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REVIEW

Beyond taxanes: the next generation of microtubule-targeting agents

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Abstract Taxanes are a standard first-line option for metastatic breast cancer (MBC), but their utility may be limited by primary or acquired resistance. New microtubule-targeting agents have been developed to overcome taxane resistance and provide additional options for improving patient outcomes. This article reviews these alternative microtubule-targeting agents and their potential clinical benefits for MBC patients. Relevant clinical data were compiled through searches within PubMed and congress abstract databases. Ixabepilone, a novel microtubule-stabilizing drug approved by the US Food and Drug Administration (FDA), has proven efficacy across multiple lines of therapy, including patients with taxane-resistant/refractory disease. In phase III trials, ixabepilone plus capecitabine significantly improved progression-free survival compared with capecitabine alone in anthracycline/taxane-pretreated patients. Eribulin has recently been approved by the FDA and by the European Medicines Agency for the treatment of patients with MBC who have received at least two prior chemotherapy regimens for late-stage disease. In a phase III trial, eribulin extended overall survival compared with the physician's treatment choice in heavily pretreated MBC patients. In addition, several investigational microtubule-targeting agents may have therapeutic potential in MBC. The development of new microtubule-targeting agents helps to address the need for additional effective regimens for patients progressing after standard treatment with anthracycline- and taxane-containing regimens.

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Introduction

Recurrent or metastatic breast cancer (MBC) continues to be an incurable disease with a poor prognosis and a median 5-year survival of only 23–26% [1, 2]. Effective long-term management of MBC poses significant clinical challenges. Modern chemotherapeutic approaches aim to improve survival duration and palliate symptoms while minimizing toxicity and maintaining quality of life [3]. Taxanes, such as paclitaxel and docetaxel, are a cornerstone of treatment across multiple lines of therapy. However, the clinical usefulness of these microtubule inhibitors is often constrained by primary or acquired resistance, the latter frequently resulting from taxane use in the adjuvant or neoadjuvant setting [4, 5]. Resistance underscores the need for additional treatment options for women progressing on standard chemotherapy. Reviewed in this article are several novel antineoplastic drugs targeting microtubules that have provided new treatment options for patients with MBC resistant to taxane therapy. Relevant clinical data were compiled through searches within PubMed and congress abstract databases with no date limits, specific inclusion, or exclusion criteria applied.

Treatment approach and role of taxanes in MBC

The selection of treatment for MBC is strongly influenced by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of the tumor [3, 6]. Systemic chemotherapy is

appropriate for women whose disease is refractory to endocrine therapy, hormone receptor-negative, or rapidly progressive with visceral involvement [3, 6]. In this setting, combination chemotherapy is associated with a rapid response but greater toxicity and similar survival outcomes compared with the sequential use of single cytotoxic drugs [3, 6]. For women with HER2-positive disease, trastuzumab-based therapy is the standard of care, and lapatinib plus capecitabine is a reasonable option in trastuzumab-refractory disease [3, 6]. The antiangiogenic drug bevacizumab improved progression-free survival (PFS) when added to weekly paclitaxel, 3-weekly docetaxel, and capecitabine in first-line treatment of MBC [7–9]. Overall survival (OS) was not prolonged compared with chemotherapy alone but OS is difficult to observe in setting with a long post-progression survival such as first-line HER2-negative MBC [10].

Taxane resistance

The increased use of taxanes in early-stage breast cancer has lead to higher rates of resistance to these drugs by the time of disease recurrence, thereby reducing their effectiveness and usefulness in the treatment of MBC. Even among taxane-naïve patients, primary resistance to taxanes is a critical factor for disease progression. Taxane resistance rates of up to 55% have been reported in anthracycline-pretreated patients and up to one-third of anthracycline-naïve patients [4].

Taxanes bind reversibly to β-tubulin, which stabilizes microtubule complexes and promotes microtubule polymerization leading to cell-cycle arrest and apoptosis [11]. Resistance to taxanes can develop via a number of different mechanisms. The overexpression of P-glycoprotein and other ATP-binding cassette transport proteins promotes drug efflux from the tumor cell, which effectively reduces drug concentrations at target sites. P-glycoprotein, encoded by the *MDR-1* gene, confers resistance to both taxanes and anthracyclines [12]. Taxane resistance can also develop from β-tubulin gene mutations, overexpression of βIII-tubulin or microtubule-associated proteins, and alterations in mitotic checkpoint signaling proteins [13].

The βIII-tubulin isotype has a different amino acid sequence and post-translational modifications compared with other β-tubulin isotypes, which leads to reduced paclitaxel binding [14–16]. The overexpression of βIII-tubulin has been associated with clinical resistance to taxanes in several studies. For example, high versus low βIII-tubulin expression was predictive of progression on paclitaxel-based chemotherapy in a cohort of 70 patients with advanced breast cancer [17]. Similarly, βIII-tubulin overexpression was associated with a significantly higher rate of disease progression in a cohort of 92 advanced breast cancer patients receiving first-line paclitaxel-based chemotherapy (35 vs. 7%, $P < 0.002$) [18]. The development of new taxanes and new taxane formulations has not resolved the problem of primary and acquired resistance, which has driven the search for alternative agents that could be used in taxane-resistant disease or replace taxanes in early stages of treatment. A number of novel agents targeting microtubules have been recently developed for use in breast cancer.

Epothilones: novel microtubule-targeting agents for MBC

The epothilones—identified initially from the myxobacterium *Sorangium cellulosum* [19]—are a novel class of microtubule-stabilizing drugs [20] that have low susceptibility to common mechanisms conferring resistance to taxanes and other cytotoxic agents, including P-glycoprotein overexpression [21]. Moreover, unlike the taxanes, the epothilones bind effectively to βIII-tubulin [16] and consequently retain activity in taxane-resistant tumors overexpressing βIII-tubulin [22, 23]. Ixabepilone is the only epothilone approved by the US Food and Drug Administration (FDA). Preclinical studies showed that ixabepilone, a semi-synthetic derivative of natural epothilone B, is active in taxane-sensitive and -resistant tumor cell lines and tumor xenografts [23, 24]. Preclinical studies also showed synergistic antitumor activity between ixabepilone and other anticancer drugs, including capecitabine [25, 26].

Clinical activity of ixabepilone in MBC

Ixabepilone is approved for use in locally advanced or MBC, either as monotherapy following progression on an anthracycline, a taxane, and capecitabine, or in combination with capecitabine following failure of an anthracycline and a taxane. It may be used in early therapy lines of MBC resistant to these other drugs. Ixabepilone (40 mg/m^2 once every 3 weeks), either alone or in combination with capecitabine 2,000 mg/m^2/day on days 1–14, was effective with acceptable toxicity in clinical trials in MBC patients including those resistant to taxanes or heavily pretreated (Table 1) [27–31]. In phase II trials, objective response rates to ixabepilone monotherapy ranged from 11.5% in patients with MBC resistant to anthracyclines, taxanes, and capecitabine [27] to 57% in MBC patients previously untreated with taxanes [36]. Median survival of patients with taxane-resistant or anthracycline-, taxane-, and capecitabine-resistant disease treated with ixabepilone was 7.9 and 8.6 months, respectively [27, 28].

Combination therapy with ixabepilone plus capecitabine was superior to capecitabine alone after failure of anthracycline and taxane treatment in two large, randomized

Table 1 Phase II clinical studies of ixabepilone monotherapy in patients with MBC

Study	Patient population	Pretreatment characteristics	ORR (%)	SD (%)	Median DOR (months)	Median PFS (months)	Median OS (months)
Ixabepilone 40 mg/m^2 i.v. on day 1 of a 3 week cycle (FDA-approved regimen)							
Perez et al. [27]	Resistant to an anthracycline, a taxane, and capecitabine ($n = 126$)	88% received ≥2 prior regimens for MBC; 48% received ≥3 prior regimens; 77% had visceral disease in liver and/or lung	11.5	50	5.7 (4.4–7.3)[a]	3.1 (2.7–4.2)[a]	8.6 (6.9–11.1)[a]
Thomas et al. [28]	Resistant to taxane[b]; prior anthracycline-based treatment ($n = 49$)	98% received taxane-based regimen as last MBC therapy; 73% progressed within 1 month of last taxane dose	12	41	10.4 (6.3–22.0)[a]	–	7.9 (6.1–14.5)[a]
Roché et al. [29]	Prior anthracycline-based adjuvant therapy[c] ($n = 65$)	17% had received a prior taxane-containing regimen	41.5	35	8.2 (5.7–10.2)[a]	–	22.0 (15.6–27.0)[a]
Ixabepilone 6 mg/m^2/day on days 1–5 of a 3 week cycle							
Low et al. [30]	Prior taxane therapy ($n = 37$)	59% received ≥2 prior regimens for MBC; 68% had visceral disease	22	35	3.9	–	–
Denduluri et al. [31]	No prior taxane therapy; no other limits to prior therapy ($n = 23$)	52% had received prior anthracyclines; 30% previously untreated with chemotherapy; 61% with visceral disease	57	26	5.6	–	–

[a] 95% CI shown in *parentheses*

[b] Patients had progressed within 4 months of taxane therapy (6 months for adjuvant taxane therapy) and received a taxane in their last chemotherapy regimen

[c] Patients may have received a taxane as part of adjuvant therapy providing ≥1 year had elapsed since completion of treatment

DOR duration of response, *ORR* objective response rate, *SD* stable disease

Table 2 Efficacy of ixabepilone in combination with capecitabine in patients with MBC in phase III trials

	Ixabepilone + capecitabine[a]	Capecitabine monotherapy[b]	HR (95% CI)	*P* value
Trial 046 (Yardley et al. [4]; Thomas et al. [32]; Hortobagyi et al. [33])				
Overall population[c]	$n = 375$	$n = 377$		
ORR[d], % (95% CI)	34.7 (30–40)	14.3 (10.9–18.3)	–	<0.0001
Median PFS[d], months (95% CI)	5.8 (5.5–7.0)	4.2 (3.8–4.5)	0.75 (0.64–0.88)	0.0003
Median OS, months (95% CI)	12.9 (11.5–14.2)	11.1 (10.0–12.5)	0.90 (0.77–1.05)	0.1936
Subset with primary taxane resistance[e]	$N = 150$	$N = 137$		
ORR, % (95% CI)	33 (25.9–41.5)	13 (8.0–20.0)	–	<0.0001
Median PFS, months (95% CI)	5.6 (4.3–7.0)	4.9 (4.0–5.7)	0.83	–
Trial 048 (Hortobagyi et al. [33], Sparano et al. [34])				
Overall population[f]	$n = 609$	$n = 612$		
ORR, % (95% CI)	43.3 (38.7–47.9)	28.8 (24.7–33.2)	–	<0.0001
Median PFS, months (95% CI)	6.2 (5.6–6.8)	4.4 (4.1–5.4)	0.79 (0.69–0.90)	0.0005
Median OS, months	16.4 (14.9–17.9)	15.6 (13.9–17.0)	0.90 (0.78–1.03)	0.1162

[a] Ixabepilone 40 mg/m^2 i.v. on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1–14 of a 3 week cycle

[b] Capecitabine 1,250 mg/m^2 PO twice daily on days 1–14 of a 3 week cycle

[c] Patients with locally advanced or MBC previously treated with or resistant to anthracyclines and resistant to taxanes. Resistance was defined by tumor progression during treatment or within 3 months of the last dose for MBC, or recurrence within 6 months of treatment in the adjuvant or neoadjuvant settings

[d] As determined by independent radiology review

[e] Primary resistance defined by progressive disease as best response in previous therapy

[f] Patients with locally advanced or MBC treated previously with an anthracycline and a taxane

ORR objective response rate

phase III studies (Table 2) [4, 32–34]. The pivotal trial included 752 patients with advanced or MBC previously treated or resistant to anthracyclines and resistant to taxanes [32]. Ixabepilone plus capecitabine significantly prolonged median PFS relative to capecitabine monotherapy (5.8 vs. 4.2 months; $P = 0.0003$) and reduced risk of disease progression by 25% [32]. Objective responses were more common with the combination than with capecitabine alone in overall population (35 vs. 14%; $P < 0.0001$) [32] and in patients with primary taxane resistance (33 vs. 13%; $P < 0.0001$) [4]. Median OS was not significantly longer in the combination therapy group (12.9 vs. 11.1 months; $P = 0.19$) [33].

Ixabepilone plus capecitabine was also evaluated in a larger phase III trial that enrolled 1,221 MBC patients previously treated with, but not necessarily resistant to, anthracyclines and taxanes [34]. Overall, 74% of the study cohort was not resistant to anthracyclines and 52% were not resistant to taxanes. The combination regimen significantly improved median PFS (6.2 vs. 4.2 months; $P = 0.0005$) and response rate (43 vs. 29%; $P < 0.0001$) compared with single-agent capecitabine [34]. Despite the PFS benefit, a significant improvement in OS was not observed (16.4 vs. 15.6 months; $P = 0.116$). Pooled analyses of the phase III clinical trials demonstrated that ixabepilone offers clinical benefits across a broad range of patients with advanced or MBC and within specific patient subsets, including taxane-resistant disease, relapse within 1 year of anthracycline/taxane therapy, triple-negative breast cancer, symptomatic with a poor prognosis, and heavy visceral disease burdens to the liver and lung [4, 35–39].

The most common ixabepilone-related adverse event was peripheral neuropathy, which was primarily sensory and generally reversible with dose reduction or delay. In the two phase III trials, the incidence of peripheral neuropathy in the ixabepilone plus capecitabine arms was 67 and 66%, respectively (including 22–24% grade 3 and <1% grade 4) [32, 34].

Other ixabepilone-based combinations

Ixabepilone has also been evaluated in combination with other agents. In the phase II Eastern Cooperative Oncology Group E2103 trial, ixabepilone was administered at a dose of 15 mg/m^2 in combination with trastuzumab and carboplatin area under curve 2 on days 1, 8, and 15 of a 4 week cycle to 59 patients with HER2-positive MBC as first-line therapy [40]. Trastuzumab was administered weekly (4 mg/kg initially, then 2 mg/kg) during chemotherapy, and then every 3 weeks (6 mg/kg) until disease progression.

Objective responses were achieved in 26 patients (44%); the median time to progression was 8.2 months and median OS was 34.7 months. The regimen had an acceptable tolerability profile and efficacy was assessed by investigators as comparable with that achieved with paclitaxel, carboplatin, and trastuzumab.

The feasibility of administering ixabepilone with an anthracycline was shown in two phase I trials. Ixabepilone plus pegylated liposomal doxorubicin (PLD) yielded objective responses in three of 13 patients (23%) with taxane-pretreated advanced breast cancer [41]. The recommended regimen for further evaluation was ixabepilone 16 mg/m^2 on days 1, 8, and 15 plus PLD 30 mg/m^2 on day 1 of a 4 week cycle. Preliminary data from a phase Ib trial indicated that ixabepilone plus epirubicin has favorable efficacy in patients with advanced breast cancer who had a progression-free interval of $\geq$3 months following adjuvant anthracyclines [42]. Partial responses were seen in 10 of 12 women with measurable disease. The suggested dose for further evaluation was ixabepilone 30 mg/m^2 plus epirubicin 75 mg/m^2 every 3 weeks.

Finally, ixabepilone plus bevacizumab was compared with paclitaxel plus bevacizumab as first-line therapy for HER2-negative MBC in a randomized phase II trial [43]. A total of 123 women were allocated to one of three treatment arms: ixabepilone 16 mg/m^2 on days 1, 8, and 15 every 4 weeks plus bevacizumab 10 mg/kg every 2 weeks; ixabepilone 40 mg/m^2 and bevacizumab 15 mg/kg every 3 weeks; or paclitaxel 90 mg/m^2 plus bevacizumab according to the schedule in the first arm. The three-week regimen of ixabepilone/bevacizumab had similar efficacy to the paclitaxel/bevacizumab regimen; the weekly ixabepilone regimen was somewhat less effective but better tolerated.

Other epothilones

Other epothilones are currently in clinical development, including epothilone B (patupilone) and the epothilone B derivative sagopilone. To date, only limited data are available with these agents in breast cancer although activity has been shown across a range of solid tumor types including taxane-resistant tumors [44]. Patupilone (10 mg/m^2 every 3 weeks) is being evaluated in a phase II trial in MBC patients with brain metastases that progressed or recurred after whole brain radiation therapy; preliminary results indicated a partial response in one of the first 17 patients (6%) [45]. Three-month PFS in the central nervous system was 8%, and grade 3/4 toxicities were mostly gastrointestinal events. The tolerability profile of patupilone may differ from that of ixabepilone, presumably because of differences in tissue distribution and metabolism [44].

Sagopilone is being investigated in a broad clinical program that includes breast cancer. In a phase II trial of 65 women with MBC who had previously received an anthracycline and a taxane, sagopilone 16 or 22 mg/m^2 every 3 weeks produced three confirmed responses (5%) [46]; sensory neuropathy and fatigue were the main treatment-related adverse events, occurring in 82 and 45% of patients, respectively. The investigators of this study concluded that sagopilone has limited activity in heavily pretreated MBC patients.

Other novel microtubule-targeting agents

Eribulin was recently approved by the FDA and the European Medicines Agency (EMA) for the treatment of patients with MBC who have received at least two prior chemotherapy regimens for late-stage disease. Several other novel non-taxane, non-epothilone, microtubule-targeting drugs are under early stages of clinical development.

Eribulin

Eribulin, a synthetic analog of the marine macrolide halichondrin B, is a microtubule inhibitor with a unique mechanism of action. Eribulin inhibits microtubule stability by blocking microtubule growth without affecting microtubule shortening, thereby sequestering β-tubulin into nonfunctional aggregates and leading to formation of abnormal mitotic spindles and ultimately apoptosis [47, 48]. Phases I and II studies indicated that eribulin has activity with acceptable toxicity in MBC, including patients pretreated with anthracyclines and taxanes. Eribulin (1.4 mg/m^2) was initially administered on days 1, 8, and 15 of a 4-week cycle but caused significant neutropenia on day 15 [49], and was subsequently evaluated using dosing on days 1 and 8 of a 3-week cycle. Phase II trials were conducted in MBC patients who had received a median of four previous chemotherapy regimens; the first enrolled anthracycline and taxane-pretreated patients, and the second enrolled patients previously treated with anthracyclines, taxanes, and capecitabine (Table 3) [49, 50]. Eribulin produced objective responses in 11.5 and 9.3% of patients in the first and second trial, respectively, and clinical benefit (which includes stable disease $\geq$6 months) in 17% of patients in both studies [49, 50]. Median OS was 9.0 months in the first trial and 10.4 months in the second trial.

On the basis of the phase II results, two open-label, randomized, phase III trials evaluated eribulin monotherapy [52]. The first trial (EMBRACE) compared eribulin versus the physician's choice of treatment in 762 patients with anthracycline and taxane-pretreated locally recurrent or MBC [51]. Patients were required to have received two to five previous

Table 3 Phases II and III studies of eribulin monotherapy in patients with heavily pretreated MBC

Study	Treatment history	Eribulin schedule	ORR (%)[a]	CBR (%)	Median PFS[a] months	Median OS months	Main treatment-related toxicities (grade 3/4)
Phase II							
Vahdat et al. [49]	Anthracycline and taxane (median 4 regimens; ≥5 in 50%)	1.4 mg/m^2, on days 1, 8 and 15 every 4 weeks or days 1 and 8 every 3 weeks ($n = 103$)	11.5 (5.7–20.1)	17.2 (10.0–26.8)	2.6	9.0	Neutropenia, 64% (febrile, 4%); leukopenia, 18%; fatigue, 5%; peripheral neuropathy, 5%
Cortes et al. [50]	Anthracycline, taxane and capecitabine (median: 4 regimens; ≥5 in 20%)	1.4 mg/m^2 on days 1 and 8 every 3 weeks ($n = 291$)	9.3 (6.1–13.4)	17.1 (12.8–22.1)	2.6	10.4	Neutropenia, 54% (febrile, 5.5%); leukopenia, 14%; asthenia/fatigue, 10%; peripheral neuropathy, 7%
Phase III							
Cortes et al. [51]	2–5 previous regimens, including anthracycline and taxane; ≥2 regimens for recurrent/MBC (median 4 regimens)	1.4 mg/m^2 on days 1 and 8 every 3 weeks ($n = 508$) versus physician's choice of treatment ($n = 254$)	12.0 versus 5.0 $P = 0.002$	23.0 versus 17.0	3.7 versus 2.2 HR = 0.87; (0.71–1.05) $P = 0.137$	13.1versus 10.6 HR = 0.81; (0.66–0.99), $P = 0.041$	Neutropenia, 45% versus 21% (febrile, 4.2% vs. 1.2%); leukopenia, 14% versus 6%; asthenia/fatigue, 9% versus 10%; peripheral neuropathy, 8% versus 2%

[a] As determined by independent radiology review

ORR and CBR data in all studies and PFS data in the phase III trial were by independent review. CBR includes partial responses plus stable disease lasting ≥6 months. *Numbers in parentheses* are 95% CIs of ORR and CBR in the phase II trials and of the HR in the phase III trials

CBR clinical benefit rate, *ORR* objective response rate

chemotherapy regimens, including at least two regimens for recurrent or MBC; 73% had previously received capecitabine. The physician's choice included any monotherapy, and no patients received supportive care alone. In total, 96% received chemotherapy, most commonly vinorelbine, gemcitabine, or capecitabine. Eribulin significantly improved median OS compared with the physician's treatment choice (13.1 vs. 10.6 months; $P = 0.041$; Table 3). On independent review, eribulin also produced a higher response rate (12 vs. 5%; $P = 0.002$) and showed a trend for improving PFS (3.7 vs. 2.2 months; $P = 0.137$). Eribulin had a manageable tolerability profile, with grade 3/4 neutropenia in 45% of patients. Notably, EMBRACE is the first phase III study to show a survival benefit for single-agent therapy in heavily pretreated MBC patients. The other phase III trial is comparing eribulin versus capecitabine in 1,102 locally advanced or MBC patients who had received up to three prior chemotherapy regimens including an anthracycline and a taxane, but no more than two regimens for advanced or MBC [52].

Ispinesib

The kinesin spindle protein plays an essential role in spindle formation during mitosis; its inhibition leads to mitotic arrest, formation of characteristic monoaster spindles, and ultimately apoptosis [53]. Ispinesib is a potent and selective small molecule inhibitor of the kinesin spindle protein. In preclinical evaluations, ispinesib had broad antiproliferative activity against a panel of breast cancer cell lines and induced tumor regression in breast cancer xenografts [54]. In these latter models, ispinesib enhanced the antitumor activity of trastuzumab, lapatinib, doxorubicin, and capecitabine. In a phase II trial, ispinesib produced a response rate of 9% in patients with locally advanced or MBC who had relapsed after prior treatment with an anthracycline and a taxane, and exhibited a relatively low neurotoxicity, gastrointestinal toxicity, and hair loss [55]. When administered on days 1, 8, and 15 of a 4-week cycle, the maximum tolerated dose (MTD) in patients with advanced solid tumors was 7 mg/m^2 and neutropenia was the dose-limiting toxicity [56]. Stable disease was the best response in 9 of 30 patients. Several phase I trials have evaluated ispinesib in combination with docetaxel, carboplatin, or capecitabine in patients with advanced solid tumors, and identified a MTD [57–59]. According to ClinicalTrials.gov, there are no active trials ongoing with ispinesib in breast cancer.

Vinflunine

Vinflunine is a semi-synthetic fluorinated *vinca* alkaloid that suppresses microtubule dynamics and treadmilling, and blocks microtubule assembly, which leads to cell-cycle arrest, accumulation of cells in mitosis, and apoptosis [60]. Preclinical data suggest that vinflunine has potential for treatment of a wide range of solid tumors, including breast cancer with greater antitumor activity than vinorelbine [60]. However, vinflunine is sensitive to P-glycoprotein-mediated resistance like other *vinca* alkaloids although it appears less likely to induce resistance than vinorelbine [60]. Vinflunine 320 mg/m^2 every 3 weeks was active with predictable and manageable toxicity when administered to MBC patients after prior anthracycline and taxane therapy, producing response rates of 30 and 12.5% when used in second-line and third-line therapy, respectively [61, 62]. Median PFS was 3.7 and 2.6 months, respectively, and median OS was 14.3 and 11.4 months, respectively. The most common grade 3/4 adverse events in these phase II trials were neutropenia (65–70%), fatigue (14–17%), and constipation (7–12%). In another phase II trial, vinflunine plus trastuzumab produced responses in 33%, clinical benefit in 71%, and PFS of 6.2 months in first-line therapy of MBC, but no advantages compared with taxane/trastuzumab or vinorelbine/trastuzumab in this setting [63]. Vinflunine is currently undergoing phase III evaluation in combination with capecitabine versus capecitabine alone in MBC previously treated with an anthracycline and a taxane, and as monotherapy versus the physician's choice of an alkylating agent in heavily pretreated MBC.

Other agents

Two other microtubule inhibitors are currently being evaluated in phase II trials for MBC. Tesetaxel (DJ-927) is an orally bioavailable docetaxel analog with greater antitumor activity than paclitaxel or docetaxel against a wide range of tumor cell lines and tumor xenografts [64]. Importantly, this agent remains active in tumor cells expressing P-glycoprotein. It is currently being evaluated as first-line therapy at a dose of 50 mg every 3 weeks.

Indibulin (D-24851) is an orally active agent that destabilizes microtubules. Unlike the *vinca* alkaloids, indibulin can distinguish between highly modified β-tubulin found in mature neuronal microtubules and less-modified tubulin in non-neuronal microtubules, thereby offering the potential for reduced risk of neuropathy [65]. Indibulin has activity against a wide range of tumor cell lines, including cells resistant to taxanes, *vinca* alkaloids, and anthracyclines [66] and is under evaluation in a phase I/II trial in MBC.

Individualizing MBC therapy beyond taxanes

The most appropriate use of non-taxane microtubule-targeting agents in clinical practice remains to be defined. Clearly, use of these agents in taxane-naïve patients will

require clinical evidence of equivalent efficacy compared with the standard-of-care taxanes, and their use following taxane failure will require continued evidence of clinical benefit. Patient/clinical characteristics, treatment history, and patient preference are important factors for non-taxane therapy in MBC. Key patient/clinical characteristics include tumor type (e.g., triple-negative breast cancer, HER2-positive disease), the presence of visceral disease, prognosis, and performance status. Ixabepilone appears to be a useful treatment option for patients with these difficult-to-treat attributes. Treatment history includes the use of taxanes and non-taxanes, number of previous regimens, previous single versus combination therapy, and availability of alternative options. Eribulin or ixabepilone plus capecitabine are effective options after previous taxane and anthracycline failure, and single-agent ixabepilone is an option once capecitabine has been used.

Conclusions

Taxanes are likely to remain a standard first-choice treatment for MBC in the near future. However, drug resistance often compromises the clinical benefits of taxanes, particularly in patients exposed to multiple lines of therapy. The use of other microtubule-targeting agents, such as ixabepilone or eribulin may bring clinical benefit to patients with taxane-resistant MBC who otherwise have very few therapeutic options. Ixabepilone has low susceptibility to most mechanisms conferring taxane resistance and has activity in patients across multiple lines of therapy in the advanced/metastatic disease setting. The recent approval of eribulin after second-line MBC treatment expands the treatment options available for patients with late-stage disease. In addition, several emerging novel microtubule-targeting agents appear to have therapeutic potential in MBC. Ixabepilone with or without capecitabine is a viable option for use in first-line or second-line therapy depending on whether taxanes had been used in the neoadjuvant or adjuvant settings, and eribulin is a promising option for use after second-line therapy. The development of these microtubule inhibitors helps to address the need for additional effective regimens for patients progressing after standard treatment with anthracycline- and taxane-containing regimens.

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