Breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related mortality among women in the US. Improvements in the treatment of early-stage disease have led to a decline in the incidence of metastatic breast cancer (MBC). Nonetheless, 20–85% of women diagnosed with early-stage breast cancer develop recurrent and/or metastatic disease, and an estimated 10% of patients present with metastatic disease at the time of their initial diagnosis. The prognosis for these patients is relatively poor, with a median survival of approximately two years and an estimated five-year survival rate of 23%. 

Anthracycline- and/or taxane-based regimens remain the preferred first-line chemotherapy treatments for MBC, but many patients develop disease that either does not respond or becomes refractory to these agents. With the increasing use of anthracyclines (e.g., doxorubicin, epirubicin) and/or taxanes (e.g., paclitaxel, docetaxel) as adjuvant therapy, a higher proportion of treatment-resistant or treatment-refractory patients is observed in the metastatic setting. Despite the number of available treatment options for MBC (see Tables 1 and 2), there remains no single standard of care for this group of patients.

Various monotherapy and combination regimens have been evaluated as candidate therapies for MBC patients who experience disease progression after treatment with anthracyclines and taxanes (A/T). At present, capecitabine, ixabepilone, and eribulin are the only cytotoxics approved by the US Food and Drug Administration (FDA) as single agents in the third-line setting and beyond. Prior to the approval of eribulin in 2010, no single agent was associated with a statistically significant improvement in overall survival (OS) in this patient population. In terms of combination therapy for human epidermal growth factor receptor-2 (HER2)-negative MBC, the FDA, based on Phase III clinical trials demonstrating benefits in progression-free survival (PFS), time to progression (TTP), objective response rates (ORR), and in some cases OS, approved the following regimens: capecitabine plus docetaxel, capcitabine plus ixabepilone, and gemcitabine plus paclitaxel. The superiority of combination chemotherapy over single-agent sequential therapy is debatable, however, in the absence of

**Abstract**

Metastatic breast cancer (MBC) remains incurable despite the many advances in cancer treatment. While anthracycline- and/or taxane-based regimens are the preferred first-line chemotherapies for MBC, many patients develop disease that is either resistant or becomes refractory to these agents. Currently, there is no single standard of care for women who experience disease progression after treatment with anthracyclines and taxanes. A number of chemotherapeutics have been evaluated as single agents and as part of combination regimens, with varying results. The US Food and Drug Administration has approved capecitabine, ixabepilone, and eribulin as single agents for third-line therapy and beyond. Combination regimens such as capecitabine plus ixabepilone or gemcitabine plus carboplatin are also available for pre-treated MBC patients. The present article will review the options available to MBC patients following prior treatment with anthracyclines and taxanes.

**Keywords**

Metastatic breast cancer, pre-treated disease, human epidermal growth factor receptor-2 (HER2)-negative, combination regimen, capecitabine, gemcitabine, vinorelbine, eribulin, ixabepilone

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Table 1: The National Comprehensive Cancer Network Preferred and Other Single-agent Chemotherapy Treatment Options for Recurrent or Metastatic Breast Cancer beyond Anthracyclines and Taxanes

<table>
<thead>
<tr>
<th>Single Agents</th>
<th>Standard Doses and Schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1,000–1,250 mg/m² PO BID on Days 1–14 of a 21-day cycle</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>800–1,200 mg/m² IV on Days 1, 8, and 15 of a 28-day cycle</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25 mg/m² IV weekly</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1.4 mg/m² IV on Days 1 and 8 of a 21-day cycle</td>
</tr>
<tr>
<td><strong>Other Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclphosphamide</td>
<td>40–50 mg/kg IV or divided doses over 2–5 days or 1–5 mg/kg/day PO</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>14 mg/m² IV on Day 1 of a 21-day cycle</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m² IV on Day 1 of a 28-day cycle</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg/m² PO on Days 1–21 of a 28-day cycle</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Initiate therapy with 3.7 mg/m² IV and gradually increase to the maximum tolerated dose</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>IV injection or infusion of varying doses and schedules</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>40 mg/m² IV on Day 1 of a 21-day cycle</td>
</tr>
</tbody>
</table>

BID = twice daily; IV = intravenous; PO = oral.

Table 2: Selected Combination Regimens for Recurrent or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Standard Doses and Schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixabepilone plus capecitabine</td>
<td>Ixabepilone: 40 mg/m² IV on Day 1</td>
</tr>
<tr>
<td>Gemcitabine plus carboplatin</td>
<td>Gemcitabine: 1,000 mg/m² IV on Days 1 and 8 or Carboplatin: AUC 4 IV on Day 1 21-day cycles²</td>
</tr>
<tr>
<td></td>
<td>Or Gemcitabine: 1,500 mg/m² IV on Day 1 Carboplatin: AUC 2.5 IV on Day 1 14-day cycles²</td>
</tr>
<tr>
<td></td>
<td>Or Gemcitabine: 800 mg/m² IV on Days 1 and 8 Carboplatin: AUC 2 IV on Days 1 and 8 21-day cycles²</td>
</tr>
</tbody>
</table>

AUC = area under the curve; IV = intravenous; PO = oral.

mandated cross-over in the single-agent arm. Therefore, sequential monotherapy tends to be favored in order to minimize toxicity and maximize patients’ quality of life. The present article provides an overview of the currently available chemotherapy options for MBC patients following treatment with A/T-based regimens. Table 3 lists the key features and mechanisms of action of the drugs reviewed.

Options for Monotherapy

Capecitabine

Capecitabine is an oral pro-drug that is preferentially converted to the antimitabolite 5-fluorouracil by thymidine phosphorylase, an enzyme found at higher levels in tumor cells versus normal cells (see Table 3).13,14 Single-agent capecitabine was approved in 1998 for use as second- or third-line treatment for MBC following disease progression on A/T-based regimens. The pivotal trial was a multicenter, single-arm Phase II trial conducted in pacilitaxel-refractory MBC patients (n=162), 91 % of whom had previously received an anthracycline.15 The ORR was found to be 20 %, and all responders had previously received an anthracycline. Median TTP was 3.0 months, and median OS was 12.8 months. The efficacy of single-agent capecitabine is supported by several other Phase II studies.16–20 The trials and pertinent findings are summarized in Table 4.

Frequently reported grade 3/4 adverse events associated with capecitabine include palmar-plantar erythrodysesthesia and diarrhea.11,12 Nausea, emesis, and stomatitis (all grades) were also reported,16 but the majority of toxicities were mild-to-moderate in severity, with few grade 4 adverse events. In addition, myelosuppression and alopecia were rare, and there were no documented treatment-related deaths.

In an effort to improve the tolerability of capecitabine, investigators conducted a safety study in which a reduction from the FDA-approved dose of 1,250 mg/m² orally twice daily to a dose of 1,000 mg/m² orally twice daily for 14 days in 21-day cycles decreased the incidence of adverse events—with the notable exception of palmar-plantar erythrodysesthesia—in patients with MBC.17 Importantly, clinical benefit was retained despite the reduced dose, and 65 % of the subjects had prior A/T-based therapy.17

Ixabepilone

Ixabepilone is a semi-synthetic analog of epothilone B. It binds directly to the β-tubulin structure on microtubules, leading to microtubule stabilization, cell-cycle arrest, and cytotoxicity (see Table 3).12,22 The β-tubulin binding site for epothilones differs from that for taxanes, so the selective mechanisms for inducing apoptosis are similar but not identical to those of paclitaxel and docetaxel. In addition, epothilones are not influenced by the resistance mechanisms known to reduce the activity of taxanes and anthracyclines (e.g., p-glycoprotein, multidrug resistance protein 1, and breast cancer resistance protein), which may provide an advantage over these standard agents.13,14

Single-agent ixabepilone demonstrated activity in a series of Phase II studies in A/T-pre-treated MBC. Patients (n=49) whose disease progressed while receiving, or within four months of receiving, taxane-based chemotherapy were enrolled in an open-label, single-arm Phase II study.23 Treatment with ixabepilone demonstrated antitumor activity, with an ORR of 12 %, median TTP of 2.2 months, and median OS of 7.9 months.23 A second, multicenter Phase II study included 126 MBC patients with disease resistant to anthracyclines, taxanes, and capecitabine; 113 patients were assessable for response, with an independently reviewed ORR of 12 %, median TTP of 2.2 months, and median OS of 8.6 months.24 Grade 3/4 treatment-related side effects included peripheral sensory neuropathy (14 %), fatigue/asthenia (13 %), myalgia (8 %), and stomatitis/mucositis (6 %).23 Other adverse events, such as nausea and emesis, were manageable and classified as grade 1/2.25 In 2007, on the basis of these data, the FDA approved ixabepilone as single-agent therapy following failure of an anthracycline, a taxane, or capecitabine in MBC.
Eribulin

Eribulin mesylate is a synthetic analog of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai. It is a novel non-taxane microtubule dynamics inhibitor; it blocks microtubule polymerization without affecting de-polymerization, inducing G2-M phase arrest and subsequent apoptosis (see Table 3). In vitro studies revealed that the activity of eribulin is more specific compared with other tubulin-targeting agents. This degree of specificity is achieved by its ability to bind selectively and with high affinity to the growing plus ends of microtubules, suppressing dynamic instability.

In mouse studies, eribulin was associated with less neuropathy than equivalent maximum tolerated dose-based amounts of paclitaxel or ixabepilone. These findings were substantiated in human subjects. In a randomized Phase II study of eribulin versus ixabepilone, eribulin led to fewer neuropathic adverse events, although the difference was not statistically significant.

Three Phase II studies investigated the efficacy and tolerability of eribulin in heavily pre-treated MBC patients. An open-label, single-arm Phase II study accrued 103 MBC patients who had received a median of four prior chemotherapy regimens (including an anthracycline and a taxane). Eribulin was associated with an independently reviewed ORR of 11.5 %, median PFS of 2.6 months, and median OS of 9.0 months, with no reported grade 4 neuropathy. Subjective toxicity was manageable, but the treatment schedule had to be modified during the trial from Days 1, 8, and 15 of a 28-day cycle to Days 1 and 8 of a 21-day cycle in order to minimize neutropenia and related dose delays or omissions. The second study included 269 patients pre-treated with an anthracycline, taxane, and capecitabine and reported an independently reviewed ORR of 14.1 %, median PFS of 2.6 months, and median OS of 10.4 months. Finally, a single-arm, open-label Phase II study of eribulin in 84 patients treated with three or less prior lines of chemotherapy resulted in an independently reviewed ORR of 21.3 %, median PFS of 112 days, and median OS of 331 days.

The open-label, Phase III EMBRACE (Eribulin monotherapy versus ixabepilone) trial was a 2:1 randomization of 762 patients with a primary endpoint of OS. Eligibility criteria included two to five prior therapeutic regimens for advanced disease and a history of A/T exposure unless medically contraindicated. Treatments of physician’s choice (TPCs) included: single-agent chemotherapy (96 %), endocrine therapy (4 %), single-agent biologic therapy and best supportive care were also provided as treatment options, but neither was used. Eribulin demonstrated a statistically significant improvement in OS compared with TPC (13.1 versus 10.6 months; hazard ratio [HR] 0.81, p=0.041) (see Figure 1). Objective responses (including three complete responses confirmed through independent review) were reported in 12.2 % of patients with measurable disease treated with eribulin, compared with 4.7 % of those receiving TPC.

The most common grade 3/4 toxicities associated with eribulin included peripheral neuropathy, neutropenia, leucopenia, and fatigue. Treatment discontinuation due to adverse events occurred in 13 % of patients on eribulin and 15 % of patients on TPC. Peripheral neuropathy was the most common adverse event associated with discontinuation of eribulin (5 %).

To date, eribulin is the only single agent that has been shown to prolong OS in heavily pre-treated MBC patients. Therefore, the updated National Comprehensive Cancer Network (NCCN) guidelines recommend eribulin as a first-line option.

Table 3: Characteristics and Mechanisms of Action of Selected Agents Used in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Characteristics</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolite</td>
<td>Capecitabine</td>
<td>Pro-drug of fluorouracil; converts to 5-fluorouracil in tumor cells</td>
<td>Inhibits thymidylate synthase; interferes with DNA and RNA synthesis</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Activated intracellularly to diphosphate and triphosphate nucleosides</td>
<td>Inhibits ribonucleotide reductase, reducing concentrations of deoxynucleotides; competes with deoxycytidine triphosphate for incorporation into DNA</td>
</tr>
<tr>
<td></td>
<td>Eribulin</td>
<td>Synthetic analog of the marine sponge natural product halichondrin B</td>
<td>Inhibits the growing plus ends of microtubules; inhibits microtubule growth and does not affect shortening; sequesters tubulin into aggregates</td>
</tr>
<tr>
<td></td>
<td>Ixabepilone</td>
<td>Semi-synthetic analog of epothilone B</td>
<td>Binds directly to the β-tubulin structure on microtubules, stabilizing microtubules</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>Semi-synthetic vinca alkaloid</td>
<td>Binds to tubulin monomers, inhibiting the formation of microtubules</td>
</tr>
</tbody>
</table>

Table 4: Summary of Phase II and III Trials of Capecitabine in Metastatic Breast Cancer Patients Previously Treated with an Anthracycline and/or a Taxane

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>Median DOR (months)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al., 1999</td>
<td>162</td>
<td>20</td>
<td>63</td>
<td>8.1</td>
<td>3.0</td>
<td>12.8</td>
</tr>
<tr>
<td>Blum et al., 2001</td>
<td>74</td>
<td>26</td>
<td>57</td>
<td>8.3</td>
<td>3.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Reichardt et al., 2003</td>
<td>136</td>
<td>15</td>
<td>62</td>
<td>7.5</td>
<td>3.5</td>
<td>10.1</td>
</tr>
<tr>
<td>Fumoleau et al., 2004</td>
<td>126</td>
<td>28</td>
<td>54</td>
<td>5.9</td>
<td>4.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Miller et al., 2005</td>
<td>230</td>
<td>19</td>
<td>NR</td>
<td>7.6</td>
<td>4.17</td>
<td>14.5</td>
</tr>
</tbody>
</table>

CBR = clinical benefit rate; DOR = duration of response; NR = not reported; ORR = objective response rate; OS = overall survival; TTP = time to progression.
Breast Cancer

Combination Chemotherapy Regimens

Combined chemotherapy regimens for HER2-negative MBC are often used in the setting of symptomatic and/or high burden disease for which a more rapid treatment response is needed, despite a potential increase in treatment-related toxicity. Many drug combinations have been evaluated in MBC patients previously treated with A/T, with varying outcomes. To date, clinical trials of single-agent chemotherapy in combination with biologic agents have been disappointing. Summaries of the key trials of chemotherapy doublets with positive findings are provided below.

Ixabepilone plus Capecitabine

A Phase II study of 62 patients with A/T-pre-treated MBC reported a median ORR of 30 % and a median PFS of 3.8 months with the combination of ixabepilone plus capecitabine. In an international open-label Phase III study of 752 patients, ixabepilone plus capecitabine, compared with capecitabine alone, significantly improved median PFS (5.8 versus 4.2 months; HR 0.75, p=0.0005) and ORR (35 % versus 14 %, p=0.0001). These findings were supported by a second Phase III trial of 1,221 patients, which demonstrated a statistically significant improvement in PFS (6.2 versus 4.2 months; HR 0.79, p=0.0005) and ORR (43 % versus 29 %, p=0.0001) in favor of ixabepilone plus capecitabine; however, no benefit in OS was observed with the drug combination compared with capecitabine monotherapy (median OS 16.4 versus 15.6 months, respectively). Reported toxicities include grade 3–4 neuropathy, neutropenia, palmar-plantar erythrodysesthesia, nausea, diarrhea, and fatigue. Ixabepilone is approved in combination with capecitabine for the treatment of MBC following failure of A/T.

Gemcitabine-based Combinations

Gemcitabine is a nucleoside analog that becomes phosphorylated within cells and incorporated into DNA as a triphosphate (see Table 3). Response rates with single-agent gemcitabine are 14–37 % in patients not previously exposed to chemotherapy and 12–30 % in patients treated with prior anthracyclines and/or taxanes.

In terms of combination regimens, gemcitabine was evaluated in combination with carboplatin in a Phase II study of patients with hormone receptor-negative, HER2-negative MBC pre-treated with A/T. The ORR was 32 %, median TTP was 5.5 months, and median OS was 11 months. Gemcitabine plus carboplatin is therefore considered a suitable option in this subset of patients.

In another Phase II trial, pre-treated MBC patients were randomized to receive bi-weekly gemcitabine plus either paclitaxel, carboplatin, or cisplatin as first-line treatment. The ORRs were 26.5 %, 17.0 %, and 15.7 % for gemcitabine plus paclitaxel, gemcitabine plus carboplatin, and gemcitabine plus cisplatin, respectively. No significant differences were observed in median OS (15.5, 22.8, and 20.1 months, respectively) or median PFS (4.8, 4.3, and 4.8 months, respectively). All three chemotherapy doublets had comparable tolerability; the most commonly reported drug-related adverse events among all subjects were nausea (54.1 %), vomiting (42.5 %), alopecia (42.5 %), and fatigue (29.5 %).

Rechallenging with Anthracyclines or Taxanes

Anthracyclines and taxanes are key treatment options in the management of breast cancer and, in recent years, their use in the adjuvant setting has increased greatly. While this has resulted in considerable benefits in terms of disease-free survival (DFS) and OS in early-stage disease, many patients still develop MBC. It is unclear if rechallenging with anthracyclines and/or taxanes in this relapsing population would be beneficial. It has been suggested that rechallenging with an anthracycline or a taxane in the metastatic setting may be an option in patients with at
Chemotherapy Options for MBC after Prior Exposure to Anthracyclines and Taxanes