In 1995, it is projected that there will be 183,400 new cases of breast cancer and 46,240 deaths from the disease, despite an emphasis on early detection [1]. Fewer than 10% of patients will present with metastatic disease, but nearly 50% of newly diagnosed patients may eventually develop it. Unfortunately, advanced breast cancer is incurable. In a classic study of untreated patients, the median survival was 2.7 years from the onset of symptoms [2].

**Molecular Events in Breast Cancer Metastasis**

**Diagnostic Workup**

**Treatment**

**Conclusions**

**References**

Recent data from work on cell lines and tumor specimens are beginning to elucidate a complex interaction between the tumor cell and its microenvironment. For a cancer cell to metastasize, a series of disparate events must occur. The cancer cell must penetrate various basement membranes, degrade the underlying mesenchymal tissues, gain access to blood and lymph vessels, and enter the stroma of the target organ [4]. Other important events include paracrine stimulation of growth factor receptors (possibly by the surrounding stromal cells), angiogenesis to support tumor growth, and the cancer cell’s evasion of host immune surveillance.

Once the mechanisms of breast cancer metastasis are understood, they will become new targets for therapy. A number of experimental models of metastasis are under study [5-7]. Table 1 lists some important targets for phase I trials. Many human cancers, including breast cancer, can be regarded as stromal-dependent tumors [8]; disabling essential mechanisms that these cancers need for growth and support may represent an approach to their treatment.

<table>
<thead>
<tr>
<th>Target</th>
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<tbody>
<tr>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>c-erbB-2 (HER2/neu) overexpression</td>
</tr>
<tr>
<td>Insulin-like growth factor receptor</td>
</tr>
<tr>
<td>Matrix metalloprotease</td>
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<tr>
<td>Angiogenesis</td>
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</table>

1: Selected Molecular Targets and Mechanisms in Breast Cancer
**History:** Once metastatic disease is suspected, careful evaluation of the primary disease history, current symptoms, and existing comorbid disease is essential. The history of the primary disease should include a review of the initial presentation, stage of disease, hormone-receptor status, pathology report, and treatment modalities employed. It may be helpful to review the primary histologic material to confirm the exact tumor type, estrogen and progesterone receptor status, and extent of nodal metastasis. Knowledge of the initial tumor type may yield clues about the sites of disease. For instance, infiltrating ductal carcinoma most commonly involves the lungs, pleura, and brain, whereas infiltrating lobular carcinoma most commonly involves the bone marrow, peritoneum, and retroperitoneal structures, such as the ureters [9]. Other ancillary information, such as DNA ploidy, S-phase fraction, and the presence of oncoprotein products, such as c-erbB-2 (HER-2/neu) or p53, has been studied in primary breast cancer [10], but the influence of these factors on metastatic disease progression is unclear. However, among patients who develop extraosseous metastatic disease, those with highly aneuploid tumors at initial presentation have significantly shorter survival than do patients with diploid tumors at initial presentation [11].

The length of the disease-free interval and the menopausal status should be ascertained. Information on hot flashes, cyclic breast tenderness, premenstrual symptoms, serum follicle-stimulating hormone/luteinizing hormone (FSH/LH), and vaginal cytology is helpful in assessing the menstrual status of women who have undergone a hysterectomy.

Any current symptoms should be carefully evaluated to assess potential metastatic sites and tumor burden. Pain, weight loss, activity constraints, nutritional status, dental health, and psychological factors are also important in determining the optimal treatment. Any coexisting medical conditions should be noted because they may affect the choice of chemotherapeutic agents.

**Physical Examination:** A comprehensive physical examination is essential for establishing the initial baseline status. The usual sites of metastasis, including soft tissues, bones, lungs, and liver, should be assessed. Evaluation of the soft tissues includes a careful survey of all the lymph-node basins of the upper torso, with documentation of the size and location of enlarged nodes and assessment of the chest wall, operative site, and all breast tissue. These areas should be examined while the patient is in both seated and recumbent positions. Photographs or diagrams of these areas often add invaluable information for subsequent comparison. A complete neurologic examination can determine the need for specific diagnostic imaging. Ascites caused by peritoneal metastases is less common but not rare.

**Laboratory Tests:** A basic laboratory evaluation includes a complete blood count with differential, liver and renal function tests, and serum calcium determination. In addition, carcinoembryonic antigen (CEA) and CA 15-3 are potentially helpful in detecting or monitoring metastatic disease. CEA levels are elevated in 40% to 50% of patients with metastases [12,13]. Benign, low elevations (3 to 10 ng/mL) can be found in patients with inflammatory disease of the gastrointestinal tract, in smokers with chronic bronchitis, and in patients with cystic breast disease [14]. The CA 15-3 test is a combination of two monoclonal antibodies bearing two reactive determinants directed against DF3 and MAM-6 antigens expressed on the mammary epithelial cells [12,15]. CA 15-3, which is much more sensitive than CEA, is elevated in 70% to 85% of patients with metastases. The false-positive rate of the CA 15-3 test is similar to that with CEA [12,15]. Unfortunately, the CA 15-3 test is not approved by the US Food and Drug Administration for evaluation of breast cancer.

**Diagnostic Imaging:** The chest radiograph is usually sufficient to assess the lungs unless there is a compressed bronchus or solitary lesion or the disease is primarily mediastinal. In addition to liver parenchymal involvement, metastases to periporal nodes with compression of the biliary tree or hepatic/portal vessels may also occur; these metastases are best detected by computed tomographic scanning or ultrasonography. The liver-spleen scan is insufficiently detailed and should not be used. Hydroureter or hydronephrosis is the most common indication of retroperitoneal metastases, particularly in patients with signet-ring or lobular variants. Only 30% to 60% of patients with a true-positive bone scan have increased alkaline phosphatase levels [16,17]. Conversely, only 20% of patients with elevated alkaline phosphatase levels are disease free [16].

If the bone scan shows areas of abnormal uptake, radiographs of the affected sites are necessary to confirm metastatic disease and to exclude benign etiologies. Impending fractures in the weight-bearing bones, such as the femur or humerus (if the patient is using crutches), or an unstable spine must be ruled out. Radiographic evaluation of the brain, leptomeninges, and spinal cord has a low yield unless the patient is symptomatic or has an abnormal neurologic finding.
**Pathology:** The histologic slides of the primary tumor should be reviewed and compared with biopsy results of lesions suspected of being metastases. Patients with solitary lesions, easily accessible lesions that may be confused with benign processes (such as chest-wall or lymph-node abnormalities), and suspicious lesions in patients with a disease-free interval longer than 5 years should undergo biopsy to confirm or rule out metastatic breast cancer. Estrogen and progesterone receptor status should be evaluated. Autopsy data from a 1993 study showed that second primary nonmammary malignancies, most commonly of the female genital and gastrointestinal systems, occurred in 11% of patients with breast cancer at a mean interval of nearly 7 years after diagnosis of primary breast cancer; half occurred in the first 4 years following diagnosis. In this series, the nonmammary primary tumor was the cause of death in 54% of patients, whereas breast cancer was the cause of death in 29% [18].

**Treatment**

The selection of treatment is guided by the results of the previous evaluations, common sense, and the realization that metastatic breast cancer differs greatly in its clinical course from one patient to another. Reports of long-term follow-up in the era predating effective systemic therapy showed that a small fraction of patients survive for 10, 15, or even 20 years [2]. Metastatic disease often follows one of two patterns [19,20]. The first pattern is a relatively asymptomatic, indolent disease. Patients whose disease follows this pattern typically have primary disease that is estrogen receptor positive, a disease-free interval of longer than 2 years, and metastases to bone, soft-tissue, or non-life-threatening visceral sites. If such a patient has a small tumor burden and positive hormone receptors, hormonal therapies should be tried. Observation of incidental asymptomatic osteoblastic metastases until they become symptomatic is reasonable. The second pattern is a highly symptomatic, estrogen receptor-negative, aggressive, widely disseminated, life-threatening visceral disease. In patients with this type of metastatic disease, cytotoxic chemotherapy, with or without incidental radiation, is the treatment of choice. The patient's age should not unduly influence the type of initial therapy. Although cytotoxic chemotherapy has not been studied extensively in elderly women, several studies have shown no difference in age-related response, time to treatment failure, survival, or major toxicity in women 70 years and older who received standard doses of conventional agents compared with younger women [21]. Regardless of the regimen, only one systemic modality should be given at a time. The addition of hormones to chemotherapy is not generally recommended. Although the exact mechanism of action of most hormonal agents is not well understood, it is known that tamoxifen (Nolvadex), the most commonly used agent in hormonal therapy, arrests cells in the G$_1$ phase of the cell cycle. This is antagonistic to the action of most of the cytotoxic agents, the majority of which are most effective against cells actively progressing through the cell cycle [22]. However, no adverse effect on response rate and survival has been reported with the use of combined hormonal and cytotoxic therapy in patients with metastatic disease [23]; in some postmenopausal women, the combination may increase the response rate by 10% to 20% [24]. Biopsy studies of metastatic lesions exposed to estrogenic recruitment before chemotherapy did show an increase in the fraction of cells in the S phase [25], but estrogenic recruitment did not translate into improved response rates, time to disease progression, or median survival duration [25,26]. However, the risk of thromboembolic phenomena is increased when hormones and chemotherapy are combined, especially with regimens using cyclophosphamide (Cytoxan, Neosar), methotrexate, and fluorouracil (CMF) and prednisone [27,28]. The choice of drugs for systemic therapy can be affected by any number of coexisting medical conditions. Diabetes may complicate the use of glucocorticoids, anabolic steroids, megestrol acetate, and neurotoxic drugs, such as vinblastine, cisplatin (Platinol), and paclitaxel (Taxol). Preexisting significant cardiovascular disease may also increase the potential cardiac toxicity of anthracyclines, mitoxantrone (Novantron), mitomycin (Mutamycin), and high-dose cyclophosphamide. Cisplatin, the aminoglycosides, and ciprofloxacin (Cipro) can potentiate existing renal insufficiency; renal insufficiency may impair methotrexate clearance, and ureteral or urethral stenosis may enhance local cyclophosphamide toxicity. Doxorubicin (Adriamycin, Rubex), vincristine (Oncovin), vinblastine, and paclitaxel, which depend on hepatic clearance, may cause toxic reactions in patients with hyperbilirubinemia. Dementias of various causes seriously limit tolerance to any treatment. At present, there is very little evidence that the biologic response modifiers have systemic efficacy in metastatic breast cancer. The one exception is intracavitary alpha interferon (IFN-alfa), which shows
promise in the palliation of ascites or pleural effusions [29].

Often overlooked in discussions with patients of the treatment of metastatic breast cancer is the important role of supportive services. Patients often require the services of social workers in obtaining compassionate-use drugs, financial assistance, hospital equipment, referral to counseling services, and disability payments. During their illness, patients may require consultation with experts in pain management and rehabilitative medicine. Women with minor children may require legal advice. Anticipation of the need for supportive services early in the course of a patient’s illness and frank discussion of the nature of the disease often relieve anxiety and facilitate therapy.

Chemotherapy

Several clinical clues may predict the likelihood of response to treatment. Usually, better performance status, smaller tumor burden, and less prior exposure to chemotherapy all translate into a higher probability of response. In a previously untreated patient with a good performance status and small tumor burden, the response rate to chemotherapy ranges from 50% to 70%. If the patient has a poor performance status and an extensive tumor burden, the probability of response to chemotherapy is only 10% to 30% [3,19]. Age, menopausal status, hormone receptor status, and dominant disease site are not related to the probability of response to chemotherapy but are important to the response to hormonal therapy. With the exception of the central nervous system and the bones, the site of disease is less important than the volume of disease when estimating the probability of response.

Although current treatment modalities are palliative in most patients, some patients achieve durable complete or partial remission with standard-dose regimens after initial induction therapy. Restoring or maintaining response after initial treatment remains a therapeutic problem and an area of controversy. Some studies have suggested that although overall survival is unchanged, quality of life, time to disease progression, and tumor response are better in patients treated with maintenance chemotherapy after induction than in patients given intermittent chemotherapy for tumor progression [30,31]. In one study, reinduction with the same chemotherapeutic regimen for metastatic breast cancer showed an overall response rate of 18% and a time to treatment failure of 3 months, but 50% of the patients had life-threatening or severe toxic reactions. Response rates were high in patients initially in complete remission (44%) or partial remission (15%) but poor in patients with stable disease or no change [32]. Unfortunately, response rates decline rapidly with subsequent salvage attempts after induction therapy.

Several recent retrospective studies have shown overall response rates of 11% to 16% to either cytotoxic or hormonal salvage therapy after induction chemotherapy, but predicting who will benefit is still difficult [33,34]. These data are in agreement with the lack of enthusiasm among community medical oncologists for administering subsequent salvage regimens [35]. Clearly, the decision to pursue maintenance therapy after induction, subsequent salvage regimens, or observation and treatment for progression depends on tumor response, extent of palliation, and the patient’s wishes.

Standard Regimens: Breast cancer is moderately sensitive to at least 25 agents; however, single-agent therapy is effective in only 20% to 30% of patients. Notably, the anthracyclines, alkylating agents, and taxanes produce response rates of 30% to 60% when given as single agents [36-38]. The most effective proven chemotherapeutic regimens are combinations of doxorubicin or its congeners, mitoxantrone, cyclophosphamide, methotrexate, and fluorouracil. Commonly used regimens are listed in Table 2 [39-41].

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Other (mg/m²)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF—oral</td>
<td>Cyclophosphamide 100 mg PO total</td>
<td>Days 1 to 14 every 28 days</td>
</tr>
<tr>
<td></td>
<td>Methotrexate 40 IV</td>
<td>Days 1 and 8 every 28 days</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil 600 IV</td>
<td>Days 1 and 8 every 28 days</td>
</tr>
<tr>
<td>CMF—IV</td>
<td>Cyclophosphamide 600 IV</td>
<td>Day 1 every 28 days</td>
</tr>
</tbody>
</table>

Table 2: Standard Chemotherapeutic Regimens in Metastatic Breast Cancer
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>40 IV</td>
<td>Days 1 and 8 every 28 days</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>600 IV</td>
<td>Days 1 and 8 every 28 days</td>
</tr>
<tr>
<td>FAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 IV (or CI)</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>(48 to 72 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>500 IV</td>
<td>Days 1 and 8 (or 4) every 21 days</td>
</tr>
<tr>
<td>VATH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>4.5 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>45 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>12 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Halotestin</td>
<td>30 mg PO</td>
<td>Total daily</td>
</tr>
<tr>
<td>AC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>60 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>NFL-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>350 mg IV</td>
<td>Days 1, 2, and 3 every 21 days</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>300 mg IV</td>
<td>Each day before fluorouracil</td>
</tr>
<tr>
<td>NFL-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>1,000 IV over 24 h</td>
<td>Daily \times 3 every 21 days</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>350 IV over 15 min</td>
<td>Daily \times 3 every 21 days</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin</td>
<td>20 IV</td>
<td>Day 1 every 6 to 8 weeks</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0.15 mg/kg IV</td>
<td>Day 1 every 3 to 4 weeks</td>
</tr>
<tr>
<td>2M</td>
<td>Mitoxantrone 6.5 IV</td>
<td>Day 1 every 21 days</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>30 IV</td>
<td>Day 1 every 21 days</td>
</tr>
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At the University of Texas M.D. Anderson Cancer Center, initial chemotherapy for metastatic breast cancer is usually a doxorubicin-based regimen, such as 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), with doxorubicin administered by a 48- to 72-hour infusion. The continuous infusion reduces nausea, vomiting, and cardiac damage [42]. Although doxorubicin is the most active single agent in the treatment of breast cancer, the difference in reported response rates between doxorubicin- and methotrexate-based regimens is only 10% to 15%, and differences in response duration and survival also have been small [43-46].

The mean time to response to chemotherapy with these regimens varies with the site of disease. The mean time to response is 6 to 9 weeks in skin and nodes, 9 to 12 weeks in lungs, 15 to 18 weeks in liver, and 18 weeks in bone [47]. The median duration of response after the first remission is 9 to 12 months; this decreases to 3 to 6 months for subsequent remissions. The data from Coates et al [30] and Tannock et al [48] suggest that continuing therapy after response improves quality of life. Treatment is generally continued for an additional 3 to 6 months after the maximum response. Unfortunately, in many patients, the disease progresses by the time treatment is scheduled to be stopped. At this point, it is reasonable to consider a trial of a phase II regimen or other single agents that the patient has not received. Analysis of older clinical trials comparing survival advantage among patients treated with polychemotherapy vs single-drug chemotherapy in the phase II setting showed a very modest survival advantage (3.7 months) for patients receiving polychemotherapy [49].

The heterogeneous behavior of metastatic breast cancer is such that some patients may still experience meaningful palliation with other standard drugs. Also, if the patient is more symptomatic from the increased tumor burden or the cumulative effect of prior treatments, toxicity is often increased. The median duration of survival is usually 24 to 30 months. Patients who have a complete remission tend to live longer than patients who have partial remissions or stable disease. However, patients whose disease is refractory to the initial chemotherapeutic regimen tend to do poorly, with a median survival of only 4 to 6 months regardless of the regimen used [50,51].

Many phase II trials currently allow only one prior chemotherapeutic regimen for metastatic breast cancer. The expected benefits and toxicity of therapy should be clearly understood by the referring physician, the phase II investigator, and the patient.

**Paclitaxel:** Paclitaxel (Taxol) is the newest agent to show significant activity in untreated, heavily pretreated, and doxorubicin-refractory patients in phase I or II trials. Phase III trials comparing paclitaxel with standard regimens are ongoing. Paclitaxel is approved by the US Food and Drug Administration at a dose of 175 mg/m² by 3-hour infusion for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, provided that the previous chemotherapeutic regimen included an anthracycline. The first reported phase II study of paclitaxel indicated an overall response rate of 56% (12% complete, 44% partial) in 25 evaluable patients, 14 of whom had previously received only adjuvant chemotherapy and 11 of whom had previously received chemotherapy for metastatic disease [52]. The median response duration was 9 months (range, 3 to 19 months), the median time to disease progression was 9 months (range, 1 to 20 months), and the median overall survival was 23 months (range, 5 to 29+ months). Only 8% of patients had progression of disease during therapy. This finding has been confirmed in phase II trials [38] of previously untreated metastatic disease. In most
In vitro studies have demonstrated marginal cross-resistance between paclitaxel and doxorubicin [55]. Investigators at M.D. Anderson Cancer Center found that three of six doxorubicin-resistant patients responded to paclitaxel [53], whereas investigators at Memorial Sloan-Kettering Cancer Center observed responses to paclitaxel in 38%, 32%, and 17% of patients who had received prior doxorubicin in one, two, and three regimens, respectively [56]. Gianni et al [57] found an overall response rate of 47% (three complete, four partial) in 15 patients with anthracycline-resistant metastatic breast cancer treated with 175 to 200 mg/m² paclitaxel given by 3-hour infusion every 21 days; the median response duration was only 7 months. Most recently, a phase I to II study using paclitaxel by 96-hour infusion in doxorubicin- or mitoxantrone-refractory patients defined the dose-limiting toxicity as mucositis and grade 4 granulocytopenia and the maximum tolerated dose as 140 mg/m², or as 105 mg/m² for patients with liver metastases and elevation of serum transaminase levels to more than 2.5 times the upper limit of normal [58]. The objective response rate was 48%, but an additional 15% of patients had clinically meaningful minor responses. The median progression-free survival was 27 weeks, and the overall survival was 43 weeks [58].

The current optimal dose for paclitaxel in untreated, heavily pretreated, or doxorubicin-refractory metastatic breast cancer is under study. Paclitaxel schedules tested are 135, 175, or 250 mg/m² given by 24-hour continuous infusion or 135 or 175 mg/m² given over 3 hours every 21 days. The use of growth factors allows dose escalation, but neurotoxicity eventually becomes dose limiting [59]. Most phase II trials have used 24-hour infusion schedules with prophylactic steroids and Hand H blockers to avoid the problem of hypersensitivity reactions (HSRs), seen in up to 18% of patients in phase I testing [60]. However, 3-hour infusions have recently been shown to be safe and less myelosuppressive and to have equivalent antitumor effect, at least in ovarian cancer [61]. A recent report of a phase I trial has also shown 1-hour infusion of paclitaxel to be safe [62].

The recommended prophylactic regimen for HSRs in these studies is dexamethasone, 20 mg orally 12 and 6 hours prior to treatment, and diphenhydramine, 50 mg, with cimetidine, 300 mg intravenously 30 minutes prior to treatment; however, some studies have used dexamethasone, 20 mg intravenously, with cimetidine and diphenhydramine given 30 to 60 minutes before treatment. Starting doses of paclitaxel are usually decreased by 25% for patients who have been heavily pretreated, for example, patients who have received prior high-dose regimens, mitomycin, irradiation to more than 30% of marrow-containing bones, or two or more regimens and patients with poor tolerance to prior therapy manifested by frequent infections or delayed hematologic recovery. Paclitaxel doses must also be reduced significantly in patients with hepatic dysfunction manifested by elevated transaminases and bilirubin [62a].

Paclitaxel has a unique pattern of toxicity. The side effects of paclitaxel given by 3- or 24-hour infusion can be divided into dose-dependent effects (for example, an early but brief granulocyte nadir, sensory and motor peripheral neuropathy, mucositis, and arthralgias/myalgias) and dose-independent effects (for example, total and sudden alopecia, HSRs, and rhythm disturbances) [63]. Neuropathy may be cumulative but is reversible upon discontinuation of the drug. Mucositis is more pronounced with 96-hour infusion schedules, in which the dose is only 60% to 80% of the dose of 3- or 24-hour infusion schedules; however, prophylaxis for HSRs is not required [58]. Recently, optic-nerve disturbances causing photopsia, scotomata, and decreased visual acuity have been described in patients receiving more than 175 mg/m² by 3-hour infusion schedules; although most cases have been readily reversible with cessation of the infusion, some patients have sustained visual loss [64,65]. Radiation-recall dermatitis following paclitaxel infusion has also been described [66], as has local irritation with extravasation [67].

Given the high single-agent response rates of doxorubicin and paclitaxel, several groups of investigators have attempted to combine the two drugs [68] in phase I/II trials of previously untreated patients. However, there is emerging evidence from in vitro studies that concurrent doxorubicin and paclitaxel exposure, at least in cell lines, may be antagonistic. Paclitaxel might cause a G/M cell-cycle block, thereby leaving fewer cells in the S phase, the most doxorubicin-sensitive phase of the cell cycle [69]. When paclitaxel and doxorubicin are given by 24- or 72-hour infusion, either sequentially or concurrently, the response rates and duration are similar to those obtained when either drug is given alone. However, toxicities are schedule and sequence dependent. With concurrent 72-hour infusion of doxorubicin and paclitaxel, the gastrointestinal toxicity is primarily in the lower gastrointestinal tract and may include abdominal pain, diarrhea, and typhilitis [70]. When 24-hour infusion of paclitaxel is followed by 48-hour infusion of doxorubicin,
stomatitis of the upper gastrointestinal tract is dose limiting [68], whereas febrile neutropenia is dose limiting with the reverse sequence. Three-hour paclitaxel infusion followed by bolus infusion of doxorubicin has the same toxicity as the reverse sequence [71]. Pharmacokinetic data indicate that prior 24-hour infusion of paclitaxel reduces doxorubicin clearance, perhaps by altering the metabolism of doxorubicin in the liver [72]. Paclitaxel has been combined with cisplatin, carboplatin (Paraplatin), or cyclophosphamide in phase I studies [73], and phase II trials of these combinations are ongoing. Because of the sequence-dependent toxicities that have been seen, combinations of paclitaxel with other drugs outside a clinical trial are not recommended.

**Docetaxel:** As initial therapy for metastatic disease, docetaxel (Taxotere) is at least as active as paclitaxel. In several phase II trials, docetaxel, at a dose of 100 mg/m² every 3 weeks, produced an overall response rate of 57% to 67% in patients previously untreated for metastatic disease [74-76], with complete remissions in 15%, including patients with metastases to visceral sites, such as the liver. In one study of previously untreated patients [74], the median duration of response was 44+ weeks; the median time to disease progression was 37+ weeks, and the median overall survival was 16+ months. Docetaxel is also active as salvage therapy; even in patients with anthracycline resistance, docetaxel produces an overall response rate of 60% (6% complete, 27% partial) and is highly active against liver metastases [77-78]. Overall response duration is reported as 38 weeks, and median time to disease progression is 23 weeks [77]. This makes docetaxel as active as or more active than conventional chemotherapy or paclitaxel for either initial or salvage chemotherapy for metastatic breast cancer. The activity of docetaxel in paclitaxel-refractory patients is unknown, and combinations of docetaxel with other drugs are currently being tested in phase I trials [79]. However, docetaxel also has significant toxicities, some of which are unique. Grade 3 or 4 neutropenia and complete alopecia are common. Neurosensory toxicity appears to be less severe than it is with paclitaxel. Unique toxic effects result in skin changes, including erythema and desquamative dermatitis, onycholysis, and fluid retention. Fluid retention has been seen in responding patients with cumulative doses of docetaxel of 400 mg/m² and has necessitated cessation of therapy. Docetaxel has not been approved by the US Food and Drug Administration for the treatment of metastatic breast cancer outside clinical trials.

**Vinorelbine:** Vinorelbine (Navelbine), a semisynthetic vinca alkaloid, has been approved in France for non-small-cell lung cancer and breast cancer. In the United States, it has been approved for non-small-cell lung cancer but is still in phase II testing for breast cancer. From phase I testing, the recommended dose is 30 mg/m² intravenously per week. However, in most trials in the United States, investigators have not been able to administer the full dose. Often, the day-14 dose must be delayed because of neutropenia. A dose of 20 mg/m² appears to be more consistently tolerated. As a single agent in patients previously untreated for metastatic disease, vinorelbine produces overall response rates of 24% to 52% [80-82], with average complete response and partial response rates of 7% and 34%, respectively. The median time to treatment failure is 6 months, the median duration of response is 9 months, and the median survival is 18 months [81] or not yet reached [80]. Furthermore, vinorelbine is active in the salvage setting for patients who have received prior anthracyclines; the drug produces overall response rates of 16% to 36% [83,84]. Combinations of vinorelbine, 25 mg/m² intravenously on days 1 and 8, with doxorubicin, 50 mg/m² by short infusion on day 1 repeated every 21 days, produced an objective response in 74% of previously untreated patients (21% complete, 53% partial) [84]. Responses were seen at all sites of disease, and no difference was noted in patients who had received anthracyclines in the adjuvant setting. The median duration of response was 12 months, and the median overall survival was 27.5 months. Neutropenia was seen, and in 10% of patients, treatment-related cardiotoxicity was noted [85]. Vinorelbine also has been combined with fluorouracil as initial therapy for metastatic disease; this combination produced an overall response rate of 70% in a small study [86]. Studies combining vinorelbine with paclitaxel are ongoing at M.D. Anderson and elsewhere. Toxic reactions associated with vinorelbine include phlebitis at a peripheral-vein insertion site, myelosuppression, peripheral neuropathy, and myalgias. Transient increases in aspartate aminotransferase and alanine aminotransferase levels were reported in approximately 50% of patients but did not require discontinuation of therapy [87]. In up to 5% of patients, a unique respiratory toxic effect may occur; it includes both an acute reaction, which resembles bronchospasm and is readily reversible with bronchodilators, and a subacute reaction of cough and dyspnea, which occurs within 1 hour and is treated with steroids [87].

**Investigational Agents:** Drug development has proceeded rapidly in the past few years in an attempt to find single agents with high activity and low toxicity that produce durable responses. Table 3 lists several of these agents [88]. Referral of patients to centers studying these agents should be
encouraged when clinically appropriate.

### Table 3: Investigational Agents for Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
</tr>
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<tbody>
<tr>
<td>Alkylator</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>Angiogenesis inhibitors</td>
<td>Adozelisin</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>TNP-470</td>
</tr>
<tr>
<td>DNA intercalators</td>
<td>Edatrexate</td>
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<td></td>
<td>Gemcitabine</td>
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<tr>
<td>Retinoids (differentiating agents)</td>
<td>All-Trans-retinoic acid (ATRA)</td>
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<td>N-(4-hydroxyphenyl) retinamide (4HPR)</td>
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<td>Topoisomerase-I inhibitors</td>
<td>Topotecan</td>
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<tr>
<td>Unknown mechanisms of action</td>
<td>Penclomide</td>
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**High-Dose Chemotherapy:** “High-dose” chemotherapy refers to the administration of pulsed, large doses of cytotoxic drugs, which results in very high peak concentrations, whereas “dose intensity” refers to the amount of drug administered per unit of time, usually reported in mg/m²/wk [89]. Autologous bone marrow or peripheral blood stem-cell infusion allows the dose intensity of the chemotherapeutic regimen to be escalated to the point of marrow aplasia. Until conclusive phase III trials are completed, high-dose chemotherapy with autotransplantation, although promising, is still considered investigational. Prospective trials comparing standard- and high-dose strategies are ongoing. High-dose chemotherapy may be a reasonable option for some patients. The overall response rate ranges from 6% to 94%, with a high fraction of complete responders (36%). Treatment-related mortality is 5% to 15%, but most patients (67%) have a relapse. Historic comparisons with patients treated with standard-dose chemotherapy have not shown an increase in median response duration and overall survival with the use of high-dose chemotherapy, although disease-free survival may be improved [90-92].

One drawback to the current studies of high-dose chemotherapy is that the agents used to achieve marrow aplasia, for example, carmustine (BiCNU), etoposide (VePesid), or cisplatin, are not the most active agents in breast cancer. The optimal regimen would escalate active agents against breast cancer to a maximum tolerated dose determined by nonmyelosuppressive toxicities. Studies by Tannock et al [48] and Engelsman et al [93] and a retrospective analysis of previous trials by Hryniuk and Bush [94] support a relationship between dose intensity and response to initial chemotherapy in metastatic breast cancer for the combination of cyclophosphamide, fluorouracil, and either methotrexate or doxorubicin. The relationship between response and dose intensity for other active agents is either unproven or under study. Generally, the best results usually are seen in patients who have responded to induction therapies.

Serious toxic effects have been noted, however, especially with carmustine-containing regimens. Toxicity increases when comorbid conditions are present. These serious toxic effects include prolonged thrombocytopenia and immunosuppression, hepatic veno-occlusive disease, and interstitial pneumonitis. Mortality may decrease in the future with more experience and with the use of colony-stimulating factors, especially thrombopoietins, and autologous stem cells.

**Complications:** Because treatment of metastatic breast cancer is primarily palliative, it is important to anticipate and recognize the complications of chemotherapy. One of the most serious problems is neutropenia with fever or rigor; patients with this condition should be presumed to have sepsis until a complete evaluation proves otherwise. In anticipation of this complication, patients should be instructed to monitor their temperatures and to contact the physician promptly if the temperature...
Hormone Receptors and Response: The probability of response to hormone therapy is directly related to the status of hormone receptors. If the tumor is negative for both ER and PR, the probability of response is less than 10%. If ER is negative and PR is positive or vice versa, the probability of response depends on the status of hormone receptors in the tumor. The second approach is to block estrogen by use of antiestrogens (such as tamoxifen) or androgens (such as halotestin); the probability of response depends on the status of estrogen receptors in the tumor. The third approach is to inhibit gonadotropin-induced estrogen production by use of gonadotropin agonist-antagonists (luteinizing hormone-releasing hormone [LHRH] inhibitory agents), which are less effective in postmenopausal women [102]. The third approach is to decrease estrogen biosynthesis by inhibiting the aromatase enzyme, which catalyzes the final step in estrogen production in humans. This does not completely block ovarian estrogen production in premenopausal women, and there is concern that use of a single agent may cause a reflex increase in gonadotropin levels and result in an ovarian hyperstimulation syndrome. Thus, aromatase inhibitors (for example, aromatase) should be used primarily in postmenopausal women [103]; they are not effective in premenopausal women [104].
independently with increased response to tamoxifen, longer time to treatment failure, and longer overall survival in patients with ER-positive tumors [107].

### Correlation of Estrogen Receptor Levels With Response Rates

<table>
<thead>
<tr>
<th>Estrogen receptor level (fmol/mg protein)</th>
<th>Response rate (%)</th>
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</thead>
<tbody>
<tr>
<td>0-9</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>10-20</td>
<td>3/10 (30%)</td>
</tr>
<tr>
<td>21-49</td>
<td>7/11 (63%)</td>
</tr>
<tr>
<td>50</td>
<td>24/31 (77%)</td>
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</table>


Approximately 30% of women whose ER status is unknown will respond to the first hormonal manipulation. Of patients with a prior history of hormonal response, 33% to 50% will respond to another hormonal regimen. Patients with low-volume disease and better performance status generally have higher response rates. The duration of first response is usually 9 to 12 months, similar to that with chemotherapy. The side-effect profile aids in the determination of which hormonal therapy to use, because the efficacy of all agents is nearly equal [19,108,109]. Additionally, for patients whose tumors are unusually sensitive to hormonal manipulation, retreatment with a previously effective agent may again be effective if a long interval has elapsed since it was discontinued.

**Side Effects:** Endocrine therapy is usually milder and more tolerable than cytotoxic chemotherapy. However, several unique complications of endocrine therapy should be anticipated. One such complication, flare, is defined clinically by an abrupt, diffuse onset of musculoskeletal pain, increased size of skin lesions, or erythema surrounding the skin lesion within the first month of endocrine therapy. There is no published evidence that tumor growth rates increase during this period. The most serious manifestation of flare is hypercalcemia, which can be seen with all hormonal therapies except aminoglutethimide and castration. Hypercalcemia usually occurs in patients with bone metastases and manifests within the first 2 weeks after treatment. The underlying mechanism is the predominating early agonist effect of hormonal agents. Low doses of prednisone (10 to 30 mg/d) may abrogate the initial flare of bone pain. The patient should be instructed about the possibility of flare and should undergo serum calcium level monitoring on a weekly basis for the first 2 weeks. If hypercalcemia develops, the calcium level should be controlled and treatment continued, provided the serum calcium level is lower than 14 mg/dL.

All hormonal regimens except the aromatase inhibitors may cause weight gain. This side effect is most common with progestins, which can lead to both a true increase in weight, from their anabolic effect, and fluid retention, secondary to their glucocorticoid effect. Progestins are the drugs most likely to cause thromboembolism; tamoxifen is the next most likely drug to cause this complication. Both drugs have been reported to prolong the prothrombin time in patients who are also receiving warfarin [110,111].

**Active Agents and Complications:** Table 5 summarizes the current recommended hormonal treatment sequences for both premenopausal and postmenopausal women [108]. Whether tamoxifen or progestins are the preferred initial therapy in postmenopausal women, is still a subject of debate [112], but the side-effect profile often dictates the choice. Several studies have shown increased response rates, improved median time to treatment failure, and improved survival with high-dose medroxyprogesterone acetate as the initial therapy, but toxicity in terms of thromboembolic events, weight gain, increased systolic blood pressure, and fatigue is increased with the use of this drug [113,114]. The aromatase inhibitor 4-OHA (4-hydroxyandrostenedione, Lentaron) is effective and widely used in the United Kingdom. It is administered intramuscularly every 2 weeks [115]. This drug is not approved for use in the United States.

<table>
<thead>
<tr>
<th>Recommended Hormonal Treatment Sequences for Metastatic Breast Cancer</th>
<th>Therapy</th>
<th>Postmenopausal</th>
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<tbody>
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<td></td>
<td>First</td>
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**Tamoxifen:** Tamoxifen is one of the least toxic hormones used in the treatment of breast cancer. Its most frequent side effect is hot flashes. Mild nausea may occur but usually disappears after a few weeks of therapy. These side effects are rarely severe enough to discontinue the regimen. Transient thrombocytopenia and, rarely, leukopenia have been seen during the first week of treatment, but they usually require no monitoring. A minority of patients experience depression and weight gain [116,117]. A dose of 20 mg at bedtime is often better tolerated than 10 mg twice daily [118].

Concern over the safety of tamoxifen in the adjuvant setting for primary breast cancer has emerged and may affect its use in the patient with low-volume, asymptomatic metastatic disease who may have a long anticipated survival. Recent reports have found that women receiving adjuvant tamoxifen for primary breast cancer for 2 years or greater have a 2- to 6-fold increase in endometrial cancer than women in the general population [119,120]. While data on the incidence of endometrial cancers developing in women taking tamoxifen for metastatic breast cancer is lacking, women with an intact uterus should undergo annual pelvic examinations and endometrial ultrasonography or biopsy, or both, should be performed when there is any abnormal finding or history of bleeding.

**Megestrol Acetate:** The most commonly used progestin is megestrol acetate (Megace). Like tamoxifen, it may cause mild nausea, flare, and hot flashes, but it is also associated with more thromboembolic effects, weight gain, glucose intolerance, and increase in blood pressure. In patients who have an intact uterus, vaginal bleeding will occur when progestins are discontinued, and patients should be so advised. A minority of patients will experience an Addisonian syndrome after withdrawal of progestins because of the glucocorticoid effects of these agents.

**Aminoglutethimide:** The major side effect of aminoglutethimide (Cytadren), which is closely related to the rarely used sedative-hypnotic glutethimide, is sedation. Initially, up to one third of treated patients may experience lethargy, but this may be ameliorated by initiating treatment at a lower dose, 250 mg twice daily, with full replacement doses of hydrocortisone. One recommended regimen is hydrocortisone, 10 mg in both the morning and afternoon with 20 mg at bedtime; alternatively, cortisone acetate, 25 mg in the morning and 12.5 mg in the evening, may be associated with fewer Cushingoid symptoms. Fludrocortisone acetate (Flurinef), 0.1 mg every other day or three times a week, may also be required for mineralocorticoid replacement. After 1 to 2 weeks, the therapeutic dose, 250 mg every 6 hours, may be started. In addition, during the initial 2 to 3 weeks of therapy, nearly 25% of patients develop a maculopapular, erythematous, pruritic rash that usually disappears without additional treatment. Some patients require a transient increase in steroid dosages [104,109]. A total of 5% to 10% of patients develop a “flu-like” syndrome of myalgia and fever that requires discontinuation of the drug. Recent data suggest that a lower dose of aminoglutethimide (250 mg twice daily) may be as effective as the standard dose of 1,000 mg daily. 4-OHA is better tolerated than aminoglutethimide, with reported side effects including pain at the injection site, hot flashes, lethargy, rash, transient leukopenia, facial swelling, and, rarely, anaphylaxis [121].

**Metastases at Specific Sites**

*Isolated Hepatic Metastases:* In a review of 1,171 patients who received chemotherapy for metastatic breast cancer at M.D. Anderson, 233 (20%) had liver metastases, either isolated or with other sites of metastatic disease [122]. Standard treatment of liver metastases is chemotherapy, although hormonal therapies may provide a transient benefit in asymptomatic patients with low-volume, ER-positive disease. Resection of liver metastases cannot be recommended, except in selected cases [123]. Hepatic artery infusion of chemotherapeutic agents may expose the tumor to a higher drug concentration. The overall response rate to intra-arterial infusion therapy is 50% [124,125]. No phase III trials have been performed to compare this approach with standard intravenous therapy. Reported phase II trials for breast cancer have used intra-arterial infusion of...
Metastatic Breast Cancer
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In 1% to 10% of patients who have metastatic breast cancer, the metastasis is an isolated lesion in a location from which it can be removed by either irradiation or surgery; the disease is then classified as stage IV with no evidence of disease (NED). From 50% to 80% of patients with stage IV-NED disease develop systemic disease within 2 years despite curative local therapies. The 5-year survival rate ranges from 4% to 36% [138-140]. The most common situation involves patients with an isolated chest-wall recurrence; 50% have distant metastases upon further investigation and 25% develop other metastases within several months. The remaining 25% have a single, isolated lesion. Half of chest-wall nodules are solitary and near the mastectomy incision. If they are not controlled, these nodules have a significant impact on the quality of life. The

Bisphosphonates are synthetic analogs of the endogenous substance pyrophosphate and are capable of regulating bone turnover by inhibiting osteoclast activity by mechanisms that are not well understood. They are used clinically to treat Paget's disease of bone, osteoporosis, and hypercalcemia, and they have been evaluated for the treatment of bone metastases in breast and prostate cancer and multiple myeloma [131]. Three bisphosphonates are currently available: etidronate (Didronel), pamidronate (Aredia), and clodronate. (Clodronate and the oral formulation of pamidronate have not been approved in the United States.) Several double-blind, placebo-controlled studies have suggested that prophylactic oral clodronate or pamidronate treatment of patients with metastatic breast cancer reduces osseous complications, such as hypercalcemic events, vertebral fractures, and bone pain, and promotes healing of osteolytic lesions [132-135]. In two studies, a survival benefit was seen [136]. These data, which suggest that the bisphosphonates also inhibit tumor growth in bone, are the basis for planned studies in the adjuvant setting. Side effects, mainly nausea and vomiting, led to drug discontinuance for some patients. Studies of less toxic oral bisphosphonates are ongoing. Pamidronate can be given safely intravenously in high doses (90 mg intravenously) in an outpatient setting on a monthly basis without significant side effects; it relieves bone pain and promotes healing of lytic lesions in 25% of patients [137].

Stage IV—No Evidence of Disease: In 1% to 10% of patients who have metastatic breast cancer, the metastasis is an isolated lesion in a location from which it can be removed by either irradiation or surgery; the disease is then classified as stage IV with no evidence of disease (NED). From 50% to 80% of patients with stage IV-NED disease develop systemic disease within 2 years despite curative local therapies. The 5-year survival rate ranges from 4% to 36% [138-140]. The most common situation involves patients with an isolated chest-wall recurrence; 50% have distant metastases upon further investigation and 25% develop other metastases within several months. The remaining 25% have a single, isolated lesion. Half of chest-wall nodules are solitary and near the mastectomy incision. If they are not controlled, these nodules have a significant impact on the quality of life. The
dismal survival rates after a chest-wall recurrence are quite different from those after a recurrence in a breast treated by conservative surgery and irradiation; 50% to 60% of these patients can be salvaged with surgery alone [141]. There is some disagreement in the literature about whether local or systemic therapy is more appropriate. It is reasonable to provide the optimum local regimen with surgery and irradiation whenever possible. Although the use of systemic therapy is controversial, the literature supports the use of CMF or FAC for 6 to 8 cycles, tamoxifen, or both in sequence or combined [142,143].

**Brain Metastases:** Metastases to the brain are usually a late finding. The overall incidence of brain metastases in autopsy studies is 30%; only 10% of patients with brain metastases were symptomatic during life [144]. Headache may occur in approximately 50% of affected patients. Computed tomography or magnetic resonance imaging with contrast is the diagnostic test of choice. The median survival after diagnosis is 4 months, with a wide range [145]. A patient with an isolated, resectable brain metastasis may improve after surgery followed by radiation therapy [146]. However, whole-brain irradiation is the treatment of choice in patients with multiple brain lesions or widespread or uncontrolled metastatic disease. Because seizure occurs in only 20% to 30% of patients with brain metastases, only these patients require anticonvulsants [147]. Of note, there is an association between the development of erythema multiforme or the Stevens-Johnson syndrome in patients receiving phenytoin and corticosteroids during whole-brain irradiation [148].

**Leptomeningeal Disease:** Metastases to the leptomeninges occur in approximately 1% to 5% of patients with metastatic breast cancer. They usually present as progressive neurologic dysfunction involving multiple central nervous system sites. Untreated, they usually are fatal in 4 to 6 weeks. Clinically, symptoms and signs are grouped by the site of origin: cerebrum, cranial nerve, or spinal cord. Treatment consists of whole-brain irradiation and intrathecal chemotherapy with methotrexate or thiopot (Thioplex). Systemic chemotherapy alone is ineffective, although there are reports of high levels of the active metabolite of thiopot achieving potentially therapeutic cerebrospinal fluid levels after intravenous administration [149]. Neurotoxic effects from radiation and chemotherapy are additive. Median survival from the time of diagnosis is 6 months in responders but only 6 weeks in nonresponders [150-151].

**Epidural Metastases:** In several large series, breast cancer was the most common malignancy to cause epidural compression of the spinal cord and cauda equina. Approximately 60% to 70% of these patients will have multiple lesions in the vertebral column; the thoracic spine is the most frequently affected site, followed by the lumbosacral spine and the cervical spine [152-155]. In patients with bony metastases, complaints of back pain, weakness, sensory loss, or sphincter dysfunction should arouse suspicion of spinal cord compression. Early diagnosis and treatment are imperative in preventing any further neurologic damage. Magnetic resonance imaging with gadolinium is the diagnostic method of choice; computed tomographic scanning with contrast is also informative. Myelography is painful and potentially dangerous. Treatment usually consists of high-dose steroids and radiation [153-155]. However, surgery can be considered in a patient who develops compression at a previously irradiated site. Surgery should also be considered a reasonable choice when the diagnosis is in question or in patients with neurologic deterioration despite radiation therapy [156,157]. Once spinal-cord compression develops, treatment may not restore any function that was lost, but it can prevent any further deterioration.

**Evaluation of Treatment Response**

The assessment of response should not be based on a single test but, rather, on the examination of the patient as a whole. Patients should be examined at regular intervals to ensure that therapy continues to be beneficial. The examination begins with a history and physical examination, with attention given to known sites of metastases and the clinical symptoms associated with these metastases. A history of improvement in clinical symptoms may provide some clinical evidence of response. Examples of such improvement include a reduction in the levels and locations of pain in patients with bony metastases; a decrease in pulmonary symptoms in patients with intrathoracic involvement; and a reduction in symptoms of anorexia, weight loss, malaise, and right upper-quadrant pain in patients with known liver metastases. All lesions accessible to physical examination should be measured and compared with baseline and prior measurements. Any neurologic finding, nonspecific headache, nausea, or vomiting should be evaluated by further diagnostic studies.

The biologic markers CEA and CA 15-3 generally parallel the clinical course. However, they may also rise paradoxically after a new treatment is initiated [158,159]. If the patient has liver metastases, liver function studies usually improve with effective therapy. However, some chemotherapeutic agents, such as methotrexate, doxorubicin, and the androgen hormones, may produce elevations in
transaminase levels. Although alkaline phosphatase is a marker of bone and liver disease, its levels also may rise with healing of bone lesions. Serum calcium levels rise during the flare response, which may begin within the first 2 weeks after treatment. A later rise in this parameter may indicate progressive disease.

The computed tomographic scan is effective in monitoring liver and abdominal metastases. Although thoracic computed tomographic scanning is more sensitive than chest x-rays in defining the sizes of intrathoracic metastases, chest x-rays are usually sufficient to evaluate responses. Bone response can be difficult to assess if the disease is primarily blastic. Improvement of lytic lesions appears on the radiograph as no change, a rim of calcification, or complete reossification. If the lytic or blastic lesion responds to treatment, the nuclear bone scan will initially show increasing intensity in the previously demonstrated lesions but no new lesions. After the healing has stopped and the bones are metabolically quiet, the intensity usually decreases. Thus, the nuclear bone scan is useful in detecting the sites of bony metastases, especially when patients develop new symptoms and plain radiographs are normal. However, reliance on the nuclear bone scan alone to determine response may be misleading [129]. In some patients, metastatic disease involves the bone marrow more than the cortical bone. Magnetic resonance imaging is the only modality that will effectively image bone and bone marrow (generally the vertebral bodies).

Conclusions

Metastatic breast cancer remains a challenging disease to manage in the 1990s. Most patients are best managed with the judicious use of local and systemic therapies to achieve maximum palliation with minimal toxicity. However, decades of research on basic tumor biology, mechanisms of resistance, drug development, radiopharmaceuticals, and hematopoietic growth factors have yielded many promising approaches for combating this common and disabling disease. Most of these approaches are being tested clinically, and many are available through clinical trials for interested patients.

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