Breast cancer is the most common type of cancer among women in the United States, and the second most common cause of cancer deaths. The number of treatments for metastatic breast cancer has increased substantially over the past several decades, and survival times for patients also have improved. However, rates of recurrence and mortality with breast cancer remain very high. Treatment options include hormonal therapies (e.g., antiestrogens and aromatase inhibitors) and several chemotherapy agents, which may be used alone or in many different combinations. Chemotherapy options include the anthracyclines (e.g., doxorubicin and epirubicin), taxane-based agents (e.g., paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel), and platinum-based agents (e.g., cisplatin). For patients who have failed to respond to taxanes and anthracyclines, options include capecitabine, vinorelbine, gemcitabine, and investigational agents. Targeted biologic therapies (e.g., trastuzumab and lapatinib) are a relatively recent approach to the treatment of metastatic breast cancer, with trastuzumab available since 1998 but other agents only approved or under consideration of approval during 2007. The epothilones are a new class of antitumor agents that are under investigation for the treatment of patients with breast cancer. Each of these agents has its own distinctive toxicities. Clinical trials continue to refine the optimal treatment combinations for patients with metastatic breast cancer.

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receptor modulators (SERM) and the “pure” antiestrogens. SERMs are nonsteroidal agents that possess both estrogenic and antiestrogenic properties. The prototypical agent in this class is tamoxifen; other agents include toremifene, raloxifene, idoxifene, and droloxifene. These agents act as estrogen blockers in some tissues (eg, the breast), but produce estrogen-like effects in other tissues (eg, the uterus). Pure antiestrogens are steroidal analogues of 17-β estradiol, and possess no estrogen-like activity.

In contrast to the antiestrogens, aromatase inhibitors prevent the conversion of androgens to estrogens primarily within the adrenal glands, a process that is carried out by the enzyme aromatase. Nonsteroidal aromatase inhibitors approved by the US Food and Drug Administration (FDA) include anastrozole and letrozole; exemestane is a US FDA-approved steroidal aromatase inhibitor. Antiestrogens may be used by premenopausal or postmenopausal women, whereas aromatase inhibitors are only indicated for the treatment of breast cancer in postmenopausal women. In individuals who are ER and/or PR positive, hormonal therapies can palliate metastatic breast cancer for a considerable period of time. In large clinical trials of antiestrogens and aromatase inhibitors for first-line treatment of metastatic breast cancer, the median time to progression with these agents was approximately 6 months to 1 year. In addition, several clinical trials have demonstrated that the aromatase inhibitors are superior to tamoxifen for the first-line treatment of metastatic breast cancer and are superior to megestrol acetate for second-line therapy.

CHEMOTHERAPY CHOICES FOR METASTATIC BREAST CANCER

First-line chemotherapy options for metastatic breast cancer include the anthracyclines (eg, doxorubicin, epirubicin, and liposomal doxorubicin), taxane-based therapies (eg, paclitaxel, docetaxel, and nanoparticle albumin-bound [nab]-paclitaxel), and platinum-based agents (eg, cisplatin). Chemotherapy regimens containing doxorubicin have been associated with high treatment response rates and survival in women with metastatic breast cancer. Single-agent doxorubicin produces a response rate of approximately 50%, which can be improved by combining doxorubicin with other active agents. At equimolar doses, doxorubicin and epirubicin produce similar response rates, although epirubicin has a more favorable tolerability profile than doxorubicin, including reports of less cardiotoxicity. Higher epirubicin doses are more effective than lower doses, and epirubicin has also been shown to be effective when used in combination treatment regimens.

Taxanes bind to and stabilize microtubules, producing cell cycle arrest and apoptosis (cell death). These agents are among the most active therapies used in the treatment of metastatic breast cancer, and produce significant benefit in adjuvant and neoadjuvant settings for node-positive breast cancer. Several combination regimens have been shown to improve the efficacy of taxane therapy, and it is likely that the best treatment strategy has not yet been identified. Clinically significant combination regimens include capecitabine and docetaxel, and gemcitabine and paclitaxel. Common adverse events with taxane agents include alopecia, myalgia, arthralgia, and peripheral neuropathy. Nab-paclitaxel is a solvent-free formulation of paclitaxel that uses albumin encapsulation to transport paclitaxel across cell membranes and concentrate it within the tumor. Nab-paclitaxel does not generally require premedication, it is administered using a short infusion time, and it is not associated with severe hypersensitivity reactions. The results of an ongoing clinical trial suggest that nab-paclitaxel is associated with a longer duration of progression-
free survival than docetaxel, with lower rates of neutropenia and mucositis.15

**CHEMOTHERAPY IN TREATMENT-RESISTANT PATIENTS**

The term “third-line” chemotherapy is used to describe agents for the treatment of patients who were previously treated with an anthracycline and a taxane, and who are not expected to benefit from additional treatment with the same agents. Patients receiving third-line chemotherapy often have significant disease-related symptoms. A single chemotherapy agent rather than combination therapy is often selected as third-line treatment, but both strategies are generally associated with a suboptimal median survival time. In addition, the chance of response decreases with increasing exposure to prior therapy. Chemotherapy agents for metastatic breast cancer in combination with or after the failure of taxanes and anthracyclines include capecitabine, vinorelbine, gemcitabine, and investigational agents (eg, vinflunine and the epothilones).

Capecitabine is an oral chemotherapy agent that is absorbed within the gastrointestinal tract and that is activated in a series of metabolic steps within the liver to yield the active agent 5-fluourouracil (5-FU). The final step of the conversion of capecitabine to 5-FU is carried out by the enzyme thymidine phosphorylase. Some tumor cells express high levels of this enzyme, and therefore, convert more capecitabine to 5-FU than the surrounding normal cells.16 Capecitabine is approved for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing regimen, or for patients who are resistant to paclitaxel and for whom additional anthracycline-containing therapy is not indicated. Capecitabine has been used in combination-therapy regimens with several other chemotherapy agents, including docetaxel and paclitaxel.17 The combination of capecitabine and docetaxel may stimulate the production of thymidine phosphorylase, resulting in increased conversion of capecitabine to 5-FU by tumor cells.18 Therefore, it is possible that combination treatment with docetaxel and capecitabine may produce a synergistic interaction with increased antitumor activity.18 In clinical trials of patients with metastatic breast cancer who had previously been treated with an anthracycline-based regimen, treatment with oral capecitabine plus docetaxel was associated with significantly higher response rates, time to disease progression, and survival than treatment with docetaxel alone.19,20

Vinorelbine has been examined in several clinical trials for the treatment of metastatic breast cancer, including studies as first-line therapy, as second-line therapy, in anthracycline-refractory patients, and in patients who are refractory to anthracycline and paclitaxel. As summarized in Table 1, vinorelbine has exhibited considerable activity in all these settings.21 Toxicities associated with vinorelbine include granulocytopenia, anemia, fatigue, nausea, constipation, bone pain, and paresthesias.

Several other chemotherapy agents have been evaluated for the treatment of metastatic breast cancer. Gemcitabine kills cells that are undergoing DNA synthesis, and therefore, affects rapidly dividing cancer cells.22 It is approved for the treatment of metastatic breast cancer, in combination with paclitaxel, in patients who have been treated with an anthracycline. Combinations with several other agents have been examined, including vinorelbine, doxorubicin, and experimental compounds. Phase II clinical trials have demonstrated that some patients respond to gemcitabine when used as a second-line, single-agent treatment for metastatic breast cancer after prior treatment with an anthracycline or a taxane.23,24 However, no

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Patients, n</th>
<th>Trials, n</th>
<th>Response Rate, %</th>
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<tbody>
<tr>
<td>First-line</td>
<td>503</td>
<td>9</td>
<td>35–59</td>
</tr>
<tr>
<td>Second-line</td>
<td>280</td>
<td>7</td>
<td>24–47</td>
</tr>
<tr>
<td>Anthracycline-refactory</td>
<td>195</td>
<td>2</td>
<td>16</td>
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<tr>
<td>Anthracycline- and paclitaxel-refactory</td>
<td>287</td>
<td>2</td>
<td>16</td>
</tr>
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</table>

Reprinted with permission from Vogel and Nabholz. *Oncologist*. 1999;4:17-33.21
response to gemcitabine was noted in a phase II study of patients who were refractory to both anthracycline and taxane therapy.\textsuperscript{25} Typical toxicities associated with gemcitabine include cytopenias, nausea, vomiting, and flu-like symptoms. Irino-tecan is an inhibitor of DNA topoisomerase I, which acts by producing DNA strand breaks, leading to tumor cell apoptosis.\textsuperscript{26} Irinotecan is currently approved for the treatment of metastatic colon cancer, and studies are in progress examining the efficacy of irinotecan in breast cancer. Vinflunine is a novel fluorinated vinca alkaloid that inhibits polymerization of tubulin (a component of microtubules).\textsuperscript{27} Laboratory studies have suggested that vinflunine may act synergistically with cis-platinum, mitomycin C, doxorubicin, and 5-FU.\textsuperscript{28} Vinflunine may produce less of an effect on microtubules within the axons of nerve cells than other vinca alkaloids, and therefore, may be less likely to produce neurotoxicity. One phase II study of patients with metastatic breast cancer has been completed,\textsuperscript{29} and studies examining vinflunine in combination with other agents are in progress.

A recent advance in the treatment of metastatic breast cancer has been the introduction of targeted biologic therapies, including trastuzumab and lapatinib. Trastuzumab is a monoclonal antibody directed against the cell signaling molecule human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is present in approximately 25% of patients with breast cancer and is associated with cancers that are highly proliferative and difficult to treat.\textsuperscript{30,31} Trastuzumab monotherapy has been associated with response rates of 26% to 40% when used as first-line therapy, and with response rates of 15% to 20% when used as second-line or third-line therapy.\textsuperscript{32-36} Trastuzumab has also been shown to improve survival in patients receiving chemotherapy. In one study, 469 patients with metastatic breast cancer were randomized to treatment with an anthracycline or paclitaxel, or to an anthracycline or paclitaxel combined with trastuzumab.\textsuperscript{37} As shown in Table 2, the response rate, time to progression, and duration of survival overall were significantly greater for patients who received chemotherapy in combination with trastuzumab. Lapatinib is an inhibitor of HER2 and a second molecule that is important in cell function, epidermal growth factor receptor.\textsuperscript{38} Lapatinib was recently approved by the US FDA in combination with capecitabine for patients with advanced or metastatic breast cancer who overexpress HER2 and who have received prior therapy with an anthracycline, taxane, and trastuzumab. Adverse effects of lapatinib include skin toxicity and diarrhea, and rare cardiac complications.

The epothilones are a group of compounds that are under investigation for the treatment of metastatic breast cancer. Antitumor effects of the epothilones ixabepilone (BMS-247550) and desoxyepothilone B (KOS-862) have been demonstrated in initial clinical studies.\textsuperscript{39,40} More than 300 epothilone derivatives have been identified, and several others are being evaluated in clinical trials. The epothilones are described in more detail in an accompanying article by Alisha Stein, RNC, BSN, OCN.

**CONCLUSIONS**

The use of hormonal agents in patients with metastatic breast cancer can palliate disease for a significant period of time. Anthracycline and taxane agents, with the addition of trastuzumab as indicated, are considered first-line therapy choices for the treatment of metastatic breast cancer. Novel agents with acceptable toxicity profiles and antitumor activity are emerging as alternatives for treatment of refractory metastatic breast cancer. Both sequential and combination regimens are being investigated, and patient participation in clinical trials of new agents should be encouraged.

![Table 2. RR, TTP, and OS with Chemotherapy vs Chemotherapy + Trastuzumab](image)

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Chemotherapy + Trastuzumab</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>32</td>
<td>50</td>
<td>.0001</td>
</tr>
<tr>
<td>TTP (mo)</td>
<td>4.6</td>
<td>7.4</td>
<td>.0001</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>20</td>
<td>25</td>
<td>.04</td>
</tr>
</tbody>
</table>

**OS = overall survival; RR = response rate; TTP = time to progression.**

Data from Slamon et al.\textsuperscript{37}
**DISCUSSION**

**Ms Shivnan:** I think that you have really highlighted the importance of the problem, the complexity of the disease, and the need for nurses to really be up-to-date on the evidence for chemotherapy and the other options that they are using in their practices to treat women with breast cancer. I wonder if you wanted to perhaps comment a bit more on the differences between receptor-positive and receptor-negative disease.

**Ms Frye:** At our institution we consistently use HER2, ER, and PR status to determine therapy for all of our patients. For patients who are ER positive or PR positive, we use hormonal therapy as a single agent or give sequentially after chemotherapy. For patients who are HER2 positive, we offer trastuzumab therapy to our patients. Lapatinib is now available as well for those patients refractory to trastuzumab. We are also doing studies in the adjuvant setting exploring the addition of lapatinib for patients who are positive for HER2. These markers are really becoming very widely used to determine therapy.

**Ms Shivnan:** I think it is worth mentioning that for some women, cost may be a factor in their decision making. Offering women the opportunity to participate in clinical trials in metastatic breast cancer can give more options to women who might not have access to these treatments otherwise.

**Ms Frye:** I believe that staff training about new medications and study requirements also helps to improve compliance to our clinical trial protocols. This becomes a regulatory issue if not done. If we do not train our nurses and physicians well, we are not following regulatory guidelines to ensure proper conduct of these trials. At MD Anderson Cancer Center there is an institutional initiative to improve and coordinate clinical trial education and the informed consent process not only for those directly involved in research but also for all nurses, physicians, and others who are involved with the patient. This is a work in progress. The tools are developed and designed to positively impact the effectiveness of our education of patients for clinical trials.

**Ms Elza-Brown:** We recently filled a new position for a clinical nurse specialist in our outpatient department, whose role is to act as a liaison between research nursing and clinical nursing. She does nurse education and acts on a daily basis to enhance communication between the research team and the clinical team. It is still too early to tell how this will affect clinical trial enrollment.

**Ms Stein:** In the community care setting, our organization is very proactive in educating physicians and nurses in community private practices. We have also been creating awareness and educating the general public on the value of clinical research and cancer care. On radio talk shows, we have discussed cancer clinical trials, how they are conducted, why they are necessary, dispelled myths associated with research, and differentiated preclinical from clinical research.

**Ms Viele:** I think as nurses involved in clinical trials we not only have a responsibility to educate our own nurses but community nurses as well. We need to keep nurses updated through our nursing education departments as well as through community programs sponsored by our local Oncology Nursing Society. In this way all nurses in the area benefit yielding to better patient information for the entire community we serve.

**REFERENCES**


