Chemotherapy Options for Metastatic HER2-Negative Breast Cancer after Prior Exposure to Anthracyclines and Taxanes

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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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Breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related mortality among women in the US.[1,2] Improvements in the treatment of early-stage disease have led to a decline in the incidence of metastatic breast cancer (MBC).[3] 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.[4] The prognosis for these patients is relatively poor, with a median survival of approximately two years[4] and an estimated five-year survival rate of 23 %.[2]

Anthracycline- and/or taxane-based regimens remain the preferred first-line chemotherapy treatments for MBC,[3] 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.[5,6] Despite the number of available treatment options for MBC (see *Tables 1*[7] *and 2*[7–10]), 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, capecitabine plus ixabepilone, and gemcitabine plus paclitaxel.[11] The superiority of combination chemotherapy over single-agent sequential therapy is debatable, however, in the absence of

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

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

BID = twice daily; IV = intravenous; PO = oral.
Source: National Comprehensive Cancer Network, 2012.[7]

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

Regimen	Standard Doses and Schedules
Ixabepilone plus capecitabine	Ixabepilone: 40 mg/m² IV on Day 1 Capecitabine: 2,000 mg/m² PO in two divided doses on Days 1–14 21-day cycles
Gemcitabine plus carboplatin	Gemcitabine: 1,000 mg/m² IV on Days 1 and 8 Carboplatin: AUC 4 IV on Day 1 21-day cycles[8] Or Gemcitabine: 1,500 mg/m² IV on Day 1 Carboplatin: AUC 2.5 IV on Day 1 14-day cycles[9] Or Gemcitabine: 800 mg/m² IV on Days 1 and 8 Carboplatin: AUC 2 IV on Days 1 and 8 21-day cycles[10]

AUC = area under the curve; IV = intravenous; PO = oral.
Source: National Comprehensive Cancer Network, 2012.[7]

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*[12] 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 antimetabolite 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 paclitaxel-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.[13,20] 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.[21] Importantly, clinical benefit was retained despite the reduced dose, and 65 % of the subjects had prior A/T-based therapy.[21]

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.[23,24]

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.[25] Treatment with ixabepilone demonstrated antitumor activity, with an ORR of 12 %, median TTP of 2.2 months, and median OS of 7.9 months.[25] 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 11.5 %, median PFS of 3.1 months, and median OS of 8.6 months. Grade 3/4 treatment-related side effects included peripheral sensory neuropathy (14 %), fatigue/asthenia (13 %), myalgia (8 %), and stomatitis/mucositis (6 %).[26] 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*[11]).[27] *In vitro* studies revealed that the activity of eribulin is more specific compared with other tubulin-targeting agents.[28] 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.[29] 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.[30]

Three Phase II studies investigated the efficacy and tolerability of eribulin in heavily pre-treated MBC patients.[31–33] 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).[31] 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.[31] 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.[32] 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.[33]

The open-label, Phase III EMBRACE (Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer) trial was a 2:1 randomization of 762 patients with a primary endpoint of OS.[34] 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 %) or 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*[35]). 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 %).[34]

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

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

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

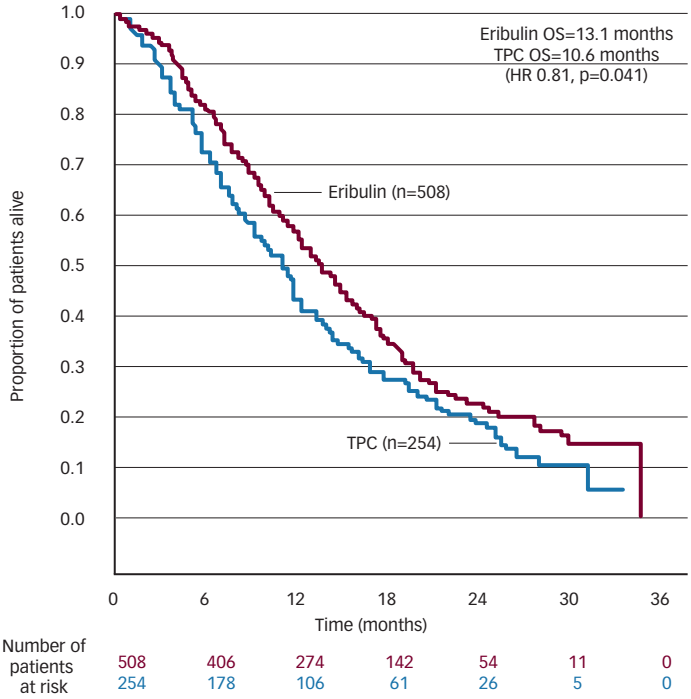
Adapted from Murphy and Seidman, 2009.[12]

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

Study	Number of Patients	ORR (%)	CBR (%)	Median DOR (months)	Median TTP (months)	Median OS (months)
Blum et al, 1999[15]	162	20	63	8.1	3.0	12.8
Blum et al., 2001[16]	74	26	57	8.3	3.2	12.2
Reichardt et al., 2003[17]	136	15	62	7.5	3.5	10.1
Fumoleau et al., 2004[18]	126	28	54	5.9	4.9	15.2
Miller et al., 2005[19]	230	19	NR	7.6	4.17	14.5

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

Figure 1: Kaplan–Meier Graph of Overall Survival with Eribulin versus Treatment of Physician's Choice in Heavily Pre-treated Metastatic Breast Cancer Patients



HR = hazard ratio; OS = overall survival; TPC = treatment of physician's choice. Adapted from Eisai, Inc., 2012.[35]

Comprehensive Cancer Network (NCCN) guidelines list it as a preferred monotherapy for patients previously treated with at least two chemotherapeutic regimens for advanced disease.[7]

Vinorelbine

Vinorelbine is a semi-synthetic vinca alkaloid that suppresses microtubule formation by binding to tubulin monomers, resulting in cytotoxicity (see *Table 3*).[36] Several clinical studies have reported on its efficacy in the treatment of A/T-refractory MBC.[37,38] For example, in a Phase II trial of 40 patients previously treated with A/T, single-agent vinorelbine resulted in an ORR of 25 %, median time to treatment failure of six months, and median OS of six months.[39] Other Phase II studies have further demonstrated the activity of vinorelbine monotherapy in A/T-pre-treated MBC.[40,41]

Although vinorelbine is not FDA-approved in the US for the treatment of resistant or refractory MBC, it is listed in the NCCN guidelines as a preferred single agent (line unspecified) for treating patients with recurrent or refractory MBC.[7,42]

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 I/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.[43] 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=0.0003) and ORR (35 % versus 14 %, p<0.0001).[44] 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).[45] 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.[46] 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.[47] 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.[48] While this has resulted in considerable benefits in terms of disease-free survival (DFS) and OS in early-stage disease,[49] 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

least a six-to-12 month disease-free interval between the completion of adjuvant chemotherapy and recurrence.[48,50,51] However, prospective, randomized trials are required to address the clinical applicability and utility of this strategy in MBC. At present, if disease recurs within 12 months of prior A/T therapy, it is generally preferable to initiate therapy with a different class of chemotherapeutic.[52]

Summary and Conclusions

Anthracycline- and taxane-based chemotherapy regimens are the current gold standards in the treatment of MBC, but there is a clear need for therapies effective in A/T pre-treated patients given the increasing use of doxorubicin, epirubicin, paclitaxel, and docetaxel in the adjuvant treatment of high-risk early-stage disease. While these treatments have significantly improved clinical outcomes, many individuals have disease that is either resistant or becomes refractory to these drugs. Several therapeutic options have been introduced as monotherapy or combination regimens after failure of A/T-based chemotherapy. While each has shown some efficacy in women with advanced disease, eribulin remains the only agent associated with a significant improvement in OS when administered as monotherapy. Future studies are needed to maximize the benefit of existing regimens as well as to develop additional alternatives. ■

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