence may help identify those who struggle with adverse effects. Pharmacists should also monitor prescriptions for drug interactions. For example, a primary care physician may start a patient on a drug that inhibits the CYP2D6 system; this could potentially affect treatment outcomes if the patient is receiving tamoxifen therapy secondary to a drug-drug interaction. Contacting the primary care physician and recommending an alternative agent could be necessary to preserve long-term outcomes for this patient.

Pharmacists practicing in outpatient infusion clinics, clinical trial research centers, and inpatient hospital settings also play a fundamental role in managing and preventing

toxicities associated with breast cancer therapy. Pharmacists are responsible for recommending appropriate dosing for chemotherapy schedules and ensuring that adequate antiemetic prophylaxis strategies and growth factor support is used in appropriate patients. They may also play a key role in maintaining the documentation of cumulative anthracycline doses.

In inpatient practices, the pharmacist may make recommendations regarding the timely and appropriate initiation of antibiotic therapy in patients with febrile neutropenia. The pharmacist may also provide pain management consults, recommendations regarding the initiation or conversion of opioid agents, or recommendations regarding the implementation of gabapentin or pregabalin for peripheral neuropathies. Pharmacists can assist practitioners in the dosing of antithrombotic agents for patients admitted with thromboembolic events secondary to tamoxifen therapy. In addition, they play a major role in educating patients regarding the significance of drug and food interactions with long-term warfarin therapy.

Overall, pharmacists play a fundamental role in managing patients with early and localized breast cancer. In several clinical settings, pharmacists can optimize the treatment of patients with breast cancer by providing education and treatment recommendations to both to the patient and other health care providers.

Conclusion

Significant progress has been made in the treatment of early and localized breast cancer. Because of research and clinical experience, the ability to identify patients at increased risk of cancer recurrence by prognostic indicators has improved. The ability to identify and tailor pharmacologic treatment regimens accordingly has minimized adverse effects without compromising OS rates. In addition, various chemotherapy and endocrine regimens and administration strategies have evolved, providing continuous improvements in DFS and OS rates. Overall, breast cancer–related mortality has decreased at a rate of 2.3% per year. Despite these improvements, women with EBC and LABC continue to have late disease recurrence. Investigations in prognostic and predictive factors, as well as pharmacologic strategies, continue.

Annotated Bibliography

1. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. *Oncologist* 2004;9:606–16.

This review article discusses data regarding several prognostic factors including axillary nodal status, tumor size, tumor grade, lymphatic and vascular invasion, proliferation markers, ethnicity, and age at diagnosis. It also discusses several predictive factors such as HR status and HER2 status. One of the major strengths of the article is that it provides guidance in applying this knowledge to individual patients. Patients with LN-positive disease, larger primary tumors, and poorly differentiated cancer cells have a higher risk of recurrence; thus, they should be treated accordingly. Women with HR-positive disease may benefit from the addition of tamoxifen or an AI. Human epidermal growth factor receptor

2 status helps predict women who should receive therapy with trastuzumab. Overall, significant progress has been made in identifying women at risk of recurrence.

2. Harris L, Fritsche H, Mennell R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007;25:5287–312.

Several tumor markers with a potential role in the assessment of an individual's risk of breast cancer recurrence have been identified. However, the use of some of these markers is controversial. The American Society of Clinical Oncology has developed guidelines to facilitate appropriate use of these markers. Thirteen categories of breast tumor markers were considered, six of which were new. Markers discussed included CA 15-3, CA 27.29, carcinoembryonic antigen, estrogen and progesterone receptors, HER2, and DNA flow cytometry-based parameters; proliferation markers discussed included Ki-67, cyclin D, cyclin E, p27, p21, thymidine kinase, uPA and PAI-1, cathepsin D, and topoisomerase II α .

This article provides evidence-based recommendations that specify the role of each marker in clinical practice. This is a major strength of the guideline. Despite recommendations, individual variation or special clinical situations among patients must be considered. One limitation of the guideline is that it does not account for these situations, nor does it offer recommendations regarding the assessment of these patients.

3. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087–106.

The authors of this meta-analysis review the effects of radiation after mastectomy or BCS on disease recurrence and cause-specific mortality in patients with EBC. Several treatment approaches are evaluated: surgery plus radiotherapy versus surgery in the absence of radiotherapy (same amount of surgery in both groups); more surgery versus less surgery in the presence of radiotherapy; and more surgery plus radiotherapy versus less surgery plus radiotherapy.

The investigators demonstrate that radiotherapy provides a substantial benefit in recurrence and mortality rates for women with breast cancer, regardless of the amount of surgery performed. Radiotherapy after BCS reduces local recurrence rates by 19% at 5 years and 5.4% at 15 years and improves both breast cancer–related and overall mortality by 5.4% and 5.3%, respectively. Radiotherapy after mastectomy reduces recurrence risks from 23% to 6% and improves 15-year breast cancer mortality by 5.4%. The investigators report a smaller (4.4%) reduction in all-cause mortality, indicating that there is an excess of non–breast cancer–related mortality. This could reflect the radiotherapy techniques used at the time the studies were performed. Since then, significant advances have been made in radiotherapy technology, making these results inconsistent with current results. This is a major limitation of the analysis. However, the article has several strengths including the long duration of follow-up, large number of trials included, and subgroup analysis of radiotherapy effects according to patient- and disease-related characteristics such as age and nodal status.

4. Micoig JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* 2007;94:1189–200.

This systematic review of several randomized controlled trials reports the evidence regarding the effectiveness of neoadjuvant chemotherapy compared with adjuvant chemotherapy in women with operable breast cancer. The review presents time-to-event data; it also quantitatively assesses the change of surgical needs using neoadjuvant therapy and discusses adverse effects. These are the strengths of this article. Overall survival data available for 4620 women show no survival difference between neoadjuvant and adjuvant chemotherapy. Eleven studies are analyzed for differences in locoregional recurrence rates, which demonstrate a significant difference favoring adjuvant chemotherapy. Of importance, the authors include three studies in which women did not receive surgery after neoadjuvant chemotherapy. It is now recognized that surgery is an important component to the locoregional treatment strategy, despite the timing of chemotherapy administration. Therefore, the results may not accurately reflect what now occurs as standard practice. This is a major limitation of the review. Excluding these three studies decreases the local recurrence rate associated with neoadjuvant treatment. Despite this limitation, the authors provide a good review of data and show that there is a safe, effective alternative to mastectomy for appropriate women who would like to preserve breast tissue.

5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.

This meta-analysis included 194 trials. Women included in the analysis of chemotherapy received CMF or anthracycline-based combination regimens. Women included in the analysis of endocrine therapy received either tamoxifen or ovarian suppression. The results demonstrate that anthracycline-based regimens provide a significant reduction in the annual breast cancer death rate compared with CMF irrespective of HR status, nodal status, and the use of adjuvant tamoxifen. The effect correlates with age, with women younger than 50 having the greatest decrease in annual breast cancer death rates. In women with ER-positive disease, treatment with 5 years of tamoxifen reduces the annual breast cancer death rate. This occurs irrespective of the chemotherapy regimen, age, and HR status, among other factors. Ovarian suppression also reduces breast cancer mortality but is only beneficial in the absence of other therapies.

This overview of randomized trials provides a thorough review and assessment of treatment approaches in EBC. It identifies specific patient populations (according to nodal status, age, and HR status) that may benefit from certain treatment approaches. This is a major strength of the review. Unfortunately, the meta-analysis was performed when studies involving taxanes, trastuzumab, raloxifene, or AIs were in progress and is an inevitable limitation of this overview.

6. Madarnas Y, Trudeau M, Franek JA, McCreedy D, Pritchard KI, Messersmith H. Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: a systematic review. *Cancer Treat Rev* 2008;34:539–57.

Data regarding the use of trastuzumab in the neoadjuvant and adjuvant settings are still immature. Several questions remain regarding its optimal dose, schedule, and duration;

the population for which it should be used; and its long-term efficacy and safety outcomes when used in the EBC and LABC settings. The authors of this article provide an extensive review of evidence supporting the use of trastuzumab as adjuvant and neoadjuvant therapy for women with HER2-expressing breast cancer. Trials that compare trastuzumab with observation and those that evaluate trastuzumab in combination with chemotherapy versus chemotherapy alone are discussed in considerable detail, allowing the reader to gain a comprehensive understanding of the current literature. This is a major strength of the review. The authors also provide a thorough discussion of several questions regarding its use in therapy, which is another major strength of the review.

7. Rabaglio M, Aebi S, Castiglione-Gertsch M. Controversies of adjuvant endocrine treatment for breast cancer and recommendations of the 2007 St Gallen conference. *Lancet Oncology* 2007;8:940–9.

This review provides a detailed discussion of the controversies of adjuvant endocrine therapy. The authors review pertinent investigations that evaluate several hormonal treatment strategies. The authors report that: (1) ovarian ablation in the absence of adjuvant chemotherapy statistically improves DFS and OS in women younger than 50 years; (2) compared with chemotherapy, ovarian ablation demonstrates similar outcomes in women with ER-positive breast cancer; and (3) the addition of tamoxifen to ovarian suppression and the combination of ovarian suppression, tamoxifen, and chemotherapy produce varying results in DFS and OS.

The authors also discuss several large, randomized, comparative trials regarding tamoxifen and AIs in postmenopausal women. The trials compared several regimens: 5 years of tamoxifen with 5 years of an AI; the combination of both approaches (tamoxifen plus an AI) for 5 years; 2–3 years of tamoxifen, followed by an AI to complete 5 years of treatment; and 5 years of tamoxifen, followed by 5 additional years of therapy with an AI. The authors report that the use of an AI is associated with a significant improvement in DFS (but not OS) and that patients should be switched to an AI at some point in adjuvant endocrine treatment.

Data regarding these comparisons are limited. Questions remain concerning the duration of hormonal interventions, the value of combining endocrine approaches, the need for chemotherapy in patients with HR-positive disease who are receiving optimal hormonal suppression, the timing of ovarian suppression in relation to chemotherapy, and the optimal use of AIs in the postmenopausal setting, among others. Due to the limited data comparing these regimens, the authors are unable to provide optimal guidance in using some hormonal strategies. This is an expected limitation of the review. However, the authors do provide a thorough review of the data and give some general recommendations that may be helpful in clinical practice.

8. Cataliotti L, Buzdar AU, Noguchi S, Bines J, Takatsuka Y, Petrakova K, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer. The Pre-Operative “Arimidex” Compared to Tamoxifen (PROACT) Trial. *Cancer* 2006;106:2095–103.

This trial compares anastrozole with tamoxifen as preoperative treatment of postmenopausal women with large operable or potentially operable breast cancer. Women received either anastrozole or tamoxifen for 12 weeks before surgery. The investigators report that the overall response and number of feasible operations after 3 months of endocrine

treatment is higher in the anastrozole group compared with the tamoxifen group, and that anastrozole produces a statistically significant reduction in tumor size and a nonsignificant reduction in axillary LN staging compared with tamoxifen.

The design of the study creates some limitations. Because the investigators allowed the use of chemotherapy in the neoadjuvant setting, the ability to quantify results provided from endocrine therapy alone is confounded. Furthermore, the investigators do not report any demographic data pertaining to the use of chemotherapy. They do not report how many patients received concomitant neoadjuvant chemotherapy, what type of regimens patients received, or if the use of chemotherapy was well balanced between groups. However, one of the strengths of the study design is that patients with varying estrogen and progesterone receptor status were allocated equally between treatment groups. It has been demonstrated that patients with progesterone-negative tumors respond better to an AI versus tamoxifen; therefore, equally allocating these patients among groups would minimize differences in efficacy outcomes because of this predictive characteristic.

9. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years’ adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;366:455–62.

The authors of this article report the combined results of two trials that investigated whether women who receive adjuvant tamoxifen would benefit from changing to an AI. Women included in this analysis underwent surgery with axillary LN dissection or sentinel LN biopsy (with or without adjuvant radiation), followed by either tamoxifen for 5 years or tamoxifen for up to 3 years, followed by an AI for 2–3 years. This analysis of two trials reports that changing from tamoxifen to an AI increases DFS by 40%. The effect on OS is not significantly different 3 years after the switch. However, a longer follow-up is needed to show a significant difference in a trial between two active treatment groups. This presents a major limitation of these data. Another limitation is that more than three-fourths of the women included in the trials had LN-negative disease. The applicability of these data to patients with higher-risk breast cancers is questionable. However, a major strength of this combined analysis includes almost identical inclusion criteria for the patients in both studies. The investigators also subdivided results based on nodal status, histologic grading, age, and HR status, which helps determine if differences in efficacy are seen in certain subpopulations.

10. McArthur HL, Hudis CA. Adjuvant chemotherapy for early-stage breast cancer. *Hematol Oncol Clin North Am* 2007;21:207–22.

The authors of this article provide a thorough review of treatment options for adjuvant chemotherapy. Information regarding the timing of adjuvant chemotherapy, rationale for adjuvant chemotherapy, dose escalation and dose density of chemotherapy, and toxicities of these regimens is discussed in relation to nodal involvement and HR status. A major strength of the article is that the authors provide guidance in choosing the best regimen for an individual patient according to disease-specific characteristics. Patient-specific characteristics (e.g., age, comorbidity) are also important in determining the best treatment approach for a patient. However, this was not discussed and is thus a limitation of the review.

11. De Laurentiis M, Canello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;26:44–52.

The authors of this meta-analysis review randomized trials that evaluate the efficacy of incorporating a taxane, given concurrently or sequentially, into an anthracycline-based regimen in women with EBC. They compare the overall effect of taxanes on both the risk of recurrence and the risk of death. The investigators found that the estimated absolute reduction from taxane therapy is 5% for DFS and 3% for OS at 5 years. The investigators also depicted results according to the taxane received, taxane schema received (sequential vs. combination), LN status, ER status, and age/menopausal status. This is a major strength of the study. However, variations in study criteria, such as the taxane regimens and schemas used, the LN status of patients, and the end points of each study, complicate the interpretation of these data. Despite these limitations, the investigators conclude that these data are sufficient to support the use of taxanes in the adjuvant setting of EBC.

12. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006;24:5381–7.

The investigators of this randomized clinical trial demonstrate that 5-year DFS rates in women who receive adjuvant therapy with TC are significantly higher than in those who receive the standard AC regimen. There is also a trend in improved OS that favors the TC regimen. A total of 1026 women were included in the trial and randomized to two treatment groups that were well balanced for age, ethnicity, stage of disease, tumor histology, HR status, and nodal status. This is a major strength of the study design. More than 70% of women included in the study had HR-positive disease, and about 90% of women had fewer than three LNs containing disease; this is one weakness of the study design. Because most of the patients had HR-positive disease and a limited number of affected LNs, the results of this study cannot be confidently extrapolated to high-risk populations. Furthermore, TC was compared with AC cycled every 3 weeks. It is now well established that dose-dense AC provides better outcomes than AC given every 3 weeks. Finally, the duration of follow-up in the study was short. This creates the question of whether the difference in OS would become statistically significant with longer follow-up.

13. Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol* 2005;23:3686–96.

A total of 3060 patients were randomized to receive standard adjuvant chemotherapy with AC or AC, followed by paclitaxel. The investigators report that adding paclitaxel to standard therapy results in a 17% reduction in the risk of DFS and a nonsignificant 7% reduction in the risk of death. The lack of statistical significance may be attributed to the short median duration of study follow-up, which presents a limitation of the study design. Another limitation is that only 4% of patients with 10 or more positive LNs were included. More than 70% of patients had only one to three positive LNs. Therefore, the applicability of these data to higher-risk patients is less clear. Furthermore, the dose of paclitaxel used

in this trial was higher than the approved dose for advanced breast cancer, although this did not appear to affect the results. This may have been because of an increased incidence of peripheral neuropathies or other toxicities, which necessitated dose reductions.

One of the strengths of the study design is that the investigators report breast cancers with HR-positive and HR-negative receptors. The effect of HR status on response to chemotherapy is a current controversy. The authors of this study were able to observe that although recurrence rate reductions are smaller in women with HR-positive disease than in those with HR-negative disease, there is no evidence of a significant impact of HR status on treatment response. Unfortunately, the study is not designed to investigate this question; therefore, absolute conclusions cannot be made.

14. Citron ML, Berry DA, Cirincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21:1431–9.

This trial evaluated the effect of dose intensity and schema on DFS and OS outcomes in women with LN-positive EBC. Results revealed that dose-dense treatment improves DFS and OS, despite the sequence of the taxane given, number of positive LNs, tumor size, and menopausal status. A major strength of this study is the number and types of dosing strategies investigated. Women were randomized into four treatment arms: doxorubicin followed by paclitaxel followed by cyclophosphamide; dose-dense doxorubicin followed by paclitaxel followed by cyclophosphamide; AC followed by paclitaxel; and dose-dense AC followed by paclitaxel. The arms were also balanced for number of positive LNs, age, menopausal status, HR status, tumor size, surgery, and tamoxifen therapy. The investigators reported results after adjusting for number of positive LNs, tumor size, and menopausal status. This is a strength because it can help divide patients into recurrence risk categories; subsequently, it can be used to determine if certain regimens offer advantages in certain risk populations.

Major weaknesses of this trial include the duration of median follow-up (36 months); subdivision of patients into only two groups based on tumor size (i.e., those less than or greater than 2 cm); and only 11% to 12% of women had 10 or more positive LNs. This limits the ability to extrapolate the results to subgroups of high-risk patients. Furthermore, tamoxifen was recommended, but not required, in premenopausal women with HR-positive tumors. This is a major limitation of the study design because the use of hormonal therapy in women with HR-positive tumors is a standard of care. In addition, postmenopausal women received tamoxifen without respect to HR status, although it has been established that endocrine therapy does not provide benefits for women with HR-negative breast cancer.

15. Hanrahan EO, Hennessy BT, Valero V. Neoadjuvant systemic therapy for breast cancer: an overview and review of recent clinical trials. *Expert Opin Pharmacother* 2005;6:1477–91.

Numerous studies have investigated the use of different chemotherapy approaches in breast cancer. The authors of this article provide a detailed review of recent studies investigating the use of chemotherapy in the neoadjuvant setting. They also review comparisons of neoadjuvant and adjuvant chemotherapy in terms of response in the axilla and

the breast and in the setting of BCS, as well as on DFS and OS.

Major strengths of this review include the comprehensive inclusion of clinical trials that investigate the use of anthracycline-based regimens, taxane-based regimens, and trastuzumab-based regimens in this setting; the subdivision of clinical data into specific categories, such as dose-dense therapy; and the discussion of controversial topics, including the use of pathologic response rates as a surrogate marker of long-term outcomes, factors associated with response to neoadjuvant chemotherapy, and methods to monitor response to neoadjuvant chemotherapy. The authors also provide their expert opinion and conclusions. These opinions may aid clinicians in clinical practice and is another strength of the review, especially since comparative trials are limited and detailed concrete treatment pathways are yet to be defined.

16. Monnier A. Clinical management of adverse events in adjuvant therapy for hormone-responsive early breast cancer. *Ann Oncol* 2007;18(Suppl 8):viii36–viii44.

Long-term adjuvant endocrine therapy decreases the risk of breast cancer mortality and recurrence. However, the endocrine agents used in breast cancer (tamoxifen and the AIs) have several associated adverse effects that may compromise adherence. This review discusses the mechanisms behind the adverse events related to each endocrine group and provides specific recommendations regarding treatment of hot flashes and other gynecologic symptoms, arthralgias and myalgias, bone loss, and cardiovascular effects as well as methods to avoid thromboembolic events and endometrial cancer. This is a major strength of the review. Unfortunately, in some cases, limited data exist for managing these adverse effects in patients with breast cancer. Therefore, the authors' ability to recommend treatment strategies was limited.

17. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results. *Cancer* 2008;112:1001–10.

The investigators of this trial evaluated the use of bisphosphonate therapy in women treated with letrozole 2.5 mg/day for 5 years. Women were randomized to receive zoledronic acid 4 mg intravenously every 6 months initiated at two different points in therapy. The first group received zoledronic acid at the start of letrozole therapy; the second received it after the baseline spine or hip T-score decreased below -2.0 , a nontraumatic clinical fracture occurred, or an asymptomatic fracture was discovered. The results of the trial demonstrate that at 12 months, the addition of zoledronic acid prevents bone loss in postmenopausal women and that more bone loss occurs when bisphosphonate therapy is delayed. These data support the early initiation of therapy. There were no differences in the rate of fractures between groups, which confounds the ability to make absolute recommendations. This limits the results of the study. The short length of follow-up after randomization (12 months) allowed only two doses of zoledronic acid at most, which is another major limitation of the study design. This may contribute to the reason that no differences in fracture rates were observed. In any case, these authors offer information regarding the appropriate approach to manage AI-induced bone loss.

18. Lee MC, Newman LA. Management of patients with locally advanced breast cancer. *Surg Clin North Am* 2007;87:379–98.

The authors extensively reviewed the management of patients with LABC. By discussing the evolution of treatment options in LABC, controversies that have evolved, and preoperative systemic regimens used in this setting, the authors enable the reader to gain a comprehensive understanding of the principles used in the optimal management of LABC. This is a major strength of the review. Various preoperative systemic regimens have been investigated in this setting. Unfortunately, many of these regimens have not been directly compared with one another. This has created several questions in clinical practice. Two weaknesses of the review include the lack of discussion regarding the clinical trials investigating these regimens and the lack of discussion regarding current controversies specific to systemic therapy. Furthermore, the authors do not comment on trials currently under way. Results of these trials could potentially change future practices or solidify evidence for current ones.

19. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: breast cancer, v.1.2009. Available at www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed February 25, 2009.

This comprehensive practice guideline provides treatment pathways that depict treatment decisions in a step-by-step approach. These are major strengths of the guideline. During the past 5 years, several new treatment strategies have been identified. Many of these regimens have not been directly compared and, in some cases, long-term safety data are lacking. Therefore, in some cases, the clinician may be faced with difficult decisions regarding the best therapeutic approach. This guideline provides a thorough review of the primary literature, identifies limitations of these data, and discusses current controversies. It then provides literature-based treatment recommendations and, in controversial cases, provides recommendations from consensus opinion among experts in the field. These recommendations aid the practitioner in choosing the regimens most effective and safe for patients, which is another major strength of the guideline.

SELF-ASSESSMENT QUESTIONS

1. P.S. is a 69-year-old woman with a history of New York Heart Association class II heart failure, coronary artery disease, and hypertension. She was recently given a diagnosis of T2N1M0 breast cancer. Additional diagnostic tests reveal that her tumor is hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) negative. In addition to mastectomy and radiation, which one of the following is the best chemotherapy option for P.S. at this time?
 - A. Doxorubicin and cyclophosphamide (AC) for four cycles, followed by paclitaxel for four cycles.
 - B. Cyclophosphamide, methotrexate, and fluorouracil (CMF) for six cycles.
 - C. Docetaxel, doxorubicin, and cyclophosphamide (TAC) for six cycles.
 - D. Docetaxel plus cyclophosphamide (TC) for four cycles.
2. J.W. is a 64-year-old woman recently given a diagnosis of stage IIA breast cancer. She has a medical history significant for type 2 diabetes mellitus, deep vein thrombosis, and osteopenia (T-score of -1). Which one of the following is the best endocrine option for J.W.?
 - A. Tamoxifen for 5 years.
 - B. Tamoxifen for 2 years, followed by letrozole for an additional 3 years.
 - C. Anastrozole for 5 years.
 - D. Goserelin for 2 years, followed by anastrozole for 3 years.
3. Tamoxifen for 2 years, followed by anastrozole for 3 years.
4. Tamoxifen for 5 years, followed by anastrozole for 3 years.
5. P.M. is a 51-year-old woman who recently was given a diagnosis of breast cancer. Examination of her cancer reveals that her tumor is 1 cm in size, lymph node (LN) negative, HR negative, poorly differentiated (grade 3 differentiation), and positive for HER2 overexpression. P.M.'s medical history is not significant; however, she has a strong family history significant for colon cancer, lung cancer, and breast cancer in her paternal grandmother. Which one of the following factors should have the greatest consideration when determining P.M.'s need for adjuvant therapy?
 - A. Stage of breast cancer.
 - B. Histologic tumor characteristics.
 - C. Family history of cancer.
 - D. Age.
6. J.T. is a 53-year-old postmenopausal woman given a diagnosis of T1N1M0 breast cancer. She will begin therapy with conventional AC, followed by paclitaxel. This will be followed by 5 years of tamoxifen therapy. A newly graduated nurse will infuse her chemotherapy today. Which one of the following concepts is best for the nurse to be educated about?
 - A. Growth factor support to prevent febrile neutropenia.
 - B. Bisphosphonate therapy to prevent endocrine-related bone loss.
 - C. Aprepitant to prevent chemotherapy-induced nausea and vomiting.
 - D. Gabapentin therapy to prevent peripheral neuropathy.

Questions 3 and 4 pertain to the following case.

T.T. is a 56-year-old perimenopausal woman with a medical history significant for appendectomy, coronary artery disease, and gout. She recently received a diagnosis of T3N2M0 breast cancer. Additional prognostic tests reveal that her tumor is HR positive, poorly differentiated, and negative for HER2 overexpression.

3. In addition to mastectomy and radiation, which one of the following systemic treatment approaches is best for T.T. at this time?
 - A. AC for four cycles, followed by paclitaxel for four cycles.
 - B. Cyclophosphamide, epirubicin, and fluorouracil for six cycles.
 - C. TC for four cycles.
 - D. CMF for six cycles.
4. T.T. elects to receive adjuvant endocrine therapy. Which one of the following endocrine agent regimens is the best option for her at this time?
 - A. Letrozole for 5 years, followed by tamoxifen for 5 years.
 - B. Letrozole for 3 years, followed by tamoxifen for 2 years.
 - C. Tamoxifen for 2 years, followed by anastrozole for 3 years.
 - D. Tamoxifen for 5 years, followed by anastrozole for 5 years.
5. P.M. is a 51-year-old woman who recently was given a diagnosis of breast cancer. Examination of her cancer reveals that her tumor is 1 cm in size, lymph node (LN) negative, HR negative, poorly differentiated (grade 3 differentiation), and positive for HER2 overexpression. P.M.'s medical history is not significant; however, she has a strong family history significant for colon cancer, lung cancer, and breast cancer in her paternal grandmother. Which one of the following factors should have the greatest consideration when determining P.M.'s need for adjuvant therapy?
 - A. Stage of breast cancer.
 - B. Histologic tumor characteristics.
 - C. Family history of cancer.
 - D. Age.
6. J.T. is a 53-year-old postmenopausal woman given a diagnosis of T1N1M0 breast cancer. She will begin therapy with conventional AC, followed by paclitaxel. This will be followed by 5 years of tamoxifen therapy. A newly graduated nurse will infuse her chemotherapy today. Which one of the following concepts is best for the nurse to be educated about?
 - A. Growth factor support to prevent febrile neutropenia.
 - B. Bisphosphonate therapy to prevent endocrine-related bone loss.
 - C. Aprepitant to prevent chemotherapy-induced nausea and vomiting.
 - D. Gabapentin therapy to prevent peripheral neuropathy.
7. K.W. is a healthy 49-year-old woman with no significant medical history. She is given a diagnosis of a T4N1M0, HR-positive, HER2-positive, well-differentiated (grade 1) breast cancer. In addition to trastuzumab and radiation, which one of the following is the best treatment option for K.W.?
 - A. Surgery, followed by chemotherapy; then endocrine therapy for 5 years.
 - B. Endocrine therapy for 4 months, followed by surgery; then endocrine therapy to complete 5 years of total endocrine therapy.
 - C. Chemotherapy, followed by surgery; then endocrine therapy for 5 years.
 - D. Endocrine therapy for 4 months, followed by surgery; then chemotherapy.
8. J.S. is a 65-year-old woman with T1N0M0 breast cancer. She has a medical history significant for hypertension,

- chronic obstructive pulmonary disease, osteopenia (bone mineral density T-score of -1), and protein S deficiency. She was recently treated with mastectomy, followed by radiation and chemotherapy with CMF for six cycles. J.S. will now receive adjuvant endocrine therapy. Knowing J.S.'s history of osteopenia, the physician wants to prevent additional bone loss. Which one of the following is the best approach for J.S.?
- Anastrozole 1 mg/day plus calcium and vitamin D supplementation.
 - Tamoxifen 10 mg/day plus calcium and vitamin D supplementation.
 - Tamoxifen 10 mg/day plus zoledronic acid 4 mg intravenously every 6 months.
 - Letrozole 2.5 mg/day plus zoledronic acid 4 mg intravenously every 6 months.
- L.Z. is a 55-year-old woman with recently diagnosed T3N1M0 early breast cancer (EBC). Her breast cancer is moderately differentiated (grade 2), HR positive, and negative for HER2 overexpression. She has a family history significant for breast cancer in her maternal aunt, who received the diagnosis at age 60, and breast cancer in her paternal grandmother, diagnosed at age 69. Which one of the following factors is most associated with a poor prognosis in L.Z.?
 - Stage of her breast cancer.
 - Histologic characteristics of her primary tumor.
 - Her family history of breast cancer.
 - Her age.
 - A.S., a 69-year-old woman with diabetes mellitus, hypertension, and chronic obstructive pulmonary disease, has a diagnosis of T4N0M0 breast cancer. Analysis of her tumor reveals that it is moderately differentiated (grade 2), ER and progesterone receptor positive, and HER2 negative. In addition to radiation therapy, which one of the following is the best approach to manage her cancer at this time?
 - Endocrine therapy for 3 months, followed by surgery and chemotherapy for four to six cycles.
 - Chemotherapy for four to six cycles, followed by surgery and endocrine therapy for 5 years.
 - Endocrine therapy for 3 months, followed by surgery and endocrine therapy to complete 5 years of therapy.
 - Surgery, followed by endocrine therapy for 5 years.
 - D.J. is a 58-year-old perimenopausal woman with early-stage breast cancer. Her primary tumor is 0.5 cm, and her LNs are pathologically negative according to her sentinel LN biopsy. Her breast cancer is well differentiated (grade 1), positive for ERs, and negative for progesterone receptors and HER2. In addition to lumpectomy and radiation, which one of the following adjuvant regimens is best for D.J. at this time?
 - CMF for six cycles, followed by anastrozole for 5 years.
 - Tamoxifen for 5 years, followed by letrozole for 5 years.
 - Fluorouracil, doxorubicin, and cyclophosphamide for four cycles, followed by tamoxifen for 5 years.
 - Anastrozole for 5 years.
 - P.C. is a 69-year-old postmenopausal woman with stage IIB breast cancer and a medical history significant for hypertension, diabetes mellitus, fibromyalgia, and rheumatoid arthritis. She has undergone mastectomy and systemic adjuvant chemotherapy; she will begin adjuvant endocrine therapy. She is concerned about some of the adverse effects associated with hormone therapy and the ways in which they will affect her current medical conditions and associated symptoms. Given her medical history and concerns, which one of the following is the best therapeutic option for P.C. at this time?
 - Anastrozole 1 mg/day orally.
 - Goserelin 3.6 mg subcutaneously every 28 days.
 - Tamoxifen 20 mg/day orally.
 - Letrozole 2.5 mg/day orally.
 - T.D., a 59-year-old postmenopausal woman, comes to the clinic with complaints of a painless, nonmobile lump in her right breast. Her examination reveals a 3-cm invasive ductal carcinoma. Pathologic tests show that it is negative for HRs but positive for HER2 and LN involvement. T.D. has a medical history significant for diabetes mellitus, hypertension, and Hodgkin's lymphoma, which was treated with mediastinal radiation therapy. T.D. and her oncologist discuss potential treatment options. During this discussion, T.D. reveals that she would like to conserve breast tissue if possible. In addition to trastuzumab therapy, which one of the following approaches is best for T.D.?
 - CMF for six cycles, followed by lumpectomy.
 - Mastectomy, followed by dose-dense AC for four cycles; then paclitaxel for four cycles.
 - Fluorouracil, doxorubicin, and cyclophosphamide for six cycles, followed by lumpectomy.
 - Mastectomy, followed by TC for four cycles.
 - A.J.B. is a 70-year-old postmenopausal woman who has been receiving tamoxifen 20 mg/day for the past 4 months for her stage IIB, HR-positive, HER2-negative breast cancer. She has been admitted to the hospital with complaints of shortness of breath, chest pain, and dizziness. She is given a diagnosis of pulmonary embolism and concomitant right lower extremity deep vein thrombosis. She is initiated on intravenous unfractionated heparin and warfarin therapy. Which one of the following approaches is best for A.J.B.'s breast cancer therapy?
 - Discontinue tamoxifen and begin exemestane 25 mg/day orally.
 - Decrease tamoxifen to 10 mg/day orally and increase the target international normalized ratio to 3.5.

- C. Discontinue tamoxifen and begin anastrozole 1 mg/day orally.
- D. Continue tamoxifen 20 mg/day but increase the target international normalized ratio to 3.5.
15. M.R., a 68-year-old woman, undergoes mammography, ultrasound examination, and core needle biopsy of the breast. Results reveal a T1N1M0 breast cancer. She was initially treated with a mastectomy, radiation, and chemotherapy with AC for four cycles. She has received adjuvant endocrine therapy with anastrozole 1 mg/day orally for the past 2 months. Today, she presents to the clinic with complaints of occasional mild hot flashes. Which one of the following is the best approach to M.R.'s complaints?
- Discontinue anastrozole and begin letrozole 2.5 mg/day orally.
 - Discontinue anastrozole and begin tamoxifen 20 mg/day orally.
 - Maintain anastrozole and start clonidine 0.1 mg/day orally.
 - Maintain anastrozole and add venlafaxine extended release 37.5 mg/day orally.
16. H.C. is a 45-year-old woman with a medical history significant for hypertension, psoriasis, and hypercholesterolemia. Her family history is significant for breast cancer in her mother, diagnosed at age 69; and breast cancer in her paternal aunt, diagnosed at age 59. H.C. was given a diagnosis of T1N1M0 breast cancer 4 years ago. She was treated with mastectomy and radiation and was then initiated on tamoxifen 20 mg/day orally. She comes to the clinic today with complaints of bloody vaginal discharge. Which one of the following causes the most concern regarding H.C.'s vaginal discharge?
- Tamoxifen.
 - Perimenopause.
 - Infection.
 - Endometrial cancer.
17. P.N. is a 67-year-old postmenopausal woman with a medical history significant for congestive heart failure, diabetes mellitus, and arthritis. Her diagnosis is T2N1M0 breast cancer. Analysis of her tumor reveals that it is ER, progesterone receptor, and HER2 positive. In addition to surgery, radiation, and endocrine therapy, which one of the following is the most appropriate adjuvant systemic option for P.N. at this time?
- Fluorouracil, doxorubicin, and cyclophosphamide for six cycles followed by trastuzumab therapy.
 - TAC for four cycles with concurrent trastuzumab therapy.
 - CMF for six cycles followed by trastuzumab therapy.
 - Docetaxel and carboplatin with concurrent trastuzumab therapy.
18. S.R. is a 62-year-old woman with a medical history significant for depression, gastroesophageal reflux disease, diabetes mellitus, coronary artery bypass graft, gastrointestinal bleeding, and, most recently, T2N1M0 breast cancer. Her medication history consists of ranitidine, insulin, and calcium and vitamin D supplementation. She recently completed dose-dense chemotherapy with AC and began sequential paclitaxel therapy. She returns to the clinic today after two doses of paclitaxel with complaints of painful numbness and tingling in her hands and feet. Which one of the following is the best approach to manage S.R.'s symptoms?
- Ibuprofen 600 mg orally three times daily.
 - Transdermal fentanyl 25-mcg patch placed every 3 days.
 - Oxycodone 5 mg orally every 4 hours as needed for pain.
 - Acetaminophen 500 mg orally twice daily.
19. C.O., an 82-year-old woman, was recently given a diagnosis of breast cancer. Mammography, core needle biopsy, axillary LN staging, and pathologic analysis of her cancer reveal that she has a T1N0M0 breast cancer that is HR positive, HER2 negative, and well differentiated. C.O. also has a history of hypertension, congestive heart failure, pulmonary embolism, and depression. Her performance status is relatively poor; however, she seeks treatment of her breast cancer. Which one of the following is the best primary treatment option for C.O. at this time?
- Mastectomy, followed by radiation; then AC for four cycles, followed by paclitaxel for four cycles and anastrozole for 5 years.
 - Tamoxifen for 4 months, followed by lumpectomy and radiation.
 - Mastectomy, followed by radiation and CMF six cycles; then tamoxifen for 5 years.
 - Mastectomy, followed by radiation and anastrozole for 5 years.
20. B.S. is a 57-year-old woman given a diagnosis of T1N1M0 breast cancer about 2 years ago. She was treated with lumpectomy, radiation therapy, and chemotherapy. Since then, she has been taking tamoxifen 20 mg/day orally. B.S. informs the pharmacist that she currently takes gemfibrozil for hypercholesterolemia, atenolol for hypertension, topical emollients for vaginal dryness, calcium and vitamin D supplementation to maintain bone mass, and, recently, paroxetine for "mood." Which one of the following concerns is most important for the pharmacist to discuss with the oncologist?
- Menopausal status.
 - Treatment of her mood.
 - Vaginal symptoms.
 - Bone mineral density.