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New Frontiers in the Science and Management of Metastatic Breast Cancer

A Review of an Adjunct Symposium of the
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Target Audience

This activity has been designed for all physicians, academicians, researchers, investigators, support staff, nurses, and program directors from the fields of oncology, with a special interest in breast cancer.

Statement of Need/Program Overview

The educational need for this activity is to educate oncologists and related specialties about management strategies for metastatic breast cancer (MBC). Topics include pharmacologic strategies, drug selection, and risk assessment issues related to MBC, with a focus on progression-free survival and overall survival, in heavily treated patients with MBC, using the evolving armamentarium of cancer therapies.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new study findings and clinical trial data in the natural history of breast cancer patients.
- Explain the results of new study findings including current clinical trials evaluating therapy in the treatment of breast cancer.
- Describe how to integrate into clinical practice the latest knowledge on emerging breast cancers.
- Identify future research directions for various therapies in breast cancer.
- Recognize how emerging breast cancer therapies can improve patient outcomes.
- Employ different methods for treating breast cancer patients in an effort to improve current prognosis.

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Current State of Therapy for Metastatic Breast Cancer

Joseph A. Sparano, MD

Today, palliation remains the primary therapeutic goal in the management of metastatic breast cancer (MBC). Thus, treatment decisions must be made by balancing the expected efficacy of the treatment regimen against its toxicity. Moreover, the treatment approach can be one of symptom palliation or symptom preemption. Current options for systemic therapy include endocrine therapy and chemotherapy. Clinicians and patients must choose between the different agents and regimens, determine whether to add a biologic agent, and choose whether to enroll in a clinical trial. Other treatment options are available for site-specific palliation, including systemic therapy with bisphosphonates and receptor activator of nuclear factor kappa B ligand inhibitors, and localized therapy with radiotherapy, surgery, or pleurodesis.

Multiple factors influence the choice of systemic therapy in patients with MBC. The primary disease-specific factors are the expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2/neu) in the tumor and the tumor burden, including the sites and volume of metastases. Important patient-specific factors include age; disease-associated symptoms; performance status; comorbidities, such as cardiac disease or neuropathy; prior treatment history; and patient preferences.

The National Comprehensive Cancer Network guidelines state that several appropriate regimens are available for the typical patient with MBC.¹ In general, combination regimens are generally more active but also more toxic. In daily practice, clinicians tend to use single-agent chemotherapy in patients with a low disease burden and combination chemotherapy in patients with a high disease burden.

Effect of Chemotherapy on Survival in MBC

Hundreds of phase III trials have been performed comparing different chemotherapy regimens for the treatment of patients with MBC. Interpretation of these trials is confounded by crossover to other agents. Relatively few trials

have shown a survival benefit for any cytotoxic agent or combination. Although overall survival (OS) is the gold-standard endpoint for a treatment to gain approval from the US Food and Drug Administration, progression-free survival (PFS) can also be an acceptable endpoint if it is measured properly and if the benefit is of sufficient magnitude. Moreover, survival must be assessed to ensure that the therapy does not negatively affect survival.

Three drugs have been approved for use in MBC since 1994, all for use in combination with paclitaxel: trastuzumab in 1998 and gemcitabine in 2004, both of which provided a survival benefit over paclitaxel alone, and bevacizumab in 2008, based on a PFS benefit over paclitaxel alone.²⁻⁴ Bevacizumab has demonstrated a PFS benefit in MBC in 3 phase III trials, which evaluated bevacizumab in combination with paclitaxel,⁴ docetaxel,⁵ and a variety of chemotherapy regimens (Figure 1).⁶

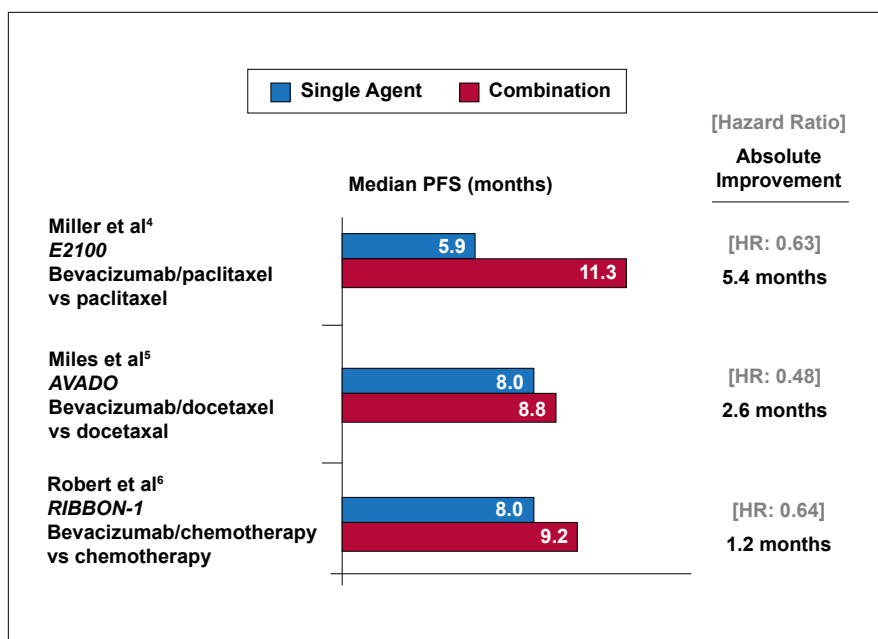
Retrospective analyses have shown that survival in patients with MBC has improved over the past 10–20 years, due to both the introduction of more effective therapies and the development of new imaging modalities allowing earlier detection.^{7,8} Thus, while the choice of agents in the first-line setting may not have a dramatic effect on survival, the availability of multiple agents used incrementally, sequentially, and properly can contribute to improvements in survival.

Role of Chemotherapy Versus Hormonal Therapy in the First-line Setting

The relative effectiveness of chemotherapy versus hormonal therapy in the first-line treatment of MBC has been a topic of multiple clinical trials. A meta-analysis of 8 randomized trials evaluating chemotherapy alone versus endocrine therapy alone showed no difference in OS between the 2 approaches.⁹ Although chemotherapy was associated with a significantly higher response rate versus endocrine therapy (odds ratio [OR], 1.25; $P=.04$), the 2 largest trials trended in opposite directions from each other, suggesting the importance of patient selection. The limited information available on toxicity suggested more

Figure 1. Progression-free survival (PFS) in front-line bevacizumab trials comparing single agents with combination therapy.

AVADO=Avastin Plus Docetaxel Chemotherapy vs Docetaxel Alone; RIBBON=Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Chemotherapy with or without Bevacizumab for First-Line Treatment of HER2-Negative Locally Recurrent or Metastatic Breast Cancer.



toxicity with chemotherapy; quality-of-life results were inconclusive. The authors concluded that for women with hormone receptor-positive MBC, endocrine therapy was recommended over chemotherapy as initial therapy, except for patients with rapidly progressive disease.

Role of Chemotherapy as Palliative Therapy

Several studies have indicated that effective cytotoxic therapy is associated with symptom improvement in patients with MBC. Geels and colleagues evaluated the palliative effect of chemotherapy in 303 patients enrolled in the MA8 trial receiving doxorubicin with or without vinorelbine.¹⁰ The study found a correlation between tumor response and symptom relief. Patients who achieved an objective response were much more likely to have improvements in pain, shortness of breath, mood, worry, and depression than patients without a response. The investigators noted that the incidence of self-recorded symptoms at baseline—most commonly cancer pain, fatigue, and dyspnea or cough—was substantially higher than the incidence reported on the case report form. This disparity suggests that physicians and caretakers may underestimate the severity of symptoms in some patients with MBC.

A meta-analysis of 21 studies in multiple tumor types conducted between 1995 and 2003 showed a similar association between radiographic tumor response and patient-reported outcomes.¹¹ Although there was significant heterogeneity between studies, tumor response correlated with formal measures of change in patient-reported out-

comes, a finding that validates the use of tumor response as an endpoint in clinical trials.

Use of Combination Therapy Versus Single Agents

The use of combination therapy versus single-agent therapy is a fundamental question in the treatment of MBC. A meta-analysis of 37 randomized trials involving 5,707 patients showed a significant improvement in overall response rate (ORR) (OR, 1.28; $P < .00001$), time to progression (TTP; hazard ratio [HR], 0.78; $P < .00001$), and OS (HR, 0.88; $P < .0001$), although there was significant variation in benefit between trials for the first 2 endpoints.¹² Combination therapy was also associated with more toxicity than single-agent chemotherapy. Moreover, results were similar with combination therapy versus single agents if limited to the first-line setting.

In comparing the 2 approaches, factors that would favor the use of combinations include a higher response rate, improved PFS, and modest improvements in survival in some studies. Factors favoring sequential single-agent therapy include its lower toxicity, ability to preserve more treatment options at disease progression, and no negative effect on survival in most settings. A strategy of sequential single-agent therapy is most likely to be successful when drugs are used at their most effective dose and schedule. However, a combination approach may be preferable in patients with advanced visceral disease or significant tumor-associated symptoms.

The role of taxane-containing regimens for MBC was explored in a meta-analysis of 21 randomized trials involving 3,643 patients.¹³ OS was slightly improved with taxane-containing regimens (HR, 0.93; $P=.05$), with no significant heterogeneity between trials. An analysis limited to the first-line setting showed no significant survival benefit.

Summary

The treatment of patients with MBC involves multiple approaches. Endocrine therapy is preferred over cytotoxic therapy in patients with estrogen receptor-positive disease; survival is not compromised by choosing this approach. In general, chemotherapy should be reserved for patients with disease resistant to endocrine therapy and in patients with symptomatic disease and/or a high tumor burden. For patients who are candidates for chemotherapy, single agents are generally preferred over cytotoxic combinations. Antitubulin agents are an important component of therapy, as has been demonstrated in multiple clinical trials.

Note

In July 2010, the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee voted to withdraw approval for bevacizumab as a breast cancer drug. The FDA is expected to make a decision in September 2010.

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What Are the Best and Most Effective Chemotherapy Regimens for Metastatic Breast Cancer?

Stefan Glück, MD, PhD, FRCPC

Survival in patients with MBC has improved slowly but significantly over the past 20 years with the introduction of more effective therapies, including both cytotoxic and targeted agents. Many combination therapy approaches have been evaluated in an attempt to improve efficacy. However, clinical trials have demonstrated that combinations of currently available cytotoxic agents do not necessarily improve outcomes over single-agent therapy. One such trial evaluating single-agent versus combination therapy was Eastern Cooperative Oncology Group (ECOG) 1193, a randomized trial comparing doxorubicin, paclitaxel, and doxorubicin plus paclitaxel in 739 patients with MBC.¹ Although combination therapy was associated with a slightly higher response rate, at 47%, versus 36% with doxorubicin and 34% with paclitaxel, there was no difference in time to treatment failure, which reflects a need to stop treatment due to progression, toxicity, or another reason. Median time to treatment failure with the 3 regimens was 8.0 months, 5.8 months, and 6.0 months, respectively.¹ Moreover, median OS was also similar between arms, at 22.0 months, 18.9 months, and 22.2 months, respectively.

Other ways to improve outcomes have been evaluated. Trials are investigating different schedules, dosing, and the use of combinations of novel agents, including chemotherapeutic agents and biologics.

Role of Schedule and Dose in Improving Treatment Efficacy in MBC

The randomized trial Cancer and Leukemia Group B (CALGB) 9840 showed that the schedule of chemotherapy can have a significant effect on treatment efficacy. In 735 patients with MBC, weekly paclitaxel was significantly more effective than every-3-week paclitaxel in regard to response rate (42% vs 29%; $P=.004$), median

TTP (9 vs 5 months; $P<.0001$), and median OS (24 vs 12 months; $P=.0092$).²

Other studies have evaluated whether higher doses of chemotherapy would be more effective. The phase III trial CALGB 9342 compared 3 different doses of paclitaxel: 175 mg/m², 210 mg/m², or 250 mg/m², each administered every 3 weeks, in 475 patients with MBC. Although the highest dose of paclitaxel was associated with a slight improvement in median TTP, it was also associated with more grade 3/4 neuropathy (Table 1).³ A phase I dose-escalation study of paclitaxel/cyclophosphamide/mitoxantrone in 50 patients with MBC revealed no difference in response rate with higher dosing.⁴ A phase III trial evaluating 3 different doses of docetaxel in 527 patients with advanced breast cancer found a significant improvement in response rate with higher doses of docetaxel but no significant improvement in TTP or OS.⁵ These findings suggest that, as with paclitaxel, higher doses of docetaxel are not beneficial.

Role of Combinations and New Formulations in Improving Treatment Efficacy in MBC

Several doublet combinations have been evaluated in an attempt to improve outcomes over those attained with a taxane alone. In a phase III trial, 511 patients with MBC previously treated with an anthracycline were randomly assigned to docetaxel at 100 mg/m² alone or docetaxel at 75 mg/m² plus capecitabine 1,250 mg/m².⁶ Capecitabine/docetaxel was more effective than docetaxel alone, providing a significant improvement in median TTP (6.1 vs 4.2 months; $P=.0001$) and a 3-month improvement in OS (14.5 vs 11.5 months; $P=.0126$).⁶

In another phase III trial, Albain and colleagues demonstrated a significant efficacy benefit with the addition of gemcitabine to paclitaxel in 529 patients previously treated with an anthracycline.⁷ Compared with paclitaxel

Table 1. Failure of Higher-Dose Paclitaxel in Metastatic Breast Cancer: Data From the CALGB 9342 Phase III Study

Outcome	Paclitaxel (N=475)		
	175 mg/m ² every 3 weeks	210 mg/m ² every 3 weeks	250 mg/m ² every 3 weeks
Overall tumor response rate	23%	26%*	21*
Median time to disease progression, months	3.9	4.1	4.9 [†]
Neuropathy			
Grade 3	7%	19%	26%
Grade 4	33%	54%	57%

**P* value was not significant.

[†]*P*=.045.

CALGB=Cancer and Leukemia Group B.

Data from Winer E et al.³

alone, capecitabine plus paclitaxel was associated with a significant improvement in median TTP (6.14 vs 3.98 months; *P*=.0002). Together, these findings suggest that couplets can be beneficial if used wisely.

New formulations of existing agents have been evaluated that may reduce toxicity and increase ease of administration compared with older formulations. One such formulation is nanoparticle albumin-bound (nab)-paclitaxel, which eliminates the need for corticosteroid premedication. In a phase III trial in 454 patients with MBC, Gradishar and colleagues reported higher response rates and longer TTP with nab-paclitaxel administered at 260 mg/m² over 30 minutes every 3 weeks versus standard paclitaxel administered at 175 mg/m² over 3 hours every 3 weeks.⁸

In a subsequent phase II trial in 300 patients with previously untreated MBC, Gradishar and colleagues evaluated nab-paclitaxel at 3 dose levels (every 3 weeks at 300 mg/m²; weekly at 100 mg/m² for 3 of 4 weeks; or weekly at 150 mg/m² for 3 of 4 weeks) versus standard docetaxel.⁹ Response rates were significantly higher with high-dose weekly paclitaxel compared with both every-3-week paclitaxel (74% vs 46%; *P*=.002) and docetaxel (74% vs 39%; *P*<.001). These findings suggest that combinations of newer agents are effective.

The addition of biologics has also been investigated as a way to improve outcomes in MBC. In the randomized E2100 trial in 722 patients with locally recurrent breast cancer or MBC, the addition of bevacizumab to paclitaxel was associated with a significant improvement in median PFS (11.8 vs 5.9 months; *P*<.001).¹⁰ In 2009, Conlin and colleagues presented results from a randomized phase II trial in 208 patients with previously untreated HER2-negative MBC ran-

domly assigned to nab-paclitaxel at 3 dose levels in combination with bevacizumab. Increasing dose frequency of nab-paclitaxel was associated with significant increases in grade 3/4 toxicity with no significant increase in response rate.¹¹ Median TTP ranged from 6.3 months to 9.0 months in a preliminary report.

Perhaps outcomes could be improved even more by combining these different variables: by using an effective combination with new formulations applied in an optimal schedule with the addition of a biologic. In 2008, Glück and colleagues presented results from a small phase II study evaluating a combination of nab-paclitaxel, bevacizumab, and gemcitabine in patients with HER2-negative MBC.¹² Of the 28 patients enrolled, 45% had triple-negative disease. The regimen was active, with complete responses in 28% of patients, partial responses in 48%, and a median TTP of 10.4 months. Based on these findings, this combination appears to be appropriate when a fast response is needed.

Summary

Chemotherapy is indicated for hormone-insensitive MBC. It is associated with substantial initial efficacy, which is improving with the use of doublets, the addition of biologic agents, and the optimization of dose scheduling. However, chemotherapy has limitations, as the median TTP for first-line therapy remains less than 1 year. Moreover, toxicity—in particular peripheral neuropathy—is manageable but remains a problem, particularly with increasing duration of therapy.

In some clinical situations, sequencing remains the best strategy, as the TTP for each line of therapy likely adds to OS (Table 2). In first-line chemotherapy, how-

Table 2. Chemotherapy for Metastatic Breast Cancer

- **Sequencing is the “best” strategy**
 - Time to progression for each line of therapy likely adds to overall survival
- **In first-line chemotherapy, consider couplets or chemotherapy plus biologics**
 - Fast-progressing tumors
 - Quick symptom control necessary
 - Visceral crisis imminent
- **Think forward: innovation and new design**
- **Novel compounds in urgent need**

ever, couplets of chemotherapy plus biologics should be considered for rapidly progressing tumors, if quick symptom control is necessary, or if visceral crisis is imminent. Clearly, novel compounds are urgently needed to improve outcomes beyond those attained with current strategies.

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Microtubules as Targets for Anticancer Drugs, Both Tried and New

Mary Ann Jordan, PhD

Microtubules are structural components of the cell that are involved in many cellular functions. Microtubules consist of protofilaments of alpha-tubulin and beta-tubulin heterodimers that form into a tube. These dynamic, polar structures continually undergo rapid shortening (known as *catastrophe*) and growth (known as *rescue*). The dynamic instability of microtubules relies on the binding of alpha-tubulin and beta-tubulin to guanosine triphosphate (GTP). Whereas the binding of alpha-tubulin to GTP is stable, GTP bound to beta-tubulin is hydrolyzed to guanosine diphosphate (GDP). The addition of GTP-bound tubulin to an existing microtubule allows the microtubule to lengthen. The subsequent hydrolysis of GTP to GDP causes a conformational change in the stable tubular structure, causing the microtubule to begin to unravel. This depolymerization continues until a sufficient amount of GTP-tubulin, microtubule-targeting drug, or other molecule caps the microtubule and causes it to start growing again.

The regulation of microtubule assembly dynamics varies based on the location of the microtubule within the cell. In a migrating cell, microtubule dynamics are slower in the front end of the cell than in the back end of the cell, where microtubules interact with points of cell adhesion to

the substrate. Signaling between the microtubule and the focal adhesion allows the cell to release and move forward. Microtubule assembly dynamics also vary depending on cellular activities. In particular, microtubule dynamics are dramatically more rapid during mitosis. Endogenous proteins also act to regulate microtubule assembly dynamics by promoting or inhibiting catastrophe and/or rescue, suppressing dynamics, and exerting other effects (Table 1).

Microtubule-targeting Agents

Microtubule-targeting drugs exert potent anti-cancer activity by suppressing microtubule dynamics (Table 2). This class of agents, which were all originally derived from naturally occurring substances, includes the taxanes (paclitaxel, docetaxel), epothilones (ixabepilone), vinca alkaloids (vincristine, vinblastine, and vinorelbine), halichondrins (eribulin), and maytansine (trastuzumab-DM1). The enhancer-type microtubule-targeting agents, including paclitaxel and ixabepilone, act by inducing polymerization; the depolymerizers, including vinorelbine, eribulin, and maytansine, stabilize microtubule dynamics at moderate concentrations and cause microtubule depolymerization at high concentrations.

Table 1. Microtubule-targeted Drugs Mimic Endogenous Regulators

Regulatory Protein	Location on Microtubule	Mechanism
Tau, MAP2, MAP4	Surfaces	↓ Dynamics, enhance G-rate
XMAP215	Surfaces	Enhance dynamicity
MCAK	+ Ends	↑ Catastrophe
EB1	+ Ends	↓ Catastrophe, ↑ rescue
CLASP 1	+ Ends	Enhance dynamicity
CLIP 170	+ Ends	↑ Rescue
Dynactin 1 (p150Glued)	+ Ends	Nucleation, recruit dynein-cargo
LIS 1	+ Ends	↓ Catastrophe, recruit dynein?
NudA (dynein homolog)	Ends	Cat, rescue frequencies, S-rate
Stathmin	- Ends, + ends, surfaces	↑ Catastrophe, sequester tubulin
Gamma-TuRC	- Ends	Nucleation
Ninein	- Ends	Nucleation, anchorage

Table 2. Similarities and Differences Among Microtubule-targeted Drugs

<p>Similarities</p> <ul style="list-style-type: none"> • Suppress microtubule dynamics • Inhibit formation of normal bipolar spindles and reduce tension on kinetochores • Inhibit Mad2 signal for entry into anaphase <p>Differences</p> <ul style="list-style-type: none"> • Binding sites on microtubules and tubulin • Affinity and reversibility of binding • Specific effects on microtubule dynamic instability • Susceptibility to multidrug resistance • Effects on different tubulin isoforms • Reversibility of cellular uptake and retention • Tissue and cell specificity • Pharmacokinetics • Optimal scheduling • Efficacy • Neuropathy and other toxic side effects

Microtubule-targeting agents vary in their binding to the tubulin molecule. Whereas vinorelbine and maytansine have overlapping binding sites, eribulin binds in a slightly different site.¹ Vinblastine and eribulin bind primarily at the microtubule tip; the vinca alkaloids have been shown to bind along the outer surface of the microtubule. Colchicine molecules are present in the middle of microtubules and co-polymerize into a microtubule, whereas paclitaxel and the epothilones bind along the interior of the microtubule.

Microtubule-targeting agents also differ in the number of molecules needed for suppression. Whereas many molecules of paclitaxel or ixabepilone are required to suppress microtubule dynamics, the binding of 1 or 2 molecules of eribulin or vinblastine at the end of the microtubule can stabilize it.

The actions of microtubule-targeting agents have a detrimental effect on cell cycle progression. During the interphase, microtubule dynamics are slow but still important to normal functions, including the delivery of molecules around the cell and organization of cell signaling, including processes important in oncogenesis, such as metastasis and angiogenesis. Microtubule dynamics accelerate by approximately 100-fold in a cell entering mitosis. During the prophase, microtubules in the cytoplasm probe out from the future spindle poles. During the metaphase, microtubules attach to condensed chromosomes and slowly bring the chromosomes to the metaphase plate of the cell. Under normal conditions, the microtubules remain dynamic at this point, causing continual movement of the chromosomes. However, the introduction of a microtubule-targeting drug stops this motion, prevent-

ing the transition to anaphase. This mitotic arrest results in cell death.

Microtubule-targeting agents affect microtubules on 2 levels: by suppressing microtubule dynamics and by causing enhancement or depolymerization of the microtubules themselves. Taxanes, ixabepilone, and the epothilones enhance microtubule polymers at high concentrations but suppress microtubule dynamics at lower concentrations. Vinca alkaloids, eribulin, and maytansine suppress microtubule dynamics but at high concentrations cause depolymerization, resulting in destruction of cellular microtubules.

In vitro time-lapse micrography studies of cells treated with microtubule-targeting agents provide a direct view of these events, allowing visualization of the quantitative analysis of the effects of different agents. Microtubule shortening rates are substantially suppressed by epothilone B and paclitaxel, less suppressed by maytansine and vinblastine, and not affected by eribulin. Conversely, microtubule growth rates are suppressed by all 5 agents. The dynamicity of microtubules, which represents the overall dynamics, is suppressed by all 5 microtubule-targeting agents at the concentration that blocks mitosis by 50%.

Fluorescent labeling of kinetochores and centromeres in the context of time-lapse micrography has been used to elucidate the effects of microtubule-targeting agents during mitosis. These studies, which allow direct visualization of the movement and separation of chromosomes during mitosis, have demonstrated that the addition of microtubule-targeting agents substantially reduces the rate of chromosome separation during mitosis.² This inhibition prevents the formation of normal bipolar spindles, reduces tension on kinetochores, and prevents the transmission of signals associated with entry into anaphase, ultimately leading to cell death.

Although the microtubule-targeting agents share a common mechanism of action, they differ in their binding to microtubules, their effects on microtubule dynamics, their susceptibilities to multidrug resistance pumps, and their reversibility of uptake and retention. These agents also differ in their pharmacokinetics, optimal scheduling, efficacy, and toxicity, particularly neurotoxicity and myelosuppression. Eribulin, for example, induces less neuropathy.³ All microtubule-targeted drugs, however, suppress microtubule dynamics in concert with mitotic arrest.

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Survival Prolongation in Metastatic Breast Cancer

Javier Cortes, MD

Two new types of microtubule-targeting agents have recently been developed that may expand the role of these agents in the treatment of MBC. These include the epothilones—ixabepilone, KOS 862 (EPO D), ZD-EPO, and patupilone—and the halichondrin B analog eribulin (E7389). As with the other microtubule-targeting drugs, these agents were originally derived from naturally occurring substances.

Ixabepilone

Mechanism of Action and Preclinical Data

Epothilone was derived from *Sorangium cellulosum*, a myxobacteria discovered on the banks of the Zambezi River in Africa. Ixabepilone, a semisynthetic analog of epothilone B, differs from epothilone B at a single moiety (Figure 1). Preclinical data have shown that ixabepilone binds specifically and uniquely to beta-tubulin, and it has tubulin polymerizing activity that is 2–10 times greater than that of paclitaxel.^{1,2} Ixabepilone is active in multiple tumor models. Because ixabepilone retains activity in tumors that use multidrug resistance pumps, it also has activity in paclitaxel-resistant tumor cells. Moreover, unlike paclitaxel, ixabepilone exhibits linear pharmacokinetics, which allows better estimation

of toxicity.³ Ixabepilone has demonstrated synergy with capecitabine, cetuximab, and trastuzumab, and in vivo data suggest greater synergy with bevacizumab than has been demonstrated with paclitaxel.⁴

Clinical Data

Ixabepilone has demonstrated significant activity in multiple clinical trials in patients with MBC. In phase II trials, single-agent ixabepilone was active in patients who had received adjuvant anthracyclines (overall response rate [ORR], 42%), in taxane-naïve patients (ORR, 57%), and in taxane-pretreated patients (ORR, 22%).⁵⁻⁷ However, the median TTP in these trials was approximately 6–8 months, and grade 3/4 neurotoxicity was high.

In patients with taxane-resistant disease, ixabepilone was associated with an ORR of 12%.⁸ The weekly regimen produced a 12–15% response, but again, the level of toxicity was too high. Among the 49 patients, 11 (22%) experienced a treatment-related serious adverse event.

Ixabepilone has been evaluated in 2 phase III trials comparing ixabepilone plus capecitabine versus capecitabine alone in patients with resistance to previous anthracycline and taxane therapy. Patients in the trials

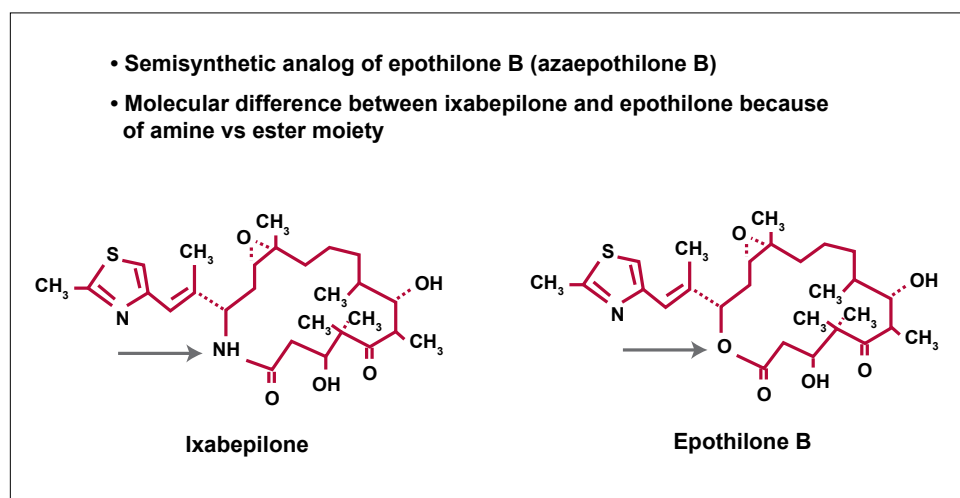


Figure 1. Ixabepilone, a semisynthetic analog of epothilone B, differs from epothilone B at a single moiety.

were required to meet strictly defined resistance criteria and had tumors that progressed rapidly in the adjuvant or metastatic setting after treatment with both anthracyclines and taxanes. Patients enrolled in CA163-046 (N=752) and CA163-048 (N=960) were randomly assigned to ixabepilone 40 mg/m² IV over 3 hours on day 1 every 3 weeks plus capecitabine 2,000 mg/m²/day twice daily for 14 days every 3 weeks, or capecitabine 2,500 mg/m² twice daily for 14 days every 3 weeks.

A combined analysis of the 2 phase III trials showed a significant improvement in PFS with ixabepilone plus capecitabine versus capecitabine alone, with median PFS of 5.26 versus 3.81 months (HR, 0.78; *P*=.0011) in Study 046 and 6.24 versus 4.40 months (HR, 0.79; *P*=.0005) in Study 048.⁹ The addition of ixabepilone to capecitabine was also associated with an increase in response rate in both trials (42.1% vs 22.5%; 43.3% vs 28.8%). Moreover, complete response was observed in approximately 3% of patients receiving ixabepilone plus capecitabine. However, the addition of ixabepilone to capecitabine did not confer a significant improvement in OS. Median OS with ixabepilone plus capecitabine versus capecitabine alone was 12.9 versus 11.1 months in Study 046 and 16.4 versus 15.6 months in Study 048.

Pooled subgroup analyses showed a benefit with ixabepilone in patients with poor prognosis factors. Among patients with triple-negative tumors, the addition of ixabepilone to capecitabine was associated with an increase of ORR (21% vs 15%) and a significant improvement in PFS (4.2 vs 1.7 months; *P*=.005). Similar improvements were seen in patients with taxane-resistant tumors (ORR, 39% vs 22%; median PFS, 5.1 vs 3.7 months; *P*=.0003) and in patients with a Karnofsky performance status of 70–80 (ORR, 35% vs 19%; median PFS, 4.6 vs 3.1 months; *P*=.0007).

Taken together, these data suggest that ixabepilone plus capecitabine was associated with a clinically meaningful efficacy in a large, heavily pretreated population with limited treatment options. The difference in median OS favored the combination, although it did not reach statistical significance. Toxicity—particularly grade 3/4 peripheral neuropathy—remains a concern. Ixabepilone was approved for use in some countries, including the United States, although the toxicity precluded its approval in other countries, including those in Europe.

Eribulin Mesylate

Mechanism of Action and Preclinical Data

Another recently developed microtubule-targeting agent is eribulin mesylate (E7389). Eribulin is a synthetic analog of halichondrin B, a natural marine sponge product with antineoplastic activity.¹⁰ This nontaxane inhibitor

Table 1. Intention-to-Treat Efficacy Summary of Phase II Eribulin Breast Cancer Studies

Characteristic/Response	201 Trial ¹⁶ (N=103)	211 Trial ¹⁷ (N=269)
Previous regimens, median n	4	4
Response rate*	13.6%	9.0%
Clinical benefit rate [†]	20.4%	17.1%
Duration of response, median	5.6 months	4.1 months

*Complete response and partial response.

[†]Complete response, partial response, and stable disease.

of microtubule dynamics uses a novel mode of action to exert potent antiproliferative effects in vitro and in vivo.^{11–13} Eribulin has no significant effect on microtubule depolymerization, but instead suppresses microtubule polymerization and sequesters tubulin into nonfunctional aggregates, causing toxicity to the cell.¹⁴ Eribulin is active against beta-tubulin–mutated cell lines and has a wide therapeutic window.¹⁰ Moreover, eribulin has been associated with a low incidence of neuropathy.¹⁵

In vitro studies have demonstrated the tubulin-based antimetabolic mechanism of eribulin. The agent causes a G2/M cell cycle block by inhibiting tubulin polymerization in vitro and disrupting mitotic spindles.¹⁰ Preclinical data indicate that eribulin is active across a range of models, including breast cancer, melanoma, ovarian cancer, and colon cancer, and it appears to have greater antitumor activity than paclitaxel in some tumor types.¹⁰

The binding site of eribulin differs from that of other microtubule inhibitors. Vinblastine binds to the positive end of microtubules and along the sides; paclitaxel, docetaxel, and epothilone B bind to the inside surface of beta-tubulin subunits. However, eribulin binds only to the positive ends of microtubules. These binding site differences could contribute to differences in mechanisms of action and activity among these agents. For example, eribulin retains activity against drug-resistant cells that harbor beta-tubulin mutations associated with taxane resistance. Differences in binding may also contribute to differences in toxicity profiles between the agents.

Clinical Data

Eribulin has been evaluated in 2 phase II trials in patients with heavily pretreated MBC (Table 1). The first trial, Study 201, enrolled 103 patients previously treated with an anthracycline and a taxane.¹⁶ The second trial, Study 211, was an open-label, single-arm, multicenter, phase II

trial in 269 patients with MBC who had previously received 2–5 chemotherapy regimens, including an anthracycline, a taxane, and capecitabine, and had documented progression that occurred by month 6 after their last chemotherapy session.¹⁷

In Study 201, eribulin was initially administered at 1.4 mg/m² over 2–5 minutes on days 1, 8, and 15 every 4 weeks.¹⁶ However, the development of neutropenia at day 15 led to a modified regimen in which eribulin was administered on days 1 and 8 of a 21-day cycle. This modified regimen was adopted in Study 211.¹⁷

In both studies, patients were heavily pretreated, with a median of 4 prior regimens. In Study 211, 11% of patients had HER2/neu-positive tumors, and 21% of patients had triple-negative tumors. The ORR in Studies 201 and 211 were 13.6% and 9.3%, respectively, with clinical benefit rates (complete response, partial response, or stable disease for at least 6 months) of 20.4% and 17.1%, respectively, and median response durations of 5.6 and 4.1 months, respectively.^{16,17} The median PFS in Study 211 was 2.6 months, with a 6-month PFS rate of 16.0%, and median OS was 10.4 months, with a 6-month OS rate of 72.3%.¹⁷

The most common grade 3/4 adverse event in Studies 201 and 211 was neutropenia, developing in 64% and 54% of patients, respectively. However, neutropenia typically occurred on day 15 and was not generally associated with treatment delays. Febrile neutropenia occurred in 4% and 6% of patients, respectively, in both trials. Notably, rates of grade 3/4 peripheral neuropathy were low, at 5% and 6%, in Trials 201 and 211, respectively. Other grade 3/4 adverse events occurring in at least 5% of patients in Trial 211 included leukopenia (14.1%) and asthenia/fatigue (10.0%). Asthenia was the most important toxicity observed in daily practice, but it did not reach grade 4.

A subgroup analysis in Trial 211 showed similar response rates across a range of tumor types, in patients with less heavily pretreated versus more heavily pretreated disease, and in patients refractory to different chemotherapeutic agents and combinations. Overall, the results appear to compare favorably with those observed with ixabepilone, while demonstrating a lower rate of neuropathy.

Eribulin is being evaluated in 2 randomized phase III trials.^{18,19} The Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus Eribulin (EMBRACE) study (Study 305) is comparing eribulin IV on days 1 and 8 every 21 days versus physician's treatment of choice in patients with MBC previously treated with an anthracycline and a taxane. At the 2010 American Society of Clinical Oncology meeting, Twelves and colleagues presented preliminary data from

the EMBRACE trial.²⁰ Eribulin was associated with a significant improvement in median OS versus physician's choice of treatment, meeting the trial's primary endpoint. The toxicity profile was consistent with previous phase II data. Another phase III trial, Study 301, is comparing eribulin versus capecitabine in the second-line treatment of MBC.¹⁹ A third randomized trial, a phase II study, is comparing rates of peripheral neuropathy with eribulin versus ixabepilone.

Summary

Many new agents currently in development are demonstrating promising results in MBC. Ixabepilone is associated with improved ORRs and TTP in patients with taxane-resistant MBC, but it is associated with toxicity, neuropathy in particular. Eribulin is the first drug to demonstrate an increase in OS in MBC patients previously treated with taxanes and anthracyclines. Given this demonstrated improvement, eribulin could become a new standard of care in heavily pretreated patients.

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