(Avastin) has improved the response rate and response duration to paclitaxel. Objective responses in previously treated patients may also be seen with gemcitabine, vinca alkaloids, capecitabine, vinorelbine, and oral etoposide, as well as a new class of agents, epothilones. There are few comparative trials of one agent versus another in metastatic disease. It is a sad fact that choices are often influenced by aggressive marketing of new very expensive agents that have not been shown to be superior to other generic agents. Platinum-based agents have become far more widely used in both the adjuvant and advanced disease settings for some breast cancers, particularly those of the "triple-negative" subtype.

HIGH-DOSE CHEMOTHERAPY INCLUDING AUTOLOGOUS BONE MARROW TRANSPLANTATION Autologous bone marrow transplantation combined with high doses of single agents can produce objective responses even in heavily pretreated patients. However, such responses are rarely durable and do not alter the clinical course for most patients with advanced metastatic disease.

STAGE III BREAST CANCER

Between 10 and 25% of patients present with so-called locally advanced, or stage III, breast cancer at diagnosis. Many of these cancers are technically operable, whereas others, particularly cancers with chest wall involvement, inflammatory breast cancers, or cancers with large matted axillary lymph nodes, cannot be managed with surgery initially. Although no randomized trials have shown any survival benefit for neoadjuvant regimens as compared to adjuvant therapy, this approach has gained widespread use. More than 90% of patients with locally advanced breast cancer show a partial or better response to multidrug chemotherapy regimens that include an anthracycline. Early administration of this treatment reduces the bulk of the disease and frequently makes the patient a suitable candidate for salvage surgery and/or radiation therapy. These patients should be managed in multimodality clinics to coordinate surgery, radiation therapy, and systemic chemotherapy. Such approaches produce long-term disease-free survival in about 30–50% of patients. The neoadjuvant setting is also an ideal time to evaluate the efficacy of novel treatments because the effect on the tumor can be directly assessed.

BREAST CANCER PREVENTION

Women who have one breast cancer are at risk of developing a contralateral breast cancer at a rate of approximately 0.5% per year. When adjuvant tamoxifen or an aromatase inhibitor is administered to these patients, the rate of development of contralateral breast cancers is reduced. In other tissues of the body, tamoxifen has estrogen-like effects that are beneficial, including preservation of bone mineral density and long-term lowering of cholesterol. However, tamoxifen has estrogen-like effects on the uterus, leading to an increased risk of uterine cancer (0.75% incidence after 5 years on tamoxifen). Tamoxifen also increases the risk of cataract formation. The Breast Cancer Prevention Trial (BCPT) revealed a >49% reduction in breast cancer among women with a risk of at least 1.66% taking the drug for 5 years. Raloxifene has shown similar breast cancer prevention potency but may have different effects on bone and heart. The two agents have been compared in a prospective randomized prevention trial (the Study of Tamoxifen and Raloxifene [STAR] trial). The agents are approximately equivalent in preventing breast cancer with fewer thromboembolic events and endometrial cancers with raloxifene; however, raloxifene did not reduce noninvasive cancers as effectively as tamoxifen, so no clear winner has emerged. A newer selective estrogen receptor modulator (SERM), lasofoxifene, has been shown to reduce cardiovascular events in addition to breast cancer and fractures, and further studies of this agent should be watched with interest. It should be recalled that prevention of contralateral breast cancers in women diagnosed with *one* cancer is a reasonable surrogate for breast cancer prevention because these are second primaries not recurrences. In this regard, the aromatase inhibitors are all considerably more effective than tamoxifen; however, they are not approved for primary breast cancer prevention. It remains puzzling that agents with the safety profile of raloxifene, which can reduce breast cancer risk by 50% with additional benefits in preventing osteoporotic fracture, are still so infrequently prescribed. They should be far more commonly offered to women than they are.

NONINVASIVE BREAST CANCER

Breast cancer develops as a series of molecular changes in the epithelial cells that lead to ever more malignant behavior. Increased use of mammography has led to more frequent diagnoses of noninvasive breast cancer. These lesions fall into two groups: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (lobular neoplasia). The management of both entities is controversial.

Ductal Carcinoma In Situ Proliferation of cytologically malignant breast epithelial cells within the ducts is termed *DCIS*. Atypical hyperplasia may be difficult to differentiate from DCIS. At least one-third of patients with untreated DCIS develop invasive breast cancer within 5 years. However, many low-grade DCIS lesions do not appear to progress over many years; therefore, many patients are overtreated. Unfortunately there is no reliable means of distinguishing patients who require treatment from those who may be safely observed. For many years, the standard treatment for this disease was mastectomy. However, treatment of this condition by lumpectomy and radiation therapy gives survival that is as good as the survival for invasive breast cancer treated by mastectomy. In one randomized trial, the combination of wide excision plus irradiation for DCIS caused a substantial reduction in the local recurrence rate as compared with wide excision alone with negative margins, although survival was identical in the two arms. No studies have compared either of these regimens to mastectomy. Addition of tamoxifen to any DCIS surgical/radiation therapy regimen further improves local control. Data for aromatase inhibitors in this setting are not available.

Several prognostic features may help to identify patients at high risk for local recurrence after either lumpectomy alone or lumpectomy with radiation therapy. These include extensive disease; age <40; and cytologic features such as necrosis, poor nuclear grade, and comedo subtype with overexpression of *erbB2*. Some data suggest that adequate excision with careful determination of pathologically clear margins is associated with a low recurrence rate. When surgery is combined with radiation therapy, recurrence (which is usually in the same quadrant) occurs with a frequency of ≤10%. Given the fact that half of these recurrences will be invasive, about 5% of the initial cohort will eventually develop invasive breast cancer. A reasonable expectation of mortality for these patients is about 1%, a figure that approximates the mortality rate for DCIS managed by mastectomy. Although this train of reasoning has not formally been proved valid, it is reasonable to recommend that patients who desire breast preservation, and in whom DCIS appears to be reasonably localized, be managed by adequate surgery with meticulous pathologic evaluation, followed by breast irradiation and tamoxifen. For patients with localized DCIS, axillary lymph node dissection is unnecessary. More controversial is the question of what management is optimal when there is any degree of invasion. Because of a significant likelihood (10–15%) of axillary lymph node involvement even when the primary lesion shows only microscopic invasion, it is prudent to do at least a sentinel lymph node sampling for all patients with any degree of invasion. Further management is dictated by the presence of nodal spread.

Lobular Neoplasia Proliferation of cytologically malignant cells within the lobules is termed *lobular neoplasia*. Nearly 30% of patients who have had adequate local excision of the lesion develop breast cancer (usually infiltrating ductal carcinoma) over the next 15–20 years. Ipsilateral and contralateral cancers are equally common. Therefore, lobular neoplasia may be a premalignant lesion that suggests an elevated risk of subsequent breast cancer, rather than a form of malignancy itself, and aggressive local management seems unreasonable. Most patients should be treated with an SERM or an aromatase inhibitor (for postmenopausal women) for 5 years and