Chemotherapeutic Strategies for Advanced Breast Cancer

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Disease-free and overall survival have improved significantly for women diagnosed with early-stage breast cancer. At the same time, systemic therapy has only slightly enhanced long-term outcomes in advanced breast cancer, a disease that remains largely incurable. Several single-agent and combination chemotherapy approaches are available to women with hormone-insensitive advanced disease that may improve overall survival and progression-free survival, minimize symptoms and complications related to the disease, and improve overall quality of life. In addition, new cytotoxic and targeted agents have been recently introduced into practice and have improved both survival outcomes and quality of life. In this review, we will provide an update on commonly used chemotherapy-based regimens for the treatment of metastatic breast cancer, with a focus on tailoring therapy to different subtypes of the disease.

Breast cancer continues to be the most commonly diagnosed malignancy in women in the United States, and is the second leading cause of cancer-related death in women, with 40,460 deaths expected in 2007.[1] Notably, breast cancer–related mortality rates have declined from 33 per 100,000 women-years in 1989 to 25 per 100,000 women-years in 2003.[2] The reduction in mortality rates is attributed mostly to the implementation of screening mammography and to optimal local and early systemic therapy.[3] Yet many women suffer a systemic recurrence of their disease, and others present with metastases at the time of initial diagnosis. Despite advances in systemic treatment during the past 30 years, metastatic breast cancer is still considered an incurable disease, with very few exceptions.

**Goals of Therapy**
The main treatment modality for metastatic breast cancer is systemic therapy, which is administered to achieve one or more aims (Table 1). The ultimate goal of treatment in both the adjuvant and metastatic settings is cure. However, the majority of patients with advanced breast cancer will experience disease progression within 12 to 24 months after treatment initiation, and only a minority (1%–3%) are expected to survive 20 years.[4]

Because cure is a rare outcome in the metastatic setting, it is not usually presented to women as a primary intent. The main goals of therapy therefore shift to improvement of overall survival, time to progression, time to treatment failure, and overall response rate. It is possible, however, that with the introduction of targeted agents, some women may enjoy long-term remissions and may be indeed cured of their disease.

In addition, a large focus of treatment is to control disease-related symptoms and to decrease the risk of serious complications while minimizing toxicity. To achieve these goals, local therapies, such
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as surgery or radiation, may also be utilized. Because cures are uncommon, quality-of-life considerations are of vast importance and the therapeutic index of a chosen therapy plays a major role in treatment recommendations.

**Prognostic and Predictive Factors**

Prognostic and predictive factors are used to determine the most appropriate treatment for an individual. Prognostic factors are used to estimate outcome for a patient independent of systemic treatment. Classical prognostic factors in the metastatic setting include time to recurrence, extent of the disease, its location, prior therapy, symptoms related to the disease, and performance status. Hormone receptor status and human epidermal growth factor receptor type 2 (also known as HER2, HER2/neu, or c-erbB2) status are also prognostic factors. In contrast, predictive factors reflect the resistance or sensitivity of a given tumor to a specific therapy. Predictive factors that are currently in use to determine treatment include hormone receptor and HER2 status. Response to prior regimens and performance status are also predictive of treatment efficacy and tolerability.

**Prognostic Factors**

Only a few investigations provide evidence-based data regarding the long-term outcome of women with metastatic breast cancer, as median survival exceeding 3 to 5 years is the exception. Whether chemotherapy improves overall survival has been the subject of much debate. Obtaining such data is not generally possible because placebo-controlled trials are not ethical in this population. Recent experience suggests that new treatments or schedules are associated with incremental improvement in overall survival. It is important to note, however, that most trials in the metastatic setting exclude women with poor prognostic features or a poor performance status. Using data from the British Columbia Cancer Agency, Chia and colleagues recently examined survival rates of patients with metastatic breast cancer who received newly introduced hormonal and chemotherapeutic agents over the past 2 decades. The investigators reported that the implementation of new substances and therapies have led to a significant improvement in survival from a population-based perspective.

A cohort of 834 patients who were included in five consecutive anthracycline-based adjuvant protocols at the M.D. Anderson Cancer Center and who subsequently developed recurrent metastatic disease between 1974 and 2000 showed a statistically significant improvement in survival when grouped according to the time of onset. The variables that predicted for longer survival in this cohort included a smaller initial tumor size, lower stage of disease, fewer involved lymph nodes, longer disease-free interval, estrogen receptor–positive tumors, and a nonvisceral dominant site of disease recurrence. Overall, the estimated 5-year survival for patients with bone metastasis was 23%, as compared to 13% for patients with visceral metastasis. Interestingly, neither the dominant site of disease nor the disease-free interval were significant factors in a study reported by the European Organisation for Research and Treatment of Cancer (EORTC). The EORTC investigators evaluated 75 patients who had achieved a complete response following combination chemotherapy or chemoendocrine treatment for metastatic breast cancer. With a median follow-up of 6 years, the authors reported that 20% of patients who achieved a clinical complete response were alive at 5 years.

M.D. Anderson Cancer Center investigators reported that in a single prospective study, 24% of women who were treated with systemic anthracycline-based therapy following locoregional salvage therapy (surgical resection with or without radiation) of a solitary metastasis (ie, stage IV disease without evidence of disease, or stage IV NED) enjoyed a 15-year disease-free survival. More than half of the metastases included chest wall recurrences. Overall, 36% to 52% of patients with solitary metastases had no evidence of metastatic disease after locoregional treatment of a recurrence after 5 years.

Another study supports a mastectomy in addition to systemic therapy in women with limited advanced disease. Together, these data suggest that an aggressive approach may be a reasonable option for a select group of women and may improve long-term outcomes. In other studies, the amplification of HER2 was found to be a prognostic factor with greater value than the commonly used factors, such as hormonal receptor status and lymph node–positive disease, both in early and advanced breast cancer. In the next decade, high throughput technologies may lead to identification of other prognostic factors. Breast cancer can be divided into several subtypes based on histopathologic features, biologic patterns, and gene-expression profiles. The designation as a specific tumor subtype may become an important factor for determination of prognosis and for treatment decision-making.

**Predictive Factors and Breast Cancer Subtypes**

The expression of biologic markers on tumor cells is an important feature with respect to the choice
of therapy. The most powerful accepted predictive factors are the steroid receptors, including the estrogen receptor (ER) and the progesterone receptor (PR); their presence generally indicates the likelihood of response to hormonal manipulations. The ER, now known as ER-alpha, is expressed in approximately 75% of newly diagnosed breast cancers.[11]

Women with disease progression following prior hormonal interventions are not expected to derive additional benefit from such treatments despite the presence of hormone receptors. Women whose tumors do not express hormone receptors and those who have shown progression following hormonal interventions are considered hormone-insensitive and will be recommended chemotherapy-based therapies. During the past decade, other predictive factors have evolved, including expression or amplification of HER2, a strong predictive factor for trastuzumab (Herceptin) efficacy.

HER2, a 185-kilodalton glycoprotein with tyrosine kinase activity, is overexpressed in about 20% of invasive breast cancers.[12] Overexpression or amplification of HER2 is associated with a poor prognosis,[9] even in early node-negative breast cancer.[13] However, the prognosis of women with HER2-positive disease who receive the recently introduced HER2-targeted therapies has improved dramatically.

The utilization of high-throughput technology such as complementary DNA (cDNA) arrays and the availability of targeted therapy have clearly led to changes in the approach to therapy. Breast cancer can now be classified according to gene-expression profiles. Perou and Sorlie described different molecular portraits of human breast tumors on the basis of gene-expression patterns using cDNA microarrays in 2000.[14] They distinguished luminal A and B, the basal-like, the HER2-positive and the normal-like subtypes. According to subtype, prognoses may differ considerably.[15] More importantly, decisions regarding the most appropriate treatment may vary greatly based on the tumor subtype. Knowledge of tumor subtypes is therefore of great importance when discussing treatment recommendations. With a better appreciation of sensitivity and resistance to specific treatments, it is hoped that women may receive the treatment most likely to benefit them upfront.

**Determining Therapeutic Approach**

Several factors are considered when determining the most appropriate therapy for women with metastatic breast cancer. The extent of metastatic disease, its location, and the symptoms related to the disease are most important. Prior locoregional treatment and systemic therapy must also be considered, as well as time to recurrence. A risk evaluation should be done before discussing a given therapy, to differentiate patients with a low risk from those with a moderate to high risk for rapid progression. Whereas treatment of the former group allows for more slowly-acting substances such as endocrine therapies, the latter group requires treatment with a substantial and quick response. Factors predictive of low or higher risk are the hormone receptor status, HER2 status, disease-free survival, metastatic burden, metastatic site, and the involvement of vital organs.[16]

Several treatments may be recommended in the metastatic setting, including endocrine treatments, chemotherapy, anti-HER2 therapies, antiangiogenic agents, and other novel therapies.

**Endocrine Treatment**

Women with hormone receptor-positive breast cancer, who are stratified as low risk for progression, should be recommended endocrine treatment. Caution should be taken in women with hormone receptor–positive disease who have presented with a rapid recurrence following adjuvant therapy. Clinical trials have consistently demonstrated that third-generation aromatase inhibitors including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are associated with improved progression-free survival compared to tamoxifen. The third-generation aromatase inhibitors are associated with a survival benefit compared to tamoxifen or progestin agents in first- or second-line therapy.[17] Novel antiestrogens, such as the selective estrogen receptor downregulator (SERD) fulvestrant (Faslodex), are also active in tamoxifen-resistant patients and are as effective as aromatase inhibitors in the second-line setting.[18] Fulvestrant is also an option in the first-line treatment of tamoxifen-resistant metastatic breast cancer or after progression on an aromatase inhibitor.[19]

Sir George Beatson demonstrated over 100 years ago that the removal of ovaries, resulting in estrogen deprivation, induced regression of metastatic tumors.[20] Another form of irreversible ovarian function suppression results from irradiation, and a reversible approach utilizes luteinizing hormone-releasing hormone (LHRH) agonists. Today, the combination of tamoxifen and ovarian function suppression may be used in premenopausal patients with advanced breast cancer, providing a higher overall response rate, longer progression-free survival, and longer overall survival compared to tamoxifen alone.[21] However, combination therapy is associated with greater risk of developing menopausal symptoms and women with minimal extent of disease may be prescribed...
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tamoxifen alone. Only limited data are available concerning the combination of aromatase inhibitors and LHRH agonists in the treatment of premenopausal women with metastatic breast cancer. The combination of anastrozole and goserelin (Zoladex) in 35 premenopausal patients revealed a promising median time to progression of 8 months, a median overall survival of 26 months, and a clinical benefit of 72%. [22]

Fewer data are available regarding the combination of any hormonal approach and concomitant chemotherapy. Due to data in the adjuvant setting suggesting that the combination of chemotherapy and tamoxifen may be inferior to the sequential use of these modalities, and until other data are available, it is generally recommended that hormonal intervention and chemotherapy should not be combined.

Chemotherapy

Indications for Chemotherapy
Chemotherapy-based treatment is recommended for women with endocrine-insensitive breast cancer, including hormone receptor-negative tumors as well as hormone receptor-positive tumors that are refractory to endocrine manipulations. Other indications are rapidly progressing visceral metastasis regardless of hormonal status and a short disease-free interval following adjuvant treatment. Women with HER2-positive tumors should be offered trastuzumab-based therapy. Several chemotherapeutic strategies have been introduced in the metastatic setting, including anthracyclines, taxanes, alkylating agents, antimetabolites, and vinca-alkaloids. These drugs can be used as single agents or in combination. The overall response rate varies from 20% to 80% when these substances are used in single-agent therapy. [23]

Whether to utilize a single agent or combination chemotherapy is often based on the bulk of disease, its location, and time to recurrence. While combination therapies may produce an improved overall response rate and/or time to progression, their impact on overall survival is small. [16] A combination of two or more agents is often accompanied by an increase in toxicity, and thus may be associated with a negative impact on the balance between symptoms related to cancer and treatment-related adverse events. Furthermore, most studies that have compared one agent to a combination have not included a crossover design.

Anthracycline-Containing Regimens
Cyclophosphamide is the most extensively studied alkylating agent and one of the first group of agents utilized in the nonhormonal treatment of breast cancer. [24] Subsequently, the introduction of the anthracycline doxorubicin in the 1970s improved response rates, median duration of response, and median duration of disease control in comparison to non-anthracycline-containing regimens. [25] A meta-analysis revealed that anthracycline-containing regimens were superior to the combination of CMF (cyclophosphamide, methotrexate, fluorouracil [5-FU]). [26] The equivalence of doxorubicin and epirubicin (Ellence) in the metastatic setting was later demonstrated in an Italian trial comparing CAF (cyclophosphamide, doxorubicin, 5-FU) with CEF (cyclophosphamide, epirubicin, 5-FU). [27]

Anthracyclines are delivered in various concentrations and combinations. The most common regimens are included in Tables 2 [28-40] and 3. [40-47] Recently, new liposomal formulations of doxorubicin were developed, which can be either pegylated or not. Pegylated liposomal doxorubicin (Doxil) at 50 mg/m² every 4 weeks was found to be equally effective to doxorubicin at 60 mg/m² every 3 weeks and significantly less cardiotoxic. [30,48-50] Other studies revealed that liposomal doxorubicin may be associated not only with decreased cardiotoxicity, but also with an improved overall response rate and a longer median time to treatment failure. [51]
### Table 2

**Large Randomized Studies of Single Agents for the Treatment of Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author (year)</th>
<th>Number of Patients</th>
<th>Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Gunderson et al.[28] 1986</td>
<td>128</td>
<td>20 mg/m² q4wk vs VAC 2/50/600 mg/m² q3wk</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Bastholt et al.[29] 1996</td>
<td>287</td>
<td>40 vs 60 vs 90 vs 135 mg/m² q3wk</td>
</tr>
<tr>
<td>Pegylated liposomal encapsulated doxorubicin</td>
<td>O'Brien et al.[30] 2004</td>
<td>509</td>
<td>50 mg/m² q4wk vs doxorubicin 60 mg/m² q3wk</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Seidman et al.[31] 1995</td>
<td>49</td>
<td>250 or 175 mg/m² q3wk</td>
</tr>
<tr>
<td></td>
<td>Perez et al.[32] 2001</td>
<td>212</td>
<td>80 mg/m² qwk</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Burris.[33] 1999</td>
<td>855</td>
<td>100 mg/m² q3wk</td>
</tr>
<tr>
<td></td>
<td>Valero.[34] 1997</td>
<td>575</td>
<td>100 mg/m² q3wk</td>
</tr>
<tr>
<td></td>
<td>Burstein et al.[35] 2000</td>
<td>29</td>
<td>40 mg/m² qwk</td>
</tr>
<tr>
<td>Albumin-bound paclitaxel</td>
<td>Gradishar et al.[36] 2005</td>
<td>489</td>
<td>260 mg/m² q3wk</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>Blum et al.[37] 2001</td>
<td>162</td>
<td>1,000–1,250 mg/m² qd, d1–14 q3wk</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Zelek et al.[38] 2001</td>
<td>40</td>
<td>25 mg/m² qwk</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Seidman,[39] 2001</td>
<td>200</td>
<td>800–1,200 mg/m² d1, 8, 15 q4wk</td>
</tr>
</tbody>
</table>

VAC = vincristine/doxorubicin/cyclophosphamide.
Based on the National Comprehensive Cancer Network (NCCN) guidelines v.2.2007 [40]

### Table 3

**Recommendations for Combined Chemotherapy in Metastatic Breast Cancer and the Underlying Randomized Studies**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Author (year)</th>
<th>Number of patients</th>
<th>Treatment Regimen</th>
</tr>
</thead>
</table>
| CAF              | Bull et al.[41] 1978 | 78                | q4wk (100 mg/m² d1–14 po<sup>1</sup>
30 mg/m² IV d1+8/500 mg/m² IV d1+8) |
| FAC              | Hortobagyi et al.[42] 1979 | 105               | q3wk (500 mg/m² IV d1+8/50 mg/m² IV d1/500 mg/m² IV d1) |
| AC               | Fisher et al.[43] 1990 | 2,194              | q3wk (60 mg/m² IV d1/600 mg/m² IV d1) |
| CMF              | Bonadonna et al.[44] 1976 | 386               | q4wk (100 mg/m² po d1–14/40 IV d1+8/600 IV d1+8) |
| Docetaxel + capcitabine | O'Shaugnessy et al.[45] 2002 | 511             | q3wk (75 IV d1/950 po bid, d1–14) |
| Paclitaxel + Gemcitabine | Albain et al.[46] 2004 | 529                | q3wk (175 mg/m² IV x 3 h IV d1/1,250 mg/m² IV d1+8, following paclitaxel) |
| FEC              | Ackland et al.[47] 2001 | 460                | q4wk (400 mg/m² IV d1+8/50 mg/m² IV d1+8/500 mg/m² IV d1+8) |

<sup>1</sup> = doxorubicin; C = cyclophosphamide; E = epirubicin; F = fluorouracil; M = methotrexate.
Based on the National Comprehensive Cancer Network guidelines v.2.2007 [40]

**Taxane-Containing Regimens**

Due to concerns regarding anthracycline-related toxicity and limited cumulative dose, many...
Clinicians elect to start taxane-based treatment in this setting. Paclitaxel, found in the bark of the American Taxus brevifolia, and docetaxel (Taxotere), isolated from the extracts of the needles of the European Taxus baccata, were first used in cancer treatment in the 1990s. The addition of taxanes to anthracyclines resulted in a significant advantage in response, a slight advantage in time to progression, and a trend for overall survival advantage.[52]

Recruiting 793 patients with metastatic breast cancer, Intergroup study E1193 subsequently revealed that the combination of paclitaxel and doxorubicin was superior to either substance alone in terms of response and time to treatment failure. Furthermore, no cross-resistance or differences in overall survival have been shown.[53] These results have led to the use of taxanes as first-line therapy in the metastatic setting and comparisons of single-agent taxanes to combination strategies.

The Cancer and Leukemia Group B (CALGB) 9840 trial was initiated to compare weekly paclitaxel to a 3-weekly infusion of paclitaxel regardless of HER2 status, and to evaluate whether the addition of trastuzumab to paclitaxel provided benefit in patients with HER2-normal tumors compared to paclitaxel alone.[54] Trastuzumab had little if any influence on the response rate in HER2-normal patients, but the weekly paclitaxel regimen was superior to the 3-weekly administration. Previously, CALGB 9342 demonstrated that a higher dose of paclitaxel failed to improve outcome in patients with metastatic breast cancer.[55] Therefore, the optimal schedule of paclitaxel is likely weekly. Recent studies compared taxanes head-to-head. Every-3-week single-agent docetaxel was superior to paclitaxel in regard to overall survival (15.4 vs 12.7 months, hazard ratio [HR] = 1.41, P = .03) and time to progression (5.7 vs 3.6 months, HR = 1.64, P < .0001). However, an increase in hematologic and nonhematologic toxicities were observed in docetaxel-treated women.[56] Both agents are appropriate for use in patients with metastatic disease who are anthracycline-naive, after minimal anthracycline treatment, or following anthracycline failure. Of note, the use of weekly paclitaxel is superior to an every-3-week administration in advanced and early breast cancer.[54,57] It is not known whether docetaxel administration every 3 weeks will provide similar or different efficacy compared to weekly paclitaxel.

Newer developments include the nanoparticle albumin-bound paclitaxel (nab-paclitaxel [Abraxane]), which demonstrated in a phase III study to have higher response rates in metastatic breast cancer when compared to paclitaxel (33% vs 19%, respectively; P = .001) and a longer time to tumor progression (23.0 vs 16.9 weeks, respectively; HR = 0.75; P = .006) with a more favorable safety profile.[36] A new study randomized patients to three different dosage levels of nab-paclitaxel (300 mg/m² every 3 weeks, 100 or 150 mg/m² on days 1, 8, and 15 every 4 weeks, or docetaxel at 100 mg/m² every 3 weeks). All three nab-paclitaxel regimens were associated with a longer progression-free survival compared to docetaxel.[58] Weekly paclitaxel has not been compared to weekly nab-paclitaxel.

Taxanes have been studied in combination with different classes of chemotherapeutic agents. Most trials may be underpowered for overall survival comparisons, and only a few trials mandated a crossover design.[16] A recently presented meta-analysis that evaluated the effects of taxanes alone or in combination with anthracyclines with respect to tumor response, progression-free survival, and overall survival in first-line chemotherapy of patients with metastatic breast cancer included 4,256 patients treated in 12 trials.[59] Hazard ratios for taxanes compared with anthracyclines as a single agent were 1.19 (confidence interval [CI] = 1.04–1.36, P = .01) for progression-free survival and 1.01 (CI = 0.88–1.16, P = .90) for overall survival. However the taxane-based combinations were superior in terms of response rate and slightly better in terms of progression-free survival. Based on the results of these various studies, docetaxel every 3 weeks, weekly paclitaxel, or weekly nab-paclitaxel are used alone or in combination to treat women with metastatic breast cancer (Tables 2 and 3).

Other Chemotherapeutic Agents

Capecitabine (Xeloda), an oral fluoropyrimidine, has a high single-agent efficacy in metastatic breast cancer.[37] The US Food and Drug Administration (FDA)-approved dose is 1,250 mg/m² twice daily on days 1 to 14 every 3 weeks. The main toxicities include lymphopenia, nausea, diarrhea, hand-foot syndrome, and fatigue.[60] Clinically however, a lower dose has often been utilized. Given capecitabine's efficacy, safety, and ease of administration, it became an attractive agent for combination strategies.[45] In one study, 511 patients were randomized to capecitabine (1,250 mg/m² po bid on days 1–14) plus docetaxel (75 mg/m²) or docetaxel (100 mg/m²) alone. The combination was superior in terms of time to progression (HR = 0.652, P = .001), overall survival (HR = 0.77, P = .0126), and overall response rate (42% vs 30%, P = .006). However, grade 3 toxicities were more common for the combination (71% vs 49%), and grade 4 adverse events were slightly...
higher with single-agent docetaxel (25% vs 31%).[45]
The pyrimidine antimetabolite gemcitabine (Gemzar) was tested as a single agent in the first- and second-line setting, and is associated with a high response rate in phase II trials.[39] Later it was compared to single-agent epirubicin in a randomized phase III trial with 410 patients. Epirubicin was superior in terms of time to progression (6.1 and 3.4 months, P = .0001), overall survival (19.1 and 11.8 months, P = .0004), and response rate (40.3% and 16.4%, P < .001).[61] Results, however, were different in combination trials. In one such trial, 529 patients were treated with gemcitabine (1,250 mg/m², days 1 and 8) plus paclitaxel (175 mg/m² every 3 weeks) or paclitaxel alone (175 mg/m²).[62] A survival benefit was demonstrated favoring the combination (1-year survival rates of 70.7% vs 60.9%, P = .019).[46] These data support the use of gemcitabine with paclitaxel as first-line therapy or as single agents in the second- or third-line setting.

Other agents with activity include vinorelbine, a third-generation semisynthetic vinca alkaloid with activity as first-line therapy alone[38,63] or in combination with doxorubicin[64] as well as in second-line treatment (Tables 2 and 3).[63]

Newer cytotoxic agents have been investigated in phase II and III clinical trials. Ixabepilone is an analog of epothilone B and a compound of a new class of tubulin-active drugs, comparable to taxanes.[65] It is not cross-resistant to taxane and was therefore examined in patients with taxane-resistant metastatic breast cancer.[66] Four recently published phase II clinical trials with ixabepilone in first-line treatment[67,68] and in taxane-resistant breast cancer[66,69] demonstrated promising activity. Further, the first results of a combination of ixabepilone and capecitabine were recently presented.[70] Preliminary data suggest that the combination was associated with improved overall response rate and time to progression but also with increased toxicity. Overall survival data have not been reported. Ixabepilone is under consideration by the FDA for the treatment of patients with metastatic breast cancer.

Overviews of chemotherapies in metastatic breast cancer recommended by the National Comprehensive Cancer Network (NCCN) are included in Table 2 (single agents) and Table 3 (combinations).

**HER2-Targeted Therapies**
The characterization of HER2 and development of targeted therapy with the recombinant humanized monoclonal antibody trastuzumab and tyrosine kinase inhibitors led to a new era of treatment of the HER2-positive breast cancer subtype.

**Trastuzumab**
Trastuzumab was first found to be effective and safe as a single agent in women whose metastatic disease progressed after several chemotherapy regimens[71,72] and subsequently established for the treatment of metastatic breast cancer in combination with chemotherapy.[73] Single-agent trastuzumab is associated with overall response rates of 11.6% to 26% and with improvement in overall survival. Importantly, after 12 months, 51% of the women who experience clinical benefit had no disease progression.[71,72,74]

Recent results of the TrAstuzumab in Dual HER2 ER-positive Metastatic breast cancer (TAnDEM) support the consideration of trastuzumab in combination with aromatase inhibitors. The addition of trastuzumab to anastrozole was associated with a doubling of progression-free survival and a significant improvement in time to progression and overall response rate compared to anastrozole alone.[75] However, overall survival was similar between the groups, and it is not known whether initiating trastuzumab earlier in the treatment of breast cancer provides overall clinical benefit.

As a single agent or in combination with an aromatase inhibitor, trastuzumab has not been compared to a combination of trastuzumab and chemotherapy. Until such data are available, trastuzumab alone or with an aromatase inhibitor can be considered for carefully selected women with low-bulk disease.

Trastuzumab can be administered with one of several chemotherapy agents or a combination (Table 4).[40,75-81] Treatment with trastuzumab plus doxorubicin (or epirubicin)/cyclophosphamide in combination or given with paclitaxel every 3 weeks was associated with an improvement in time to progression, a higher overall response rate, a longer duration of response, a lower rate of death at 1 year, and a longer overall survival compared to chemotherapy alone.[73] A high proportion of cardiac events was observed in the group treated with doxorubicin/cyclophosphamide and trastuzumab, and therefore, a combination of trastuzumab and anthracyclines is not recommended.
Other highly active combinations include trastuzumab and weekly paclitaxel,[76] docetaxel,[78] or vinorelbine.[79] A multicenter prospective randomized trial of the combination of trastuzumab with either vinorelbine or paclitaxel revealed comparable results in terms of efficacy and tolerability.[83] Trastuzumab with paclitaxel and carboplatin in a weekly[81] or 3-weekly[80] schedule was associated with an improved overall response rate and progression-free survival compared to paclitaxel and trastuzumab. In contrast, the Breast Cancer International Research Group (BCIRG) 007 study revealed similar high response rates for trastuzumab/docetaxel compared to the combination of trastuzumab, docetaxel, and carboplatin.[84] The combination of trastuzumab, carboplatin, and docetaxel or paclitaxel was associated with a higher toxicity profile compared to trastuzumab and docetaxel or paclitaxel, respectively.[80,84]

The results of studies that evaluated trastuzumab-based therapy support the administration of agents that target HER2 with chemotherapeutic agents for women whose tumors overexpress or amplify HER2. The cumulative data support the use of single-agent chemotherapy in combination with trastuzumab. Whether to continue trastuzumab following disease progression with one or more trastuzumab-based therapies is controversial. Ongoing research is aimed at identifying factors that will predict sensitivity to trastuzumab-based therapy and mechanisms of resistance. A new generation of antibodies and small molecules targeting HER2 are also under intensive investigation.

**Pertuzumab**

Like trastuzumab, the humanized monoclonal antibody pertuzumab (Omnitarg) binds to the extracellular part of HER2 but to a different domain,[85] thus preventing HER2/HER3 heterodimerization and subsequent cell signaling. In combination with trastuzumab, this second-generation HER2 antibody was associated with promising activity.[86] The treatment was well tolerated in patients with pretreated HER2-positive breast cancer that progressed during treatment with trastuzumab, with diarrhea as the most common side effect (71%).

**Tyrosine Kinase Inhibitors**

The tyrosine kinase inhibitors represent a new approach of targeted therapy. These small molecules compete with adenosine triphosphate (ATP) for the binding site of ATP in the receptor, thereby preventing its phosphorylation and downstream effects in cells.[87]

- Lapatinib—The best studied tyrosine kinase inhibitor in breast cancer is lapatinib (Tykerb). It is an
orally active selective inhibitor of epidermal growth factor receptor (EGFR) and HER2.[88] In a phase III study, patients with HER2-positive locally advanced or metastatic breast cancer that progressed following anthracyclines, taxanes, and trastuzumab were randomized to either capecitabine combined with lapatinib or capecitabine alone.[89] A longer median time to progression was demonstrated for the combination, which led to FDA approval. In contrast to the antibody trastuzumab, lapatinib is a small molecule that is able to penetrate the blood-brain barrier. Indeed, fewer central nervous system (CNS) progressions were observed in the lapatinib/capecitabine arm compared to capecitabine alone.[90] Since the incidence of brain metastases is high (28%–43%) among patients with HER2-positive breast cancer,[91] lapatinib has been studied in women with CNS metastasis, despite this group's traditional exclusion from clinical trials. This development is a welcome sign of progress.

**Agents That Target Angiogenesis**

Tumor growth is widely dependent on angiogenesis. Therefore, angiogenesis has been an important target for new drug development. New blood vessel formation requires a certain balance between factors that enhance or inhibit the process. A major stimulator of angiogenesis is the vascular endothelial growth factor (VEGF). A first generation of therapies targeting angiogenesis includes anti-VEGF antibodies.

**Bevacizumab**

Directed against VEGF, the humanized monoclonal antibody bevacizumab inhibits the growth of human tumors in animal models.[92] A phase II study demonstrated the efficacy of bevacizumab monotherapy in pretreated patients with metastatic breast cancer.[93] Subsequently, a large phase III trial was initiated to compare capecitabine with the combination of capecitabine and bevacizumab in the treatment of patients who have previously received anthracyclines and taxanes.[94] Combination capecitabine/bevacizumab was associated with an improved overall response rate (19.8%) compared to capecitabine alone (9.1%, P = .001). However, progression-free and overall survival did not differ significantly between the two arms.

In the Eastern Cooperative Oncology Group (ECOG) E2100 trial, 722 patients who had undergone no prior treatment for metastatic breast cancer were randomized to either paclitaxel monotherapy or a combination of paclitaxel and bevacizumab. A first analysis demonstrated that the combination of the taxane and bevacizumab was associated with an improved outcomes compared to paclitaxel alone, including overall response rate (28.2% vs 14.2%, P < .0001), progression-free survival (10.97 vs 6.11 months, HR = 0.498, P < .0001) and overall survival (HR = 0.674, P = .01).[82]

Subsequently, a study of first-line bevacizumab in combination with capecitabine in HER2-negative breast cancer demonstrated an overall response rate of 38.5%, which is superior to the response seen in the initial bevacizumab/capecitabine study, and comparable to first-line paclitaxel/bevacizumab.[95]

Together, these results suggest that bevacizumab may be most effective in earlier stages of the disease. As hypertension and bleeding are the most common bevacizumab-associated adverse events, patients should be carefully selected prior to initiation of the agent.[93] Ongoing studies evaluating markers of angiogenesis may help define a group of patients most likely to benefit from anti-VEGF agents.

**Tyrosine Kinase Inhibitors**

In addition to targeting the EGFR family, other tyrosine kinase inhibitors target the VEGF receptor. Axitinib, a novel small-molecule inhibitor of the receptor tyrosine kinases with picomolar potency against VEGFR-1, -2, and -3, and nanomolar potency against PDGFR-beta and KIT administered with docetaxel was associated with a significant increase in overall response rate compared to docetaxel plus placebo.[96]

**Future Directions**

Much work is ongoing to introduce new drugs into the treatment of metastatic breast cancer. Various multitargeted tyrosine kinase inhibitors against VEGF are under examination, including sorafenib (Nexavar), sunititinb (Sutent), pazopanib, and vandetanib (Zactima). The role of tyrosine kinase inhibitors that target EGFR (eg, erlotinib [Tarceva] and gefitinib [Iressa]), if any, in the management of breast cancer has not been established. Other cytotoxics like vinflunine have also demonstrated activity in small studies. Finally, new doses or schedules of standard chemotherapy agents with or without new therapies are under study.

**Conclusions**

Many therapies are available to women with metastatic breast cancer. The aims of the treatment in this stage of the disease are to improve overall survival, prolong time to progression, and ameliorate quality of life. Therapies should be reasonably well tolerated and targeted based on known predictive
markers and tumor subtypes. With the large number of new agents and combinations, and with emerging novel therapies, it is the responsibility of the treating physician to adjust the optimal dose, schedule, and combination to the needs of the individual patient. Given these and other new advances, we hope that cure can become an achievable goal in the near future.

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