CHAPTER 11

Stages III and IV breast cancer

Lori Jardines, MD, Bruce G. Haffty, MD, Melanie Royce, MD, PhD, and Ishmael Jaiyesimi, MD

This chapter addresses the diagnosis and management of locally advanced, locally recurrent, and metastatic breast cancer, ie, stages III and IV disease. Approximately 20%-25% of patients present with locally advanced breast cancer. Inflammatory breast cancer is a particularly aggressive form of breast cancer that falls under the heading of locally advanced disease and accounts for 1%-3% of all breast cancers.

Locoregional recurrence of breast cancer remains a major clinical oncologic problem. Rates of locoregional recurrence may vary from < 10% to > 50%, depending on initial disease stage and treatment.

Metastatic disease is found at presentation in 5%-10% of patients with breast cancer. The most common sites of distant metastasis are the lungs, liver, and bone.

The optimal therapy for stage III breast cancer continues to evolve. Recently, the use of neoadjuvant chemotherapy has been effective in downstaging locally advanced breast cancer prior to surgical intervention. The optimal neoadjuvant chemotherapeutic regimens continue to evolve, and studies are being performed to evaluate new agents and delivery methods.

Diagnosis

Locally advanced disease

Patients with locally advanced breast cancer do not have distant metastatic disease and are in this group based on tumor size and/or nodal status. Such patients often present with a large breast mass or axillary nodal disease, which is easily palpable on physical examination. In some instances, the breast is diffusely infiltrated with disease, and no dominant mass is evident.

Patients with inflammatory breast cancer often present with erythema and edema of the skin of the breast (peau d’orange) and may not have a discrete mass within the breast. These patients often are treated with antibiotics unsuccessfully for presumed mastitis.

Mammography is beneficial in determining the local extent of disease in the ipsilateral breast, as well as in studying the contralateral breast.
**Fine-needle aspiration (FNA) or biopsy** The diagnosis of breast cancer can be confirmed by either FNA cytology or core biopsy. Core biopsy is preferred to perform the wide variety of marker analyses.

**Search for metastasis** The presence of distant metastatic disease should be ruled out by physical examination, chest radiography, CT of the liver, bone scan, and CT of the chest. Fluorodeoxyglucose-positron emission tomography (FDG-PET) has moderate accuracy for detecting axillary metastasis. It is highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified but fails to detect small nodal metastasis. The addition of FDG-PET to the standard workup of patients with locally advanced breast cancer may lead to the detection of unexpected distant metastases. Abnormal PET findings should be confirmed to prevent patients from being denied appropriate treatment.

**Locoregional recurrence**

**Biopsy or FNA** Locoregional recurrence of breast cancer can be diagnosed by surgical biopsy or FNA cytology. Whichever modality is appropriate, material should be sent for hormone-receptor studies, since there is only an 80% concordance in hormone-receptor status between the primary tumor and recurrent disease. When the suspected recurrent disease is not extensive, the biopsy procedure of choice is a negative margin excisional biopsy. For an extensive recurrence, an incisional biopsy can be used.

**Search for distant metastasis** Prior to beginning a treatment regimen for a patient with locoregional recurrence, an evaluation for distant metastasis should be instituted, since the findings may alter the treatment plan.

**Distant metastasis from the breasts**

Metastatic breast cancer may be manifested by bone pain, shortness of breath secondary to a pleural effusion, parenchymal or pulmonary nodules, or neurologic deficits secondary to spinal cord compression or brain metastases. In some instances, metastatic disease is identified after abnormalities are found on routine laboratory or radiologic studies.

**Assessment of disease extent** by radiography, CT, and radionuclide scanning is important. Organ functional impairment may be determined by blood tests (liver/renal/hematologic) or may require cardiac and pulmonary function testing. Biopsy may be required to confirm the diagnosis of metastasis; this is especially important when only a single distant lesion is identified.

**Metastasis to the breasts**

The most common source of metastatic disease to the breasts is a contralateral breast primary. Metastasis from a nonbreast primary is rare, representing < 1.5% of all breast malignancies. Some malignancies that could metastasize to the breast include non-Hodgkin’s lymphoma, leukemias, melanoma, lung cancer (particularly small-cell lung cancer), gynecologic cancers, soft-tissue sarcomas, and GI adenocarcinomas. Metastasis to the breasts from a nonbreast pri-
mary is more common in younger women. The average age at diagnosis ranges from the late 30s to 40s. Treatment depends on the status and location of the primary site.

**Mammographic findings** Mammography in patients with metastatic disease to the breasts most commonly reveals a single lesion or multiple masses with distinct or semidiscrete borders. Less common mammographic findings include skin thickening or axillary adenopathy.

**FNA or biopsy** FNA cytology has been extremely useful in establishing the diagnosis when the metastatic disease has cytologic features that are not consistent with a breast primary. When cytology is not helpful, core biopsy or even open biopsy may be necessary to distinguish primary breast cancer from metastatic disease.

**Treatment**

**TREATMENT OF LOCALLY ADVANCED DISEASE**

The optimal treatment for patients with locally advanced breast cancer has yet to be defined, due to the heterogeneity of this group. There are approximately 40 different substage possibilities with the different combinations of tumor size and nodal status. Between 66% and 90% of patients with stage III breast cancer will have positive lymph nodes at the time of dissection, and approximately 50% of patients will have four or more positive nodes.

Patients with locally advanced breast cancer have disease-free survival rates ranging from 0% to 60%, depending on the tumor characteristics and nodal status. In general, the most frequent type of treatment failure is due to distant metastases, and the majority of them appear within 2 years of diagnosis.

With the increased utilization of multimodality therapy, including chemotherapy, radiation therapy, and surgery, survival for this patient population has improved significantly.

**Neoadjuvant systemic therapy**

Neoadjuvant therapy with cytotoxic drugs permits in vivo chemosensitivity testing, can downstage locally advanced disease and render it operable, and may allow breast-conservation surgery to be performed. Preoperative chemotherapy requires a coordinated multidisciplinary approach to plan for surgical and radiation therapy. A multimodality treatment approach can provide improved control of locoregional and systemic disease. When neoadjuvant therapy is used, accurate pathologic staging is not possible.

**Active regimens** Preoperative chemotherapy regimens reported to result in high response rates (partial and complete responses) include CAF (cyclophosphamide [Cytoxan, Neosar], doxorubicin [Adriamycin], and fluorouracil [5-FU]), FAC (5-FU, Adriamycin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate, and 5-FU), and CMFVP (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). Combination chemotherapy with
an anthracycline-based regimen—FAC or AC—is used most often. Recently published data suggest that the AT regimen of Adriamycin and docetaxel (Taxotere) given concomitantly may produce equivalently high response rates.

Combination agents for metastatic breast cancer also include paclitaxel plus trastuzumab (Herceptin) with carboplatin (Paraplatin), gemcitabine (Gemzar)
and paclitaxel, and capecitabine (Xeloda) and docetaxel (Table 1). Although not yet definitive, recent data indicate that enhancing dose density may increase the pathologic complete response rate for women with locally advanced disease. The doses of these combination chemotherapy regimens are given in Table 1, chapter 10.

There seems to be no difference in survival in women with locally advanced disease who receive chemotherapy before or after surgery. Neoadjuvant chemotherapy results in complete response rates ranging from 20%-53% and partial response rates (≥ 50% reduction in bidimensionally measurable disease) ranging from 37%-50%, with total response rates ranging from 80%-90%. Patients with large lesions are more likely to have partial responses. Pathologic complete responses (pCRs) do occur and are more likely to be seen in patients with smaller tumors. A pCR in the primary tumor is often predictive of a com-

<table>
<thead>
<tr>
<th>Drug/combination</th>
<th>Dose and schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel or paclitaxel + carboplatin + trastuzumab (every-3-week dosing)</strong></td>
<td>Docetaxel 75 mg/m² IV on day 1 every 21 days OR Paclitaxel 175 mg/m² IV on day 1 every 21 days PLUS Carboplatin AUC of 5 to 6 on day 1 every 21 days PLUS Trastuzumab 4 mg/kg IV loading dose on day 1, followed by 2 mg/kg weekly</td>
</tr>
<tr>
<td><strong>Note:</strong> Patients must be premedicated with dexamethasone prior to docetaxel.</td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab</strong></td>
<td>4 mg/kg IV loading dose, then 2 mg/kg weekly 8 mg/kg IV loading dose, then 6 mg/kg every 3 weeks</td>
</tr>
<tr>
<td><strong>Paclitaxel or docetaxel + carboplatin + trastuzumab (weekly dosing)</strong></td>
<td>Paclitaxel 80 mg/m² IV on day 1 every week OR Docetaxel 35 mg/m² IV on day 1 every week PLUS Carboplatin AUC 2 IV on day 1 every week PLUS Trastuzumab 4 mg/kg IV loading dose, then 2 mg/kg every week</td>
</tr>
<tr>
<td><strong>Gemcitabine + paclitaxel</strong></td>
<td>Gemcitabine 1,250 mg/m² IV on days 1 and 8 (as a 30-minute infusion) every 21 days Paclitaxel 175 mg/m² IV on day 1 (over 3 hours) every 21 days</td>
</tr>
<tr>
<td><strong>Note:</strong> Standard paclitaxel premedications should be given.</td>
<td></td>
</tr>
<tr>
<td><strong>Pegylated doxorubicin</strong></td>
<td>Doxil 30 to 50 mg/m² IV on day 1 every 21 to 28 days</td>
</tr>
</tbody>
</table>
plete axillary lymph node response. Patients with locally advanced breast cancer who have a pCR in the breast and axillary nodes have a significantly improved disease-free survival rate compared with those who have less than a pCR. However, a pCR does not entirely eliminate the risk for recurrence.

Patients should be followed carefully while receiving neoadjuvant systemic therapy to determine treatment response. In addition to clinical examination, it may also be helpful to document photographically the response of ulcerated, erythematous, indurated skin lesions. Physical examination, mammography, and breast ultrasonography are best for assessing primary tumor response, whereas physical examination and ultrasonography are used to evaluate regional nodal involvement.

The role of MRI in evaluating response to preoperative chemotherapy is still evolving. Dynamic contrast-enhanced MRI performed at baseline, during chemotherapy, and before surgery has yielded more than 90% diagnostic accuracy in identifying tumors achieving a pCR and can potentially provide functional parameters that may help to optimize neoadjuvant chemotherapy strategies. However, despite its high sensitivity, a large number of patients still may have either false-negative or false-positive results on MRI scanning.

**Multimodality approach**

A multimodality treatment plan for locally advanced breast cancer (stage IIIA and IIIB, M1 supraclavicular nodes) is shown schematically in Figure 1. This approach has been shown to result in a 5-year survival rate of 84% in patients with stage IIIA disease and a 44% rate in those with stage IIIB disease. The most striking benefit has been seen in patients with inflammatory breast cancer, with 5-year survival rates of 35%-50% reported for a multimodality treatment approach including primary chemotherapy followed by surgery and radiation therapy and additional adjuvant systemic therapy. The same chemotherapy drugs, doses, and schedules used for single-modality therapy are employed in the multimodality approach.

**Surgery** Traditionally, the surgical procedure of choice for patients with locally advanced breast cancer has been mastectomy. In recently published studies, some patients with locally advanced breast cancer who responded to treatment with neoadjuvant chemotherapy became candidates for breast-conservation therapy and were treated with limited breast surgery and adjuvant breast irradiation. Patients who have been downstaged using neoadjuvant chemotherapy should be evaluated carefully before proceeding with conservative treatment. It may be helpful to mark the site of the primary tumor with the placement of a clip during the course of percutaneous biopsy prior to beginning adjuvant therapy. There can sometimes be a complete clinical and/or radiographic response after neoadjuvant chemotherapy or hormonal therapy, and this may facilitate a wide local incision.

The role of sentinel node biopsy in the treatment of breast cancer after neoadjuvant chemotherapy has yet to be defined. Studies have shown that pathologically positive axillary lymph nodes can be sterilized when neoadjuvant che-
motherapy is utilized. There are other biologic concerns with sentinel node biopsy after neoadjuvant chemotherapy. The lymphatics may undergo fibrosis or may become obstructed by cellular debris, making the mapping procedure unreliable, with false-negative rates of up to 25%. The rate of conversion from positive to negative nodes can be enhanced when four cycles of a doxorubicin-based regimen are followed by four cycles of docetaxel. Sentinel node biopsy will only be accurate then if all the metastatic deposits within the axilla respond

**FIGURE 1:** Multimodality approach to locally advanced breast cancer

For women with hormone-receptor-positive tumors (ER and/or PR positive): endocrine therapy

---

*The extent of surgery is determined by response, but always includes axillary lymph node dissection.*
in a similar fashion to chemotherapy. Preliminary data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial demonstrated an 11% false-negative rate in women who underwent sentinel node biopsy after receiving four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel. However, patients with clinically positive nodes prior to neoadjuvant chemotherapy should have full node dissection.

**Radiation therapy** remains an integral component of the management of patients with locally advanced breast cancer. For patients with operable breast cancer undergoing mastectomy, radiation therapy to the chest wall and/or regional lymph nodes (to a total dose of 5,000-6,000 cGy) is usually employed, as discussed in chapter 10. Recent randomized trials suggest that postmastectomy patients with any number of positive nodes derive a disease-free and/or overall survival benefit from postmastectomy irradiation.

Available data do not suggest a problem in delaying radiation therapy until the completion of systemic chemotherapy. Even in patients undergoing high-dose chemotherapy with autologous bone marrow or stem-cell transplantation, irradiation is generally indicated following mastectomy for patients with locally advanced disease (primary tumors ≥5 cm and/or ≥ four positive axillary nodes).

For patients whose disease is considered to be inoperable, radiation therapy may be integrated into the management plan prior to surgery.

**High-dose chemotherapy** Patients with locally advanced breast cancer and those with multiple positive nodes may be candidates for protocol treatment with high-dose chemotherapy plus autologous stem-cell support. Preliminary results from three prospective, randomized trials of high-dose chemotherapy with autologous stem-cell support in women with high-risk primary breast cancer were recently presented. All three trials are summarized in Table 2, and two of the trials are discussed in more detail below.

In the largest trial yet reported, investigators from all of the bone marrow transplant centers in the Netherlands randomly assigned 885 women with stages II and III breast cancer with four or more tumor-positive nodes to a standard therapy arm of five courses of FEC (5-FU, epirubicin [Ellence], and cyclophosphamide) followed by radiation therapy and tamoxifen or an investigational treatment arm of four cycles of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin with peripheral blood stem-cell support followed by radiation therapy and tamoxifen. After a median follow-up of 57 months, there was a trend for improved 5-year relapse-free survival rates in the high-dose group, but it was not statistically significant (hazard ratio [HR] = 0.83; \( P = .09 \)). In the subgroup of patients with 10 or more positive nodes, however, the relapse-free survival rate reached statistical significance (HR = 0.71; \( P = .05 \)). There was also a suggestion that the benefit seen in the high-dose group may be confined to patients with HER-2/neu-negative tumors.

The second-largest trial evaluating high-dose chemotherapy was conducted by the Cancer and Leukemia Group B (CALGB) in patients with stage II or III breast cancer involving 10 or more axillary lymph nodes. This trial examined the value of consolidation high-dose therapy with cyclophosphamide, cisplatin,
and carmustine (BiCNU) with autologous stem-cell support following adjuvant therapy with cyclophosphamide, doxorubicin, and 5-FU. Preliminary results of this study, with 783 participants, showed a reduction in relapse frequency of over 30% in patients receiving high-dose chemotherapy; a 3-year survival rate of 68% was observed in patients treated with high-dose chemotherapy, vs a 64% rate in those who received intermediate-dose consolidation therapy with the same drugs. However, follow-up is not yet long enough to define the ultimate benefit of this approach. Moreover, toxicity to date has been significantly higher and the relapse rate significantly lower in the high-dose group.

Nonrandomized studies of high-dose chemotherapy plus autologous stem-cell support have shown a disease-free survival of ~70%, as compared with historic data showing a 30% 5-year disease-free survival rate with conventional-dose chemotherapy.

To date, the results of available clinical trials have not all shown improved disease-free and overall survival in patients treated with dose-intensive regimens. However, trial design, power, and strategy have all been questioned. Outside the context of a clinical trial, high-dose chemotherapy cannot be recommended for patients with primary or metastatic breast cancer.

### TREATMENT OF LOCOREGIONAL RECURRENCE AFTER EARLY INVASIVE CANCER OR DCIS

When a patient develops a local failure after breast-conservation treatment for early invasive cancer or ductal carcinoma in situ (DCIS), it is generally in the region of the initial primary tumor. The risk of ipsilateral breast tumor recurrence after conservative treatment in patients with early invasive cancer ranges from 0.5%-2.0% per year, with long-term local failure rates plateauing at about 15%-20%. Local failure rates after wide excision alone for DCIS vary from 10%-63%, as compared with rates between 7% and 21% after wide excision plus radiation therapy. Most patients whose disease recurs after conservative treatment for DCIS can be treated with salvage mastectomy. In one study, 14% of patients who developed local recurrence had synchronous distant metastatic disease.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Number of patients</th>
<th>Follow-up (median)</th>
<th>Survival benefit?</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodenhuis et al</td>
<td>885</td>
<td>36 mo</td>
<td>Yes</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Peters et al</td>
<td>783</td>
<td>36 mo</td>
<td>No</td>
<td>NS</td>
</tr>
<tr>
<td>Scandinavian Breast Cancer Study Group</td>
<td>525</td>
<td>20 mo</td>
<td>No</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant
FIGURE 2: Treatment approach to metastatic breast cancer

Low-risk hormone receptor-positive patients

Aromatase inhibitor or fulvestrant for postmenopausal women; tamoxifen, LHRH against +/- aromatase inhibitor for premenopausal women

If partial or complete response, continue therapy until progressive disease

Progressive disease

Megestrol acetate or tamoxifen

If partial or complete response, continue therapy until progressive disease

Progressive disease

Trial of third-line hormone

Hormone-refractory disease

Intermediate- or high-risk hormone receptor-negative patients

No prior anthracycline: pegylated doxorubicin, FA/EC, CA/EF, A/ET

Prior anthracycline: taxane (paclitaxel or docetaxel) single agent or in combination (such as paclitaxel/gemcitabine or docetaxel/capecitabine)

If partial or complete response, continue 2 cycles past best response or until disease progression or unacceptable toxicity

Progressive disease

Trial of paclitaxel or docetaxel: if taxane-resistant, use single-agent vinorelbine or capecitabine

If no response, consider referral for investigational trial

Trastuzumab + taxane +/- platinum until partial response or complete response

Maintain on trastuzumab until disease progression

Change chemo (eg, vinorelbine, gemcitabine) +/- continue trastuzumab

If no response to two consecutive chemotherapy regimens + poor performance status, give symptomatic/supportive care

*Low-risk patients include those with a long disease-free interval, tumors that are positive for hormone receptors (estrogen and progesterone), or bone-only disease, as well as those without extensive visceral involvement

Intermediate- or high-risk patients include those with rapidly progressive disease, visceral involvement, hormone-refractory disease, or tumors that are negative for hormone receptors
The optimal treatment of a local or regional recurrence after mastectomy has yet to be defined. Locoregional recurrences are associated with initial nodal status and primary tumor size. Appropriate treatment may result in long-term control of locoregional disease. In many instances, these patients develop simultaneous distant metastasis, or distant disease develops some time after the locoregional recurrence manifests itself.

Recurrence of invasive cancer after breast conservation

Recurrence after wide excision and breast irradiation For patients with early invasive cancer who have undergone conservative surgery followed by irradiation and whose cancer recurs in the ipsilateral breast, salvage mastectomy is the most common treatment modality. The same is true for ipsilateral recurrence (of invasive or in situ disease) after conservative treatment for DCIS, when there is no evidence of distant metastatic disease.

Some studies with limited follow-up have reported acceptable results with repeated wide local excision for ipsilateral breast tumor relapses following conservative surgery and radiation therapy. Selection criteria for this approach are unclear, however, and use of this salvage procedure remains controversial. Although the use of limited-field reirradiation has been reported, selection criteria for this management option and long-term follow-up data are lacking.

Recurrence after wide excision alone In patients initially treated with wide local excision alone who sustain an ipsilateral breast tumor recurrence, small series with limited follow-up suggest that wide local excision followed by radiation therapy to the intact breast at the time of local recurrence may be a reasonable treatment alternative. In this situation, standard radiation doses would be employed.

Recurrent disease in the chest wall after mastectomy

In general, patients who develop minimal recurrent disease in the chest wall after a long disease-free interval may be treated by excision alone, although this approach is controversial and may not be ideal. Locoregional control obtained by radiation therapy alone is related to the volume of residual disease and may not be durable. When possible, disease recurring in the chest wall or axillary nodes should be resected and radiation therapy should be delivered to aid in local control.

Radiation treatment techniques are generally similar to those employed for patients treated with standard postmastectomy irradiation and consist of photon- and/or electron-beam arrangements directed at the chest wall and adjacent lymph node regions. Treatment planning should strive for homogeneous dose distributions to the target areas while minimizing the dose to the underlying cardiac and pulmonary structures.

Radiation dose and protocol Conventional fractionation of 180-200 cGy/d to the area of locoregional recurrence and immediately adjacent areas at risk, to a total dose of 4,500-5,000 cGy, is indicated. A boost to the area of recurrence or gross residual disease, to a dose of approximately 6,000 cGy, results in acceptable long-term locoregional control.
CANCER MANAGEMENT: A MULTIDISCIPLINARY APPROACH

Radical chest wall resection

A select group of patients with local chest wall recurrence secondary to breast cancer may be candidates for a radical chest wall resection, which may include resection of skin, soft tissue, and bone. Flap coverage or prosthetic chest wall reconstruction is required. Appropriate candidates would include patients who do not have distant metastases and who have persistent or recurrent chest wall disease after chest wall irradiation and patients who present with a chest wall recurrence after a long disease-free interval.

ADJUVANT SYSTEMIC THERAPY FOR LOCOREGIONAL RECURRENCE

Ipsilateral breast tumor recurrence

Limited data support the use of adjuvant systemic therapy at the time of ipsilateral breast tumor recurrence. Retrospective studies have suggested a 20%-50% risk of systemic metastases in patients who sustain an ipsilateral breast tumor recurrence. A study conducted at Yale University found that ipsilateral breast tumor recurrence was a significant predictor of distant metastases, particularly among women who relapsed within 4 years of the original diagnosis; these women had a rate of distant metastasis of approximately 50%. Similar findings were noted by the NSABP investigators.

These data suggest that women whose tumors recur in the ipsilateral breast within the first few years following the original diagnosis may be considered for adjuvant systemic therapy. Given the lack of prospective, randomized data, specific treatment recommendations for these women remain highly individualized.

Regional nodal recurrence and postmastectomy recurrence of disease in the chest wall

Although there are limited data addressing the use of adjuvant systemic therapy at the time of locoregional relapse following mastectomy, given the high rate of systemic metastasis in this population, these patients may be considered for adjuvant systemic therapy. A recently reported randomized trial demonstrated a disease-free survival benefit with the use of adjuvant tamoxifen fol-
lowing radiation therapy at the time of postmastectomy recurrence of disease in the chest wall in patients with estrogen-receptor–positive tumors. The 5-year disease-free survival rate was increased from 36% to 59%, and median disease-free survival was prolonged by > 4.5 years.

Patients with estrogen-receptor–negative tumors and aggressive locoregional recurrences may also be considered for systemic cytotoxic chemotherapy, given their relatively poor prognosis and the high rate of metastasis.

MEDICAL TREATMENT OF METASTATIC BREAST CANCER

Patients with metastatic cancer can be divided into two groups: those with stage IV disease at presentation and those who develop metastases after primary treatment. The management of stage IV disease depends on the site and extent of metastases, comorbid conditions, and clinical tumor characteristics.

Patients with delayed metastatic disease can be divided into two groups, ie, so-called low risk and intermediate or high risk, based on the biologic aggressiveness of the disease. As shown schematically in Figure 2, the management approach to these two groups differs.

Low-risk patients

The low-risk group includes patients who develop metastatic disease after a long disease-free interval (ie, a long disease-free interval from primary breast cancer diagnosis to presentation with metastasis), those whose tumors are positive for hormone receptors (estrogen and progesterone), those with bone-only disease, and those without extensive visceral organ involvement.

Hormone therapy Low-risk patients, whose tumor is hormone receptor-positive (ie, estrogen receptor-positive and/or progesterone receptor-positive), may be treated with a trial of hormone therapy.

First-line hormonal therapy consists of an aromatase inhibitor, with careful serial assessment of clinical and disease responses.

Hormone therapy may be associated with a “flare” response, a temporary worsening of signs and symptoms of disease within the first few weeks of treatment. This response generally means clinical benefit will follow.
If the tumor initially responds to first-line hormone therapy and then progresses, a second hormonal manipulation is warranted. Various hormonal agents are available (Table 3). They may be used sequentially and may provide disease palliation for prolonged periods in some patients.

**Second-line hormonal agents** The choice of second-line endocrine therapy depends on the front-line endocrine agent used. Typically, if tamoxifen was used, the second-line agent includes an aromatase inhibitor or fulvestrant (Faslodex) for postmenopausal women. For premenopausal women, the choice may be megestrol acetate or induction of menopause with an LHRH agonist with or without an aromatase inhibitor. If aromatase inhibitors were used as front-line agents for postmenopausal women, second-line options can be to change to another class of aromatase inhibitor, fulvestrant, or tamoxifen.

The most commonly used second-line hormonal agents had been progesterational drugs, such as megestrol. Recent randomized trials have indicated that the aromatase inhibitors, such as anastrozole (Arimidex), letrozole (Femara),
fulvestrant, and exemestane (Aromasin), are equally effective for palliation of metastatic disease, have less toxicity, and may provide a survival advantage compared with megestrol. Therefore, they are the drugs of choice for second-line therapy following tamoxifen administration. Tamoxifen may also be considered as second-line therapy for patients initially treated with an aromatase inhibitor.

Hormonal therapy continues until evidence of disease progression or drug-related toxicity precludes further therapy with the same agent. If a partial or complete response to the first hormonal treatment is documented at the time of disease progression, a second hormonal agent may provide further palliation of symptoms and avoid the initiation of systemic chemotherapy. However, subsequent hormonal responses tend to be of shorter duration, and, ultimately, the disease will become refractory to hormonal treatment.

**Cytotoxic agents** Hormone-refractory disease can be treated with systemic cytotoxic therapy. FAC, paclitaxel, TAC (Taxotere [docetaxel], Adriamycin [doxorubicin], cyclophosphamide), or docetaxel may be used in this situation. (For a more detailed discussion of these agents, see section on “Intermediate- or high-risk patients.” For doses, see Table 1.)

**Intermediate- or high-risk patients**

Intermediate- or high-risk patients include those with rapidly progressive disease or visceral involvement, as well as those with disease shown to be refractory to hormonal manipulation by a prior therapeutic trial.

**Anthracycline-containing combinations** such as FAC (see Table 1), are preferred for these patients. However, newer combinations of doxorubicin and a taxane are gaining favor for use in patients who have not received > 450 mg/m² of an anthracycline and whose relapse has occurred more than 12 months after the completion of adjuvant therapy.

**Single agents** Many single cytotoxic drugs have shown some activity in metastatic breast cancer (Table 1). They include vinblastine, mitomycin (Mutamycin), thiotepa, capecitabine, vinorelbine (Navelbine), and gemcitabine.

**Paclitaxel** One of the most active agents is paclitaxel. It has demonstrated anti-tumor activity in patients with anthracycline-resistant disease, as well as in those who have received three or more prior chemotherapy regimens for metastatic disease.

High-dose paclitaxel (250 mg/m² over 3 hours) has not been shown to be superior to 175 mg/m² over 3 hours. The higher dose regimen is associated with greater hematologic and neurologic toxicities.

**Docetaxel**, approved by the US Food and Drug Administration (FDA) for anthracycline-resistant locally advanced or metastatic breast cancer, has demonstrated overall response rates of 41% in patients with doxorubicin-resistant disease. It has been shown to be superior to mitomycin/vinblastine in patients whose disease progressed after an anthracycline-based chemotherapy regimen.
The recommended starting dose of docetaxel—100 mg/m² as a 1-hour IV infusion—requires premedication with dexamethasone to avoid fluid retention and the capillary leak syndrome. The usual regimen of dexamethasone is 8 mg bid for a total of 3 days, beginning 24 hours prior to the administration of docetaxel.

Although 100 mg/m² is the dose of docetaxel approved by the FDA, many recent trials have demonstrated a high rate of grade 4 hematologic toxicity at this dose level; a dose of 60-70 mg/m² may achieve equivalent therapeutic benefit with improved safety. As with paclitaxel, the docetaxel dosage must be modified in patients who have hepatic impairment, manifested by elevated transaminase or alkaline phosphatase levels.

Capecitabine, an orally active fluorinated pyridine carbonate, has been shown to have substantial antitumor effect in patients whose disease has recurred or progressed after prior anthracycline chemotherapy or after taxane therapy. Prolonged survival, limited toxicity, and response in visceral as well as soft-tissue disease add to the benefit of capecitabine. Toxicities include diarrhea, stomatitis, and hand-foot syndrome.

New approaches Multiple new approaches to treating metastatic breast cancer are being explored. Weekly schedules of docetaxel and paclitaxel have been reported to produce high response rates and lower toxicity than 3-week schedules. Combinations of doxorubicin with paclitaxel or docetaxel have also shown substantial antitumor activity, as have combinations of capecitabine and docetaxel, carboplatin and paclitaxel, and gemcitabine and cisplatin. These newer combinations need to be compared with standard AC or FAC (CAF) regimens in phase III trials. Recent studies also suggest that sequential weekly chemotherapy may be as effective as more intensive combinations with respect to overall survival in patients with metastatic breast cancer.

Monoclonal antibody therapy

Trastuzumab, a humanized monoclonal antibody to the HER-2/neu protein, has been approved for use as a single agent in second- and third-line therapy for metastatic breast cancer and in combination with paclitaxel as first-line therapy in this setting. A randomized trial consisting of 469 women showed that the combination of trastuzumab with chemotherapy yielded a 45% overall response rate, as compared with a 29% rate with chemotherapy alone—a 55% increase. The addition of trastuzumab had the greatest impact on response when combined with paclitaxel. Among the study group as a whole, 79% of women...
treated with trastuzumab chemotherapy were alive at 1 year, as compared with 68% of those given chemotherapy alone.

A recent update of those data has shown a superior median overall survival with chemotherapy plus trastuzumab compared with chemotherapy alone (25.4 vs 20.9 months). The survival advantage was seen with both AC plus trastuzumab and paclitaxel plus the monoclonal antibody.

In another single-arm trial involving 222 women who had not responded to prior chemotherapy, trastuzumab shrunk tumors by 50% in 14% of women, with a median duration of response of 9 months. Overall, trastuzumab was well tolerated in both trials. Due to an increased risk of cardiac dysfunction observed in women treated with trastuzumab plus an anthracycline, trastuzumab should not be used in combination with this drug class.

It is important to point out that trastuzumab also produces cardiac toxicity when administered by itself, particularly in patients who have had extensive prior exposure to an anthracycline. Finally, essentially all of the clinical benefit of trastuzumab (alone or in combination) is confined to patients whose breast cancer expresses high (3+) levels of the HER-2/neu oncoprotein.

**High-dose chemotherapy**

Patients who present with or subsequently develop distant metastasis may be candidates for high-dose intensive chemotherapy programs with autologous stem-cell support. Multiple feasibility and phase II studies of this approach have been undertaken. The majority of programs include the use of multiple alkylating agents. The role of high-dose chemotherapy in metastatic disease remains controversial, and analysis and observation of ongoing clinical trials continue to be important.

The results from multiple centers indicate an overall 5-year disease-free survival rate of 25% in patients with metastatic disease treated with high-dose chemotherapy. However, it must be remembered that these results were obtained in a select patient population—generally individuals < 60 years of age with good performance status; chemotherapy-sensitive disease; and normal cardiac, pulmonary, renal, and hepatic function. The use of intensive supportive out-

**TABLE 4: Randomized studies of high-dose chemotherapy in metastatic breast cancer**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Number of patients</th>
<th>Median follow-up (yr)</th>
<th>Survival rate (%)</th>
<th>High-dose treatment</th>
<th>Standard treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadtmauer et al</td>
<td>553</td>
<td>3</td>
<td>32.0</td>
<td>38.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Lotz et al</td>
<td>61</td>
<td>5</td>
<td>29.8</td>
<td>18.5</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant
patient care, such as colony-stimulating factors and antibiotics, has significantly reduced the morbidity and mortality associated with the high-dose chemotherapy approach.

In recently presented randomized trials of high-dose chemotherapy in patients with metastatic breast cancer (Table 4), it appears that most of the benefit occurs in women with low-bulk disease, especially those in complete clinical remission. A recent meta-analysis with longer follow-up also demonstrated a benefit for the addition of high-dose therapy to standard, anthracycline-containing chemotherapy for advanced disease in the setting of patients in complete clinical remission. This therapeutic modality remains investigational for patients with stage IV disease, however; women referred for high-dose therapy should be enrolled in a clinical trial.

Adjunctive bisphosphonate therapy

Multiple published reports have now confirmed the benefit of bisphosphonates as an adjunct to treatment of patients with bone metastasis. Use of these agents results in a significant reduction in skeleton-related events, including pathologic fracture, bone pain, and the need for radiation therapy to bone. Pamidronate (Aredia) and zoledronic acid (Zometa), both in IV formulations, are available in the United States. Oral bisphosphonates used for this indication, such ibandronate and clodronate, are not in the US market.

Patients with breast carcinoma who had all types of bone metastases (osteolytic, mixed, or osteoblastic) were randomized to receive treatment with either 4 mg or 8 mg of of zoledronic acid as a 15-minute infusion or 90 mg of pamidronate as a 2-hour infusion every 3-4 weeks for 12 months. The proportion of patients who had a skeleton-related event (defined as a pathologic fracture, spinal cord compression, radiotherapy, or surgery to bone) was comparable between treatment groups (approximately 45%). However, among patients who had breast carcinoma with at least one osteolytic lesion, treatment with 4 mg of zoledronic acid was more effective than 90 mg of pamidronate in reducing skeletal complications.

The most commonly reported adverse events for either zoledronic acid or pamidronate were bone pain, nausea, fatigue, emesis, and fever. The 4-mg dose of zoledronic acid results in elevated serum creatinine levels in about 7.7% of patients, vs 6.0% with pamidronate. A larger proportion of patients had elevated serum creatinine levels with 8-mg of zoledronic acid; therefore, this
dose is not recommended. Symptomatic hypocalcemia, although relatively rare, requires frequent monitoring of calcium and phosphate levels during treatment.

**ROLE OF RADIATION THERAPY IN METASTATIC DISEASE**

Irradiation remains an integral component of the management of metastatic breast carcinoma. Although bone metastases are the most commonly treated metastatic sites in patients with breast cancer, brain metastases, spinal cord compression, choroidal metastases, endobronchial lung metastases, and metastatic lesions in other visceral sites can be effectively palliated with irradiation.

**Radiation dose and schedule** Depending on the disease site and volume of the radiation field, fractionation schedules ranging from 20 Gy in 5 fractions to 30 Gy in 10 fractions are used most commonly. In some situations, more protracted courses using lower daily doses may be indicated.

**Bone metastasis** For patients with widespread bone metastasis, hemibody irradiation (6-7 Gy in one fraction to the upper body or 8 Gy to the lower body) has been shown to be effective. Strontium-89 chloride (Metastron) and other systemic radionuclides also provide effective palliation for widespread bone disease.

**Consolidation after high-dose chemotherapy** Since patients with metastatic disease treated with high-dose chemotherapy and autologous bone marrow or stem-cell transplantation often develop progressive disease in previously involved sites, studies have suggested the use of “consolidative radiation therapy” for patients undergoing high-dose chemotherapy. Although this approach appears to be well tolerated and preliminary data are encouraging, whether it will affect survival remains to be determined.

**ROLE OF SURGERY IN METASTATIC DISEASE**

There are selected indications for surgical intervention in patients with metastatic breast cancer, and the role of surgery at this point is generally palliative. Most commonly, palliative surgery is offered to patients with brain metastases, spinal cord compression, fractures, or symptomatic pleural or pericardial effusions not controlled by other means. It is also used for GI complications stemming from metastatic deposits. The curative benefit of surgery in the treatment of metastatic disease to the lungs or liver is not proven, but, in highly selected cases, surgery may be beneficial.

**Spinal cord compression** Patients with spinal cord compression who have progressive symptoms during irradiation, disease recurrence after irradiation, or spinal instability or who require diagnosis are candidates for surgery.

**Solitary brain metastasis** Patients with a long disease-free interval and solitary brain metastasis may be candidates for resection. Evidence suggests an improved disease-free survival, overall survival, and quality of life in this subset of patients when treated with surgery combined with postoperative cranial irradiation, as compared with radiation therapy alone.
Gamma- and cyber-knife radiosurgery is increasingly used to manage brain metastases. In some instances, these modalities have been used in patients who have multiple metastatic brain lesions or in patients who had previously received conventional treatment modalities for brain metastases, including whole-brain irradiation. No radiation-induced dementia and a remarkably low incidence of local failure were reported with these treatments. Although in the past, local control of brain metastasis was an issue, these treatment modalities are shifting the question of survival to that of systemic control.

**Chest wall resection** It is extremely rare for a patient with distant metastatic disease to be a candidate for chest wall resection; however, patients with symptomatic recurrence of disease in the chest wall who have limited distant disease and a life expectancy of > 12 months may be appropriate candidates.

**Follow-up of long-term survivors**

For recommendations on the type and timing of follow-up evaluations, see chapter 10.

**SUGGESTED READING**


