ABSTRACT

Survival rates of metastatic breast cancer have improved considerably in the past 2 decades. However, the median survival of patients with metastatic breast cancer remains 2 to 3 years, with only 5% to 10% achieving long-term remission. Treatment goals for this population should be primarily palliative, designed to maintain quality of life and prolong survival or at least delay disease progression. Primary therapies include hormonal options, systemic chemotherapy, and targeted therapies. Prognosis varies based on the tumor’s Scarff-Bloom-Richardson grade, hormonal and human epidermal growth factor receptor type 2 expression, previous response to hormonal therapies and/or chemotherapy, length of time before disease progression, existing comorbidities, and volume and site of metastases.

Choosing the appropriate therapy depends on the hormonal receptor status of the tumor, comorbidities (particularly liver or kidney abnormalities), disease severity, and location of metastases, as well as patient preference. Growth factor inhibitors, combinations of hormonal and targeted therapies, and newer agents, such as kinesin spindle protein inhibitors and epothilones, offer additional options for the near future.


TREATMENT-EXPERIENCED BREAST CANCER

Although the mortality rate from breast cancer in the United States has steadily declined over the past 20 years, 1% to 5% of women with breast cancer will present with metastatic disease at the time of diagnosis. Another 10% to 15% will relapse with distant metastases, primarily to the bone, liver, or lung. Seventy-five percent of metastatic breast cancer cases develop within 5 years of the original diagnosis. Metastatic breast cancer is not a curable disease, although 5-year survival rates are increasing.

Metastatic breast cancer is a disease with wide heterogeneity. Some patients experience a rapid course of metastases and physical decline despite systemic treatment, whereas others follow an indolent course with long periods of stability. These latter patients tend to be postmenopausal with estrogen receptor (ER)-positive tumors. They may survive in the absence of active treatment for more than 10 years. However, the median survival of patients with metastatic breast cancer is 2 to 3 years, and only 5% to 10% of patients achieve long-term remission (>5 years), with patients who respond to chemotherapy exhibiting a longer survival. Overall, just 5% to 15% of women with metastatic breast cancer achieve a complete response.

Prognostic factors for metastatic breast cancer include the volume and site of metastases. Patients with metastases to the skin, lymph nodes, or bone tend to survive longer than those with visceral metastases to the lungs, liver, or brain. Comorbidities, such as diabetes, arthritis, or cardiovascular disease, also play a significant role in survival. Patients with more than 2 comorbidities tend to exhibit a poorer survival rate. However, comorbidities are also an independent prognostic factor given their tendency to impact patients’ ability to tolerate therapy or a therapeutic dose, either of which may result in a poorer clinical response.
A patient’s response to previous therapy, whether systemic or hormonal, also affects prognosis. A longer previous disease-free interval predicts a better prognosis.

Finally, tumor receptor status plays an important role in prognosis. Women with ER-positive tumors generally have increased survival compared to those with ER-negative tumors and human epidermal growth factor receptor type 2 (HER2)-receptor amplification, who tend to have a more aggressive course of disease. ER-positive tumors also tend to respond better to hormonal therapies, both chemical and surgical. Overall, approximately 50% to 60% of ER-positive tumors respond to hormonal therapies compared to approximately 6% of ER- or progesterone receptor (PR)-negative tumors. Approximately 70% of women with breast cancer, most of them postmenopausal, have ER-positive tumors.

In contrast to ER-positive tumors, only 20% to 30% of women exhibit tumors with HER2 amplification/overexpression. This tumor type appears in approximately 33% of women with breast cancer aged younger than 50 and predicts a poor response to hormonal therapy. However, HER2 amplification predicts a good response to chemotherapy in metastatic disease and in the adjuvant setting, particularly the anthracycline doxorubicin and the taxane paclitaxel.

TREATMENT GOALS AND OPTIONS IN METASTATIC BREAST CANCER

The treatment goals for metastatic breast cancer are to palliate symptoms, prolong survival, increase progression-free survival or delay disease progression, and improve the quality of life for the patient.

In rare cases, surgery or radiotherapy may be attempted for isolated metastases, but the primary therapies used are systemic chemotherapy, endocrine therapy, biologic agents, and bisphosphonates (for bone metastases). Hormonal options and chemotherapy are the standard treatments, although many biologic targeted agents are exhibiting promise for this stage of cancer. In some instances, women may opt for alternative therapies in addition to traditional treatments.

The selection of appropriate therapy depends on several patient and tumor factors. The factor most often driving endocrine therapy is whether a patient has an ER on the cancer cells. In addition, patients who have multiple comorbidities or vital organ abnormalities, particularly renal or hepatic dysfunction, have a high risk of chemotherapy toxicities. Other factors that suggest hormonal therapy as an initial option include a previous response to endocrine therapy, evidence of indolent disease, postmenopausal status, and lack of visceral involvement.

In contrast, patients considered good candidates for chemotherapy include those with aggressive disease, visceral involvement, ER-negative status, and HER2-positive tumors.

The Figure depicts an algorithm for the treatment of advanced breast cancer and the 5 most commonly used options. As the Figure demonstrates, patients with ER- and/or PR-positive tumors generally begin treatment with hormonal therapies. If they become refractory to hormonal therapies, or if the tumors are ER and/or PR negative, patients then initiate chemotherapy. If the tumor also expresses HER2, trastuzumab is added to chemotherapy. However, if the patient is triple negative with no tumor expression of estrogen, progesterone, or HER2, chemotherapy alone is the preferred option.

HORMONAL THERAPY

The antiestrogen tamoxifen is typically the first-line hormonal therapy for premenopausal women with metastatic breast cancer. If patients have a risk factor that does not allow for tamoxifen therapy, then ovariectomy (surgical or radiation therapy), or medical oophorectomy with luteinizing hormone-releasing...
hormone (LHRH) analogues (eg, goserelin or leupro-lique) may be used. If the patient initially responds but then becomes refractory, whichever option has not already been attempted may be used. For instance, if the patient is refractory to surgical or medical oophorectomy, begin an antiestrogen; if she becomes refractory on an antiestrogen, move to ovarian ablation or LHRH analogue. If ovarian function ceases after first-line therapy, the patient should continue on tamoxifen.

If relapse occurs after all approaches, third-line therapy options include fulvestrant or progestins (eg, megestrol acetate or medroxyprogesterone acetate), or, possibly, aromatase inhibitors (eg, anastrozole, letrozole, or exemestane). However, the usefulness of aromatase inhibitors in premenopausal women remains questionable.3

Aromatase inhibitors, as well as antiestrogens, are indicated as first-line hormonal therapies for postmenopausal women, followed by progestins or androgens (fluoxymesterone) if disease recurs.3

Adverse effects of tamoxifen include hot flashes (64%), fluid retention (32%), vaginal discharge (30%), nausea (26%), irregular menses (25%), increased bilirubin levels (2%), increased creatinine levels (2%), thrombocytopenia (2%), deep vein thrombosis (0.8%), pulmonary embolism (0.5%), and skin changes (19%).8

Adverse effects of progesterone include mild fluid retention, menstrual irregularities, and nausea. The aromatase inhibitors may result in arthralgia (15%–20%), hot flashes, blood clots (1%), and edema (7%). Finally, the most common adverse effects of gonadotropin-releasing hormone (GnRH) agonist inhibitors are hot flashes (50%), decreased libido (9%), and gynecomastia (9%).9-11

Adverse effects of progestrone include mild fluid retention, menstrual irregularities, and nausea. The aromatase inhibitors may result in arthralgia (15%–20%), hot flashes, blood clots (1%), and edema (7%). Finally, the most common adverse effects of gonadotropin-releasing hormone (GnRH) agonist inhibitors are hot flashes (50%), decreased libido (9%), and gynecomastia (9%).9-11

**SYSTEMIC CHEMOTHERAPY**

Although many chemotherapy regimens show activity in metastatic breast cancer, no single agent or combination has emerged as the standard. Instead, drug selection is based on adverse effect profile, prior therapy, and patient preferences.3,7,12 In most instances, chemotherapy begins with an anthracycline or taxane. On average, these drugs produce a 13% complete remission rate and approximately a 30% to 40% partial remission with a median duration of response of approximately 10 months.3,7,13

However, with each successful chemotherapy treatment, the response rate and duration of response drops. There does not appear to be a dose-response curve for metastatic breast cancer, thus, high-dose chemotherapy is not recommended.3,7,13

In certain situations, adding hormonal therapy to systemic chemotherapy in patients with widely metastatic disease may prolong survival, but this outcome is variable.3,7,13

**DURATION AND DISCONTINUATION OF CHEMOTHERAPY**

Once chemotherapy begins, most patients continue until disease progression or prohibitive toxicity occurs. In patients with indolent disease and an extended period of response, a chemotherapy “holiday” of up to 1 year or until recurrence is an option.

Signs of overt tumor recurrence are typically addressed with a change to a different chemotherapy regimen. It is not unusual for patients with metastatic breast cancer to undergo 3 to 4 chemotherapy regimens.14-17

**COMMON CHEMOTHERAPY TREATMENT REGIMENS**

The typical chemotherapy regimens for metastatic breast cancer include the anthracyclines, taxanes, fluoropyrimidines, vinorelbine, and gemcitabine. The Table18-30 depicts the recommended dosing and adverse effects for each chemotherapy.

**TARGETED THERAPIES**

To date, trastuzumab is the only targeted therapy established in the treatment of metastatic breast cancer. As a single agent, it does not appear as effective as chemotherapy, producing only a 17% to 32% partial response. However, in combination with docetaxel or capecitabine, the response rate and duration of response are higher (45%–70%, with some complete responses). Adverse effects include coronary heart failure, asthenia, headache, insomnia, dizziness, rash, rinitis, pharyngitis, nausea/vomiting, diarrhea, anorexia, back pain, cough, dyspnea, sinusitis, and infusional toxicity.31

Lapatinib, an oral agent, is a small-molecule, reversible inhibitor of the intracellular tyrosine kinase domain of 2 members of the HER family, HER1 and HER2.32 The US Food and Drug Administration recently approved it in combination with capecitabine for patients whose cancers had not responded to trastuzumab or other therapies. Potential adverse effects include arrhythmia (rare), extreme dizziness or...
fainting, severe diarrhea, and white patches or sores inside the mouth or on the lips. 31

The anti-vascular endothelial growth factor monoclonal antibody bevacizumab, already used as part of chemotherapy regimens for colorectal cancer, may be beneficial in the treatment of metastatic breast cancer. One trial showed that combining bevacizumab with capecitabine resulted in a greater response rate than bevacizumab alone (19.8% vs 9.1%, \( P = .001 \)). However, the combination did not affect the primary

Table. Chemotherapy Options in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dosage</th>
<th>Response Rate</th>
<th>Toxicities</th>
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<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
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<tr>
<td>Doxorubicin</td>
<td>60–75 mg/m² IV Q 3 wk</td>
<td>32%–43% (1st)</td>
<td>Stomatodynia, nausea/vomiting, mucositis, cardiac toxicities, and alopecia</td>
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<tr>
<td></td>
<td>or 15 mg/m² wk</td>
<td>22%–29% (2nd)</td>
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<tr>
<td>Epirubicin</td>
<td>75–90 mg/m² IV Q 3 wk</td>
<td>36%–41%</td>
<td>Stomatodynia syndrome, nausea/vomiting, mucositis, cardiac toxicities, and alopecia (better tolerated in the elderly than gemcitabine and doxorubicin, particularly in terms of bone marrow toxicities)</td>
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<tr>
<td></td>
<td>or 20–30 mg/m² wk</td>
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<tr>
<td>Pegylated liposomal doxorubicin</td>
<td>40–50 mg/m² IV monthly</td>
<td></td>
<td>Less gastrointestinal, cardiac, and hand-foot syndrome toxicity than doxorubicin and epirubicin</td>
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<td><strong>Taxanes</strong></td>
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<tr>
<td>Paclitaxel</td>
<td>135–175 mg/m² IV Q 3 wk</td>
<td>32%–43% (1st)</td>
<td>Stomatodynia syndrome, peripheral neurotoxicity, alopecia, fluid-retention syndrome, and hypersensitivity reactions*</td>
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<tr>
<td></td>
<td>or 80–100 mg/m² IV weekly (dose dense)</td>
<td>50%–55% response rate (1st), 48% (2nd)</td>
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<tr>
<td>Docetaxel</td>
<td>100 mg/m² IV Q 3 wk</td>
<td>48% (1st)</td>
<td>Stomatodynia syndrome, mucositis, fluid-retention syndrome, alopecia, and nail abnormalities Greater bone marrow toxicity than with paclitaxel</td>
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<td></td>
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<tr>
<td><strong>Fluoropyrimidines</strong></td>
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<tr>
<td>Capecitabine (oral)</td>
<td>1000–1250 mg/m² in 2 daily doses, 14 of 21 d</td>
<td>30%–37% (1st)</td>
<td>Mucositis, diarrhea, hand-foot syndrome, and mild bone marrow suppression*</td>
</tr>
<tr>
<td></td>
<td>1250 mg/m² BID on d 1–14 IV docetaxel (75 mg/m²) on d 1 Q 21 days for patients with progressive metastatic breast cancer previously treated with anthracycline-based chemotherapy</td>
<td>40%–70% (mean duration of response 6–9 mo)</td>
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<tr>
<td><strong>Other Chemotherapies</strong></td>
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<tr>
<td>Vinorelbine</td>
<td>25 mg/m² IV weekly</td>
<td>25%–40% (1st)</td>
<td>Myelosuppression, constipation, and neuropathy (particularly in taxane-treated patients)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>800–1200 mg/m² IV for 3–4 wk</td>
<td>15%–37% (1st)</td>
<td>Hematologic, nausea, rash, fatigue, and flu-like symptoms Greater toxicity in the elderly</td>
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</tbody>
</table>

*Toxicities differ based on cycle of therapy. Greater neurotoxicity with weekly dosing; greater bone marrow toxicities with 3-week dosing.

1US FDA-approved daily dose is 2500 mg/m² but high levels of toxicity generally require a reduced dosage, which appears to have minimal effect on efficacy. 31 A lower dose is preferred in the elderly. 31

2Including cohort of elderly.

3Particularly useful in anthracycline- and taxane-refractory patients.

Data from Paridaens et al; Sledge et al; Gasparini et al; O’Shaughnessy; Seidman et al; Seidman et al; Stemmler et al; O’Shaughnessy et al; Bajetta et al; O’Shaughnessy et al; Zelek et al; Feher et al; Ershler.
endpoint of progression-free survival (4.86 vs 4.17 months, hazard ratio 0.98) or overall survival (15.1 vs 14.5 months). Bevacizumab is also under investigation in combination with gemcitabine or vinorelbine for the treatment of metastatic breast cancer.31

Another option is metronomic chemotherapy with frequent oral, low-dose administration, particularly with cyclophosphamide (1 mg/kg/day), often in combination with hormonal therapy. This method results in minimal toxicity. Thus, it is better tolerated and may be particularly beneficial in the elderly.33

**Novel or Investigational Agents**

Clinical trials with growth factor inhibitors, a combination of tamoxifen and lapatinib, and newer agents such as the kinesin spindle protein inhibitor, ispinesib, are ongoing.31 One exciting new class is the epothilones, which is exhibiting excellent response rates in chemotherapy-resistant populations.34-37

In October 2007, ixabepilone became the first epothilone approved for marketing in the United States.38 It is indicated for the treatment of metastatic or locally advanced breast cancer in combination with capecitabine in patients who failed an anthracycline and a taxane, and as a monotherapy for the treatment of metastatic or locally advanced breast cancer in patients who failed an anthracycline, a taxane, and capecitabine. The product information carries a black box warning that ixabepilone in combination with capecitabine is contraindicated in patients with aspartate aminotransferase or alanine aminotransferase greater than 2.5 x upper limit of normal (ULN) or bilirubin greater than 1 x ULN due to increased risk of toxicity and neutropenia-related death.39

**Conclusions**

Several new agents for the treatment of metastatic breast cancer are in late-stage clinical trials and may be available soon. They should continue to improve survival in patients with metastatic breast cancer.

**Discussion**

**Dr Zamboni:** What percentage of patients with either premenopausal or postmenopausal metastatic breast cancer are patients who are triple negative—with negative ER, PR, and HER2 receptors?

**Dr Ignoffo:** Probably around 8% to 10%. It is very low.

**Dr Zamboni:** I assume they do the worst?

**Dr Ignoffo:** Generally. But I have not seen a study examining the clinical course of just these patients.

**Dr Adel:** There are no hormonal options for these patients. They start on chemotherapy immediately. Usually, the options are limited for these patients. According to some clinical trials, epothilones showed some activity in patients whose tumors were triple negative. We are seeing some efficacy, but we do not know how effective it is. I also want to add one thing about aromatase inhibitors: the importance of recognizing the increase in triglycerides in clinical trials of women taking aromatase inhibitors.

**Dr Medina:** However, the major side effect of aromatase inhibitors is osteoporosis. As far as the third-line hormonal treatments, we usually change to systemic therapy instead of using third-line hormonal options in our patients.

**Mr Solimando:** Do you even get to second line? In my clinics, the women get a trial of tamoxifen, and if they fail that, they go right to chemotherapy.

**Dr Medina:** It depends on how long a response we get to the hormonal therapy. If the patient responds for 1 year, and then fails, we will try a second hormonal approach. It also depends on whether they have visceral or bone-only metastatic disease.

**Mr Solimando:** In premenopausal women, we see them start progressing after 3 or 4 months on tamoxifen. At that point, they usually go right to chemotherapy. In fact, I think some oncologists are actually going straight to systemic chemotherapy in this population figuring they will need to use it early in the treatment cycle anyway. As far as the third-line hormonal treatments, we usually change to systemic therapy instead of using third-line hormonal options in our patients.

**Dr Medina:** And certainly aromatase inhibitors are not used in this population outside of a clinical trial. And most of these trials are conducted in combination with ovarian suppression. Thus, using the aromatase inhibitors as a third-line hormonal treatment, even with tamoxifen or GnRH antagonists to block both sources of estrogen, or as a single agent in premenopausal women, is just not done much.

**Dr Waddell:** Is anyone seeing patients taking these aromatase inhibitors or tamoxifen who self-treat their hot flashes with alternative therapies?

**Dr Ignoffo:** Yes. There have been many trials looking at black cohosh, for instance, published in the *Journal of Clinical Oncology* and other journals, showing some benefit. Some patients try vitamin E or other...
alternatives. There have been no good studies, to my knowledge, showing these options have been able to control hot flushes well.

Dr Waddell: But what should community pharmacists tell patients who ask about these plant-based options?

Dr Ignoffo: They should recommend against it because we do not know what they do in an ER-positive patient. I have not personally seen cases in which they exacerbated the disease, but it does not sound like the appropriate thing to do.

Dr Kuhn: Which is better in the metastatic setting: paclitaxel as a single agent every 3 weeks or weekly?

Dr Ignoffo: This should be taken into a randomized trial. Just looking at the numbers, it appears that the weekly dosing is approximately 10% to 15% better. But to know if it is truly better, we have to await the results of a big clinical trial. Still, it is an option, although I am not ready to make that jump to saying it is the preferred option.

Dr Kuhn: In my opinion, although you can make a case for the 3-week protocol in combination with other drugs, I would never recommend the 3-week schedule of paclitaxel alone for patients with metastatic cancer.

Dr Waddell: Also, you have to remember that these are patients with metastatic cancer with lives to live. If it turns out that the toxicity and efficacy is no different, than certainly the patient would rather come in every 3 weeks rather than once every week.

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