Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

August 2012 Volume 10, Issue 8, Supplement 13

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New Treatment Paradigms for Optimizing Survival in Advanced and Metastatic Breast Cancer

A Review of an Adjunct Symposium of the 2012 American Society of Clinical Oncology Annual Meeting
June 3, 2012
Chicago, Illinois

A CME Activity
Approved for 1.25
AMA PRA
Category 1 Credit(s)™

Sponsored by Postgraduate Institute for Medicine

PIM Postgraduate Institute for Medicine

Release date: August 2012
Expiration date: August 31, 2013
Estimated time to complete activity: 1.25 hours
Project ID: 8851

ON THE WEB:
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Supported through an educational grant from Eisai Co., Ltd.

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

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Statement of Need/Program Overview

As the number of available therapies for metastatic breast cancer expands, there is a growing challenge in discerning how to best apply these agents to attain therapeutic goals. Questions remain regarding the best ways to sequence therapies, whether to use combinations, and how to incorporate biologic agents. An area of great recent interest in breast cancer research is the development of personalized medicine. Multiple factors must be considered in selecting the most appropriate therapy for each patient, including tumor biology, tumor burden, age, disease-associated symptoms, performance status, comorbidities, and treatment history. Results from recently published clinical trials have the potential to change clinical practice. Agents have been developed against a variety of targets identified as relevant to breast cancer biology. These agents will likely play an increasingly important role in the management of patients with metastatic breast cancer.

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

- Incorporate new clinical trial data in the management of patients with advanced or metastatic breast cancer
- Develop individualized management strategies for patients with advanced or metastatic breast cancer
- Explain the mechanisms of action of novel agents in breast cancer
- Identify future research directions in the management of patients with advanced or metastatic breast cancer

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This monograph was authored by an independent medical writer, Melinda Tanzola, PhD, based on presentations given at "New Treatment Paradigms for Optimizing Survival in Advanced and Metastatic Breast Cancer," an adjunct symposium of the 2012 American Society of Clinical Oncology Annual Meeting, held on June 3, 2012.

Current State and Future Directions in Metastatic Breast Cancer Treatment

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The treatment of breast cancer has evolved dramatically over the past several decades. To appreciate these advances, one need only look at trends in the use of adjuvant chemotherapy over the past 30 years. In the 1980s and early 1990s, the vast majority of patients receiving adjuvant therapy received cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). However, over time, this regimen declined in use and was replaced by anthracyclines and taxanes, which dominate today.[1] This evolution in adjuvant therapy has an influence on management of metastatic breast cancer, as general practice is to try to avoid using the same agents in the metastatic setting, unless the metastatic disease occurs many years after the original diagnosis of invasive breast cancer.

Today, the duration of survival for patients with metastatic breast cancer is dependent primarily on the aggressiveness of the disease; tumor biology is therefore central to prognosis. Although recent years have seen tremendous progress in the understanding of the biologic processes of breast cancer, the median survival for patients with metastatic disease remains limited at 18–24 months. According to previous studies, the 5-year overall survival (OS) rates are approximately 20–25%. An ongoing goal of clinical trials is to attain survival improvements not only by extending median OS but also by increasing the proportion of patients alive at 5 years; perhaps newer treatments will be able to increase 5-year OS rates to 30–35%.

Agents have been developed against a variety of targets identified as relevant to breast cancer biology, including polyADP ribose polymerase (PARP), mammalian target of rapamycin (mTOR), phosphoinositide 3 (PI3) kinase, MEK, topoisomerase I, and fibroblast growth factor (FGF), as well as human epidermal growth factor receptor 2 (HER2). These targets are all being evaluated in randomized phase II and/or phase III trials; they will likely play an increasingly important role in the management of patients with metastatic breast cancer. Knowledge of these ongoing advances, which reflect new strategies based on the biology of the disease, should give hope to individuals living with metastatic breast cancer.

Management of Hormone Receptor–Positive Metastatic Breast Cancer

Hormone receptor–positive breast cancers, which are characterized by expression of estrogen receptor (ER) and/or progesterone receptor (PR), account for approximately 60–70% of breast cancer tumors. Although the other 2 subtypes—HER2-positive and triple negative—are often considered to be more aggressive, the majority of breast cancer deaths occur in the setting of an initial hormone receptor–positive disease.

The standard treatment of hormone receptor–positive metastatic breast cancer varies according to HER2 status. For patients with HER2-negative disease, first-line strategies today include aromatase inhibitors, according to the patient's menopausal status, tamoxifen, and ovarian function suppression. Initial therapy may also include chemotherapy, with or without a targeted agent, depending on the aggressiveness or extent of disease. In the second-line setting, treatment often involves the nonsteroidal aromatase inhibitor exemestane with or without everolimus, plus fulvestrant, which is now administered at doses higher than were used initially.

Looking forward to the next several years, the treatment of patients with hormone receptor–positive, HER2-negative breast cancer may evolve as current clinical trials are completed and analyzed (Figure 1). Two ongoing phase III trials are currently evaluating an aromatase inhibitor or tamoxifen with or without bevacizumab. Other trials are evaluating the potential role of PI3 kinase inhibitors and FGF inhibitors.

Management of HER2-Positive Metastatic Breast Cancer

Approximately 15–20% of invasive breast cancers are HER2-positive. Of these, about half are ER-positive and half are HER2-positive, ER-negative. Although HER2 testing currently forms the basis for therapeutic decision-making in breast cancer, other markers

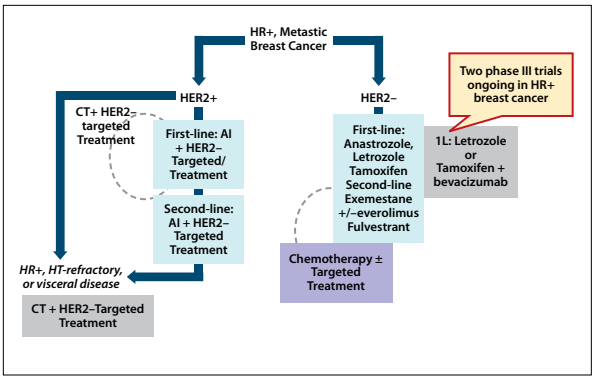

Figure 1. The treatment of patients with hormone receptor–positive, HER2-negative breast cancer may evolve as current clinical trials are completed and analyzed. AI=aromatase inhibitor; CT=computed tomography; HER=human epidermal growth factor receptor.

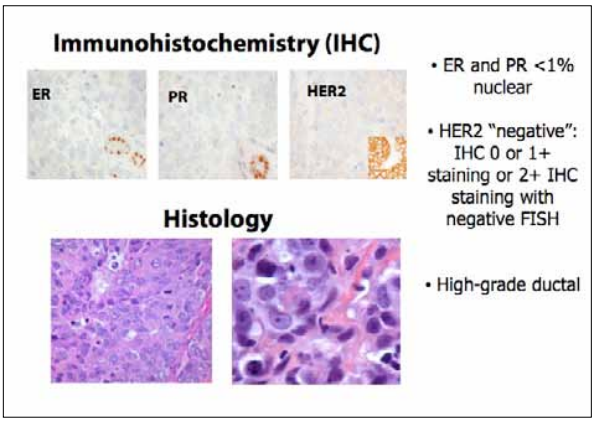

Figure 2. Triple-negative breast cancer lacks expression of ER, PR, and HER2. ER=estrogen-receptor; FISH=fluorescence in situ hybridization HER=human epidermal growth factor; PR=progesterone receptor.

are currently under evaluation to further individualize anti–HER2-based therapies.

Currently, therapeutic options for first-line therapy in HER2-positive metastatic breast cancer consist of trastuzumab in combination with chemotherapy, which may include paclitaxel with or without carboplatin, docetaxel, or vinorelbine.[2] Other approaches are undergoing evaluation in ongoing clinical trials, such as the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, which is evaluating pertuzumab in the first-line setting,[3] and the MARIANNE (A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/ Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer) trial, which is evaluating the antibody-drug conjugate trastuzumab-DM1 (trastuzumab linked to DM1) in the first-line setting.[4] These studies may lead to changes in the management of previously untreated HER2-positive metastatic breast cancer in the next few years.

For patients requiring second-line therapy for HER2-positive metastatic breast cancer, the only approved option for most patients worldwide has been combination therapy with lapatinib and capecitabine. This regimen has therefore been the standard of care, although many physicians have instead chosen to continue trastuzumab administered in combination with another chemotherapeutic agent, capecitabine, or lapatinib.

The treatment of second-line HER2-positive metastatic breast cancer may soon change, based on the recent results of the EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine Plus Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial, which demonstrated a significant improvement in progression-free survival (PFS) with T-DM1 compared with capecitabine and lapatinib.[5] Not only was T-DM1 associated with a significant efficacy benefit over capecitabine and lapatinib, but it was also associated with less toxicity and improved quality of life.

Other important ongoing trials are investigating novel strategies for second-line therapy in HER2-positive metastatic breast cancer. Several trials are evaluating a combination of a chemotherapeutic agent plus trastuzumab, either alone or with everolimus. One trial is using paclitaxel as the chemotherapy and another is using vinorelbine. Another novel strategy being evaluated in this patient population is an anti-HER2 therapy with or without a PI3 kinase inhibitor. Results of these studies are expected in the next few years.

Management of Triple-Negative Breast Cancer

Currently, chemotherapy remains the mainstay of therapy for patients with triple-negative breast cancer, which lacks expression of ER, PR, and HER2 (Figure 2). Recent years have seen a significant evolution in the approach to chemotherapy for metastatic breast cancer, moving from the early regimens of CMF or vincristine/prednisone (VP) to the introduction of anthracyclines, vinorelbine, taxanes, and capecitabine, to the development of novel antitubulins and other advanced cytotoxic agents.

The main obstacle to improving treatment options for patients with triple-negative breast cancer is identifying appropriate targets. Next-generation gene sequencing studies are identifying additional breast cancer subsets that can be classified according to their molecular profile; this has allowed greater characterization of breast cancers, including among patients with triple-negative disease. These advances in breast cancer characterization will likely lead to a decline in the proportion of breast cancers described simply as "triple-negative." Improvements in classification will hopefully lead to improvements in therapeutic options.

The future will also likely bring an increasing movement toward "omic" approaches to prevent or manage metastatic breast cancer, in which genome-scale molecular analyses are being applied to characterize molecular features associated with metastatic disease.[6] This may lead to the development of anatomic, histologic, and blood-based strategies that could possibly detect tumors likely to metastasize, enable greater monitoring of disease activity, and identify personal markers that will be important for therapeutic decision-making. Ongoing research will also focus on elucidating the genomic diversity and complexity of cancer, and identifying the pathways important in disease pathogenesis.[7,8]

In summary, improving the management of patients with metastatic breast cancer will require maximizing the therapies available today, understanding mechanisms of resistance and developing strategies to overcome them, developing better biomarkers to predict responses to therapy, and increasing our understanding of the role of genetics—of both the tumor itself and of the individual as a whole.

Acknowledgment

Dr. Perez has received grants and research support from Sanofi Oncology, Genentech, and GlaxoSmithKline.

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Optimizing Current Treatment Options in Metastatic Breast Cancer

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As the number of available therapies for metastatic breast cancer expands, there is a growing challenge in discerning how to best apply these agents to attain the therapeutic goals important to patients diagnosed with metastatic breast cancer. Questions remain regarding the best ways to sequence therapies, whether to use combinations, and how to incorporate biologic agents. There are multiple goals and factors that must be weighed, including prolongation of survival, palliation of symptoms, and quality of life. On a personal level, patients living with the disease often express a desire to continue to travel and spend time with their families, minimizing their time in the clinic.

There are multiple therapeutic options today that have demonstrated improvements in overall survival, response rate, and/or progression-free survival, in appropriately selected patients (Table 1). These therapies are also associated with hematologic and nonhematologic toxicities that can lead to dose reductions, dose delays, and missed doses (Table 2).

A global view of survival from 1991 to 2001 indicates that access to new agents has led to improvements in overall survival in women with metastatic breast cancer, even before the most recent advances.[1] Symptom palliation is also an important therapeutic goal; correlative studies have shown an association between response to therapy and quality of life, including pain, shortness of breath, and mood.[2] Attainment of stable disease can also be important, as it is associated with a significant benefit over progressive disease in multiple quality-of-life domains.

Role of Biologic Agents in First-Line Therapy

The role of chemotherapy versus biologic agents in different metastatic breast cancer subsets has been an

Table 1. Therapeutic Options for Advanced and Metastatic Breast Cancer

Modality	Selection	Improvement in		
		Relative Response	Progression-Free Survival	Overall Survival
Chemotherapy[1,2]	ER/PR-negative, visceral metastases, failed endocrine therapy	Yes	Yes	Yes
Endocrine[1,2]	ER and/or PR-positive	Yes	Yes	Yes
Trastuzumab, lapatinib[1,2]	HER2/neu-positive	Yes	Yes	Yes
Bevacizumab[3-5]	HER2/neu-negative, first-line therapy	Yes	Yes	No
RANKL inibitors, bisphosphonates[1,2]	Osteolytic bone metastasis	No	Yes	No

ER=estrogen-receptor; HER=human epidermal growth factor; PR=progesterone receptor.

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Table 2. Nonhematologic Toxicities Associated With Current Therapies for Advanced and Metastatic Breast Cancer

Agent	Nonhematologic Toxicities
Endocrine therapy	Hot flushes, gynecologic symptoms
Bevacizumab	Hypertension, thromboembolic disease
Trastuzumab	Cardiac dysfunction
Lapatinib	Diarrhea
Cytotoxic agents • Anthracyclines • Paclitaxel • Docetaxel • Ixabepilone • Eribulin • Vinorelbine • Capecitabine • Gemcitabine	 • Cardiomyopathy • Neuropathy • Fluid retention • Neuropathy • Neuropathy • Obstipation, neuropathy • Hand-foot syndrome • Fever, dyspnea

important ongoing question. In patients with ER-positive disease, a meta-analysis of 8 randomized trials involving 817 patients showed no significant difference in OS with chemotherapy versus endocrine therapy, although chemotherapy was associated with more toxicity.[3] Based on those findings, the study authors concluded that the first therapy in women with hormone receptor–positive metastatic breast cancer should be endocrine therapy rather than chemotherapy, except in the presence of rapidly progressive disease. For patients with HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy has demonstrated a significant improvement in response rate and PFS compared with chemotherapy alone in several randomized trials, despite extensive crossover (Figure 3).[4,5]

The use of bevacizumab in metastatic breast cancer has been a topic of great controversy. The 3 major trials of bevacizumab added to chemotherapy in first-line (primarily HER2-negative) metastatic breast cancer showed a benefit with bevacizumab in regard to PFS and response rate, suggesting that VEGF inhibition enhanced the efficacy of chemotherapy. However, none of these trials showed a significant improvement in median OS with bevacizumab.[6-8] A 2010 meta-analysis of OS outcomes from these 3 trials confirmed that chemotherapy plus bevacizumab was more effective than chemotherapy alone in regard to ORR (49% vs 32%; $P<.05$), median PFS (9.2 vs 6.7 months; hazard ratio [HR], 0.64; $P<.0001$), and 1-year survival (82% vs 77%; $P<.003$), but there was no difference in median OS (26.7 vs 26.4 months; $P=.54$).

Role of Biologic Agents in Second-Line Therapy

Several randomized trials have evaluated the role of biologic agents for patients with previously treated metastatic breast cancer. Geyer and colleagues demonstrated the efficacy of lapatinib plus capecitabine, which showed a significant improvement in time to progression (TTP) and ORR versus capecitabine alone in women with HER2-positive advanced breast cancer that had progressed after an anthracycline, a taxane, and trastuzumab.[9] The phase III RIBBON-2 (A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab In Combination with Chemotherapy for Second-Line Treatment of HER2-Negative Metastatic Breast Cancer) trial showed a PFS improvement with the addition of bevacizumab to chemotherapy in the second-line treatment of patients with HER2-negative metastatic breast cancer.[10] However, neither of these trials demonstrated a significant improvement in overall survival.

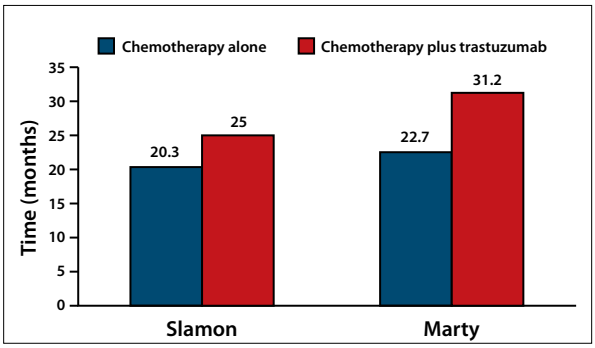

Figure 3. For patients with HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy has demonstrated a significant improvement in progression-free survival compared with chemotherapy alone in several randomized trials, despite extensive crossover. HER=human epidermal growth factor. Data from Slamon DJ et al. *N Engl J Med*. 2001;344:783-792 and Marty M et al. *J Clin Oncol*. 2005;23:4265-4274.

Single Agents Versus Combinations

An important, long-standing question in the use of chemotherapy for metastatic breast cancer has been whether to use single agents or a combination regimen. In a 2009 meta-analysis of 43 randomized trials involving 9,742 patients, combination regimens demonstrated a significant effective advantage over single-agent therapy, showing a modest improvement in OS (HR, 0.88; 95% confidence interval [CI], 0.83–0.94; *P*<.0001), and improvements in TTP (HR, 0.78; 95% CI, 0.74–0.82; *P*<.00001) and response rate (odds ratio, 1.29; 95% CI, 1.14–1.45; *P*<.0001).[11] However, combination chemotherapy is also associated with increased toxicity, including neutropenia, alopecia, nausea, and vomiting. Moreover, the survival benefits of combination chemotherapy observed in earlier trials have not been evident in more recent trials, which could be due to improvements in other aspects of management, including advances in supportive care, the evolution of chemotherapy regimens, the introduction of biologics, and improvements in hormonal therapies.

Several individual clinical trials have demonstrated an efficacy improvement with combination chemotherapy over single-agent therapy in the first-line treatment of metastatic breast cancer. In 2008, Albain and colleagues reported a significant improvement with gemcitabine plus paclitaxel versus paclitaxel alone in regard to median OS (18.6 vs 15.8 months; HR, 0.78; *P*=.0187), TTP (6.1 vs 4.0 months; *P*=.0002), and ORR (41% vs 26%; *P*=.0002).[12] In 2009, Sparano and colleagues reported a significant efficacy improvement with pegylated liposomal doxorubicin (PLD) plus docetaxel vs docetaxel alone as assessed by median TTP (9.8 vs 7.0 months; *P*=.000001) and ORR (35% vs 26%; *P*=.0085), but not OS.[13] However, patients likely received multiple lines of therapy after this initial regimen, which complicates survival analyses.

For patients with previously treated metastatic breast cancer, O'Shaughnessy and colleagues demonstrated a significant improvement in TTP and OS with capecitabine plus docetaxel versus docetaxel alone in anthracycline-pretreated patients.[14] Subsequently, 2 randomized trials demonstrated a PFS benefit with ixabepilone plus capecitabine versus capecitabine alone.[15,16] More recently, an open-label phase III trial demonstrated a significant improvement in OS with eribulin monotherapy versus treatment of physician's choice in women with heavily pretreated metastatic breast cancer.[17] The ability of eribulin to provide a significant survival difference in women who had received more than 2 prior regimens for advanced disease was encouraging. This benefit reflected not only the activity of eribulin but also its tolerability.

Summary

Both single-agent chemotherapy regimens and combinations of cytotoxic chemotherapy are reasonable options for the first-line systemic therapy of advanced breast cancer. One approach is to start with a combination regimen, then discontinue 1 agent after the anticipated benefit has been attained. Clinical practice guidelines recommend single-agent chemotherapy as the preferred choice over combinations, except in cases of rapid clinical progression, life-threatening visceral metastases, or a need for rapid symptom and/or disease control.[18,19] There is ongoing debate on whether biologics are considered a component of combination therapy.

In conclusion, treatment regimens for patients with metastatic breast cancer should be individualized. It is important to identify and prioritize therapeutic goals, and to select the least toxic option required to achieve those goals. The decision should be based on multiple factors, including disease-specific factors (HER2/neu status, ER/PR status) and patient-specific factors, including prior treatment history, performance status, age, comorbidities, and patient preference, particularly regarding toxicity. The disease is not alike in any 2 patients, and the next-generation molecular analyses under way today will likely reveal significant variability in the molecular features of different breast cancers.

Acknowledgment

Dr. Burris has no real or apparent conflicts of interest to report.

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Targeting Microtubules in Cancer Therapy

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Microtubules are complex structures that are essential to normal cell functions. Outside of cell division, microtubules are essential to cell shape maintenance, motility, intracellular trafficking-transport and secretion, and signal transduction.[1-4] Microtubules are the railroad system of the cell, as they transport proteins around the cell. For example, signal transduction proteins key to cancer biology, including p53, BRCA1, and others, are moved along microtubules. Microtubules also play a central role during mitosis, controlling the precise separation of chromosomes to daughter cells (Figure 4).

These structures are quite dynamic, changing in length in response to the changing needs of the cell.[1] The dynamicity increases dramatically during cell division to attain proper chromosome separation. Therefore, these dynamics are critical for cell viability and division. Microtubule dynamicity is precisely controlled through the functions of numerous endogenous proteins. Some of the compounds found in nature that alter microtubule dynamics likely act by mimicking the actions of these endogenous proteins.

Microtubules are heterodimers that each contain 1 subunit of α-tubulin and 1 subunit of β-tubulin. The joining of these 2 subunits occurs as a result of chaperone activity during the protein formation and folding process. Microtubule formation arises from a microtubule organizing center and begins when a single αβ tubulin heterodimer joins to other heterodimers to form a linear filament. These filaments grow in a polar

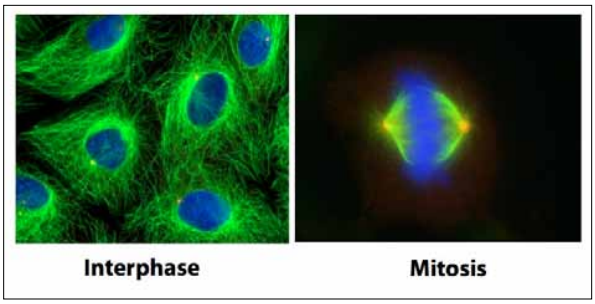

Figure 4. Microtubules play a central role during mitosis, controlling the precise separation of chromosomes to daughter cells. Microtubules are in green, DNA is in blue, and centrosomes are in red.

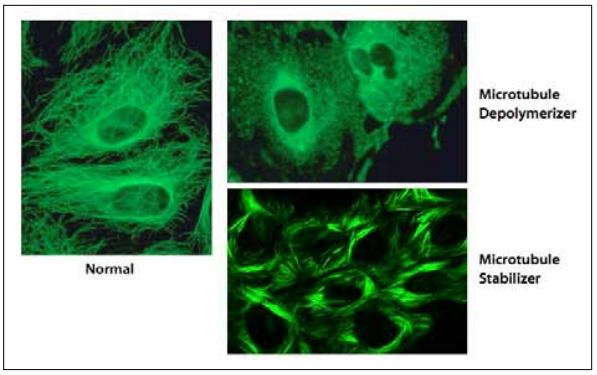

Figure 5. Cellular effects of microtubule targeting agents.

fashion, with growth occurring at the β-tubulin end (the positive end) and growing away from the α-tubulin unit (the negative end). A microtubule is formed when 13 filaments join together side-by-side to form a hollow, tubular structure.[2]

Microtubules continuously alternate between growth, maintenance of length, and shortening. Elongation of microtubules occurs at the positive end. During the pause period, the length does not change. Catastrophe is a rapid change from growth to shrinkage. Microtubule dynamics vary within a cell; some microtubules remain in pause for a long duration, whereas others may grow quickly, perhaps at the periphery where a cell is migrating or is changing in response to the needs of the environment there.

Microtubule elongation and shortening occurs in a process called dynamic instability. In a stable microtubule, the positive end contains a GTP cap. The loss of this cap causes the structure to become unstable, resulting in depolymerization of the microtubule.

Microtubules as a Target in Breast Cancer

Microtubule-targeting agents disrupt normal microtubule dynamics, although different agents act in diverse ways. The 2 major classes of microtubule-targeting agents are microtubule destabilizers, which inhibit polymerization, causing a net loss of cellular microtubules, and microtubule stabilizers, which stimulate polymerization, causing an increase in the density of cellular microtubules (Figure 5).[1-3] Examples of microtubule destabilizers include the vinca alkaloids (vinblastine, vincristine, and vinorelbine) and the halichondrins (eribulin). Examples of microtubule stabilizers include taxanes (paclitaxel, docetaxel, nab-paclitaxel) and epothilones (ixabepilone).

The effects of microtubule-targeting drugs on interphase microtubules are dramatic; however, at the lowest concentrations, these agents all inhibit mitosis and are classified as antimitotic agents, as mitosis is highly dependent on properly functioning microtubule dynamics.[1-3] Suppressed microtubule dynamics leads to abnormal DNA alignment and aberrant formation of mitotic spindles, resulting in mitotic arrest and cell death.[1]

Recent research indicates that interphase microtubules are also important targets for cancer therapy. It has been suggested that the steady presence and constant physiologic role of microtubules in cellular metabolism, and their role in intracellular trafficking, makes interphase microtubules a key target.[4] Ongoing studies are continuing to evaluate the molecular mechanisms of microtubule-targeting agents in different parts of the cell cycle.

Although microtubule-targeting agents all act to disrupt microtubule dynamics, there are significant differences between individual agents. Characteristics that differ among these agents include the sites of binding within the tubulin subunits and on the microtubule structure itself, sensitivities to tubulin isotypes, tissue and tumor susceptibilities, forms of resistance, mechanism of suppressing microtubule dynamics, and degrees of reversibility and cellular persistence.

Eribulin belongs to a new class of microtubule-disrupting drugs that are derived from halichondrin B, a natural product from the marine sponge.[5] These agents induce cell death by disrupting mitotic spindle organization, causing mitotic arrest, and inducing apoptosis.[6,7] The in vitro potency of eribulin correlates with its antimitotic activity.[6]

Mechanistic Differences Between Microtubule-Targeting Agents

Different microtubule-targeting agents bind to different sites on microtubules. Vinblastine binds to the vinca sites both at the ends of microtubules and along the protofilaments. Conversely, paclitaxel does not bind at the end, but binds in the middle of the microtubule, along the inner surface of the hollow structure. It reaches the inner surface by diffusing through the spaces present between the α and β heterodimers.

Some forms of β-tubulin may create smaller pores that are less amenable to paclitaxel diffusion, which may result in paclitaxel resistance.

Eribulin binds microtubules differently than either vinblastine or paclitaxel. Like vinblastine, eribulin binds on the end of the microtubule, although it does not bind along the protofilament.[8] Instead, in binds to a single site on tubulin. Eribulin binds tubulin with high affinity; the maximum stoichiometry is 14.7 eribulin molecules per microtubule, indicating that approximately 1 eribulin molecule binds to each of the 13 protofilaments across the top of a microtubule. Few molecules of eribulin are needed to inhibit microtubule growth. At the concentration that inhibits microtubule growth by 50%, 1 molecule of eribulin is bound per 2 microtubules. This suggests that a single molecule of eribulin can inhibit microtubule dynamics.

Studies of molecular dynamics have shown that eribulin makes 5 different contacts with tubulin at 5 hydrogen binding sites on the β-tubulin molecule.[5] This occurs in close proximity to the exchangeable GTP site, suggesting that binding of eribulin to the microtubule prevents binding of the GTP cap. Eribulin binds near the vinca site, so that the binding sites are nearby but not overlapping.

Other studies on the effects of eribulin have shown that eribulin inhibits microtubule growth but has no effect on the microtubule shortening rate.[6] This may relate to the proximity of the eribulin binding site to the GTP binding site; although eribulin prevents growth, it may act to prevent depolymerization similar to GTP. Laboratory studies have also shown that eribulin differs from other microtubule-targeted agents in its irreversibility. Whereas the mitotic blockade induced by vinblastine is reversible, eribulin induces an irreversible mitotic blockade, maintaining complete mitotic block 10 hours after drug washout.[9] Eribulin also differs from other microtubule-targeting agents in its propensity to induce neuropathy, a toxicity characteristic of these agents that disrupt axonal transport. Recently, Wozniak and colleagues compared the neuropathy-inducing propensity of 3 different microtubule-targeting agents in an animal model.[10] The researchers reported that eribulin produced no significant negative effects on nerve conduction, whereas ixabepilone and paclitaxel produced significant deficits in nerve conduction. Moreover, eribulin caused milder, less frequent effects on nerve morphology than the other agents. These findings suggest that eribulin induces less neuropathy in animals than other microtubule-targeting agents at equivalent dose levels.

In summary, microtubule-targeting agents are highly effective drugs used in the treatment of breast cancer. These agents all act by suppressing microtubule dynamics, leading to mitotic arrest and apoptosis.[6] However, there are mechanistic differences among these microtubule-targeting drugs. Eribulin is a new microtubule destabilizer with a unique mechanism of inhibiting microtubule dynamics.[6] It binds with high affinity to the positive ends of microtubules in a novel way to inhibit microtubule growth. This disruption of microtubule dynamics interferes with normal microtubule functions and causes mitotic arrest, ultimately leading to apoptosis.

Acknowledgment

Dr. Mooberry is a member of the Eisai Eribulin Preclinical Advisory Board. She has received grants/research support from Phoenix Biotechnology.

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Emerging Strategies in Metastatic Breast Cancer Treatment

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The prognosis for patients with breast cancer has improved in recent decades, with progress in early detection, advances in adjuvant chemotherapy, and the development of new therapies that extend survival in metastatic disease. Today, most women with breast cancer are diagnosed at an early stage and will not die from the disease. The introduction of newer therapies in the past 2 decades have led to improvements in survival and in quality of life, allowing patients to continue leading active lives free of significant debility and frequent hospitalizations.

In metastatic disease, extending survival is the primary goal, both in previously untreated patients and in patients who have already received 1 or more lines of therapy. Multiple trials have demonstrated an improvement in survival with certain therapies over others in metastatic breast cancer, although many have not been adequately powered to detect differences in survival. There is heterogeneity in the outcomes of these studies that may be due only to statistical chance. Another confounding factor is that patients often receive additional therapies after the study drug, which complicates survival analyses. With all of these factors, it can be difficult to ascertain the degree of benefit of chemotherapy for improving survival.

Microtubule-Targeting Agents in Breast Cancer

A variety of microtubule-targeting agents are available: the taxanes (docetaxel, paclitaxel, nab-paclitaxel), the vinca alkaloids (vinorelbine, vinflunine), the epothilones (ixabepilone, KOS 862, ZK-EPO, patupilone), and the halichondrin B analogues (eribulin). These agents differ in their sites of action and in their associated mechanisms of resistance. The molecular mechanisms and characteristics of microtubule-targeting agents remain an area of active research, and continued investigation into this class of drugs will likely bring additional novel microtubule-targeting agents in the future.

Novel Microtubule-Targeting Agents: Ixabepilone

Ixabepilone is a semi-synthetic analogue of epothilone B, a natural macrolide produced by the myxobacterium *Sorangium cellulosum.* Because unicellular organisms lack an immune system, they must manufacture their own compounds to fight foreign invaders. Many of these compounds that serve to protect against bacteria and fungi also inhibit rapidly growing cells. This finding has led to the development of multiple antineoplastic drugs based on natural products that are subsequently modified to optimize their pharmacokinetic and pharmacodynamic properties.

Ixabepilone binds specifically and distinctly to β-tubulin with 2- to 10-fold greater activity than paclitaxel. In preclinical studies, ixabepilone has demonstrated activity in paclitaxel-resistant tumor cells and has demonstrated synergy with capecitabine, bevacizumab, and trastuzumab.[1] In phase II studies, single-agent ixabepilone demonstrated activity in patients with previously treated metastatic breast cancer, yielding an ORR of 11.5% and a PFS of 3.1 months in heavily pretreated patients (Table 3).[2-5]

The results of these phase II studies led to the design of 2 randomized, phase III trials evaluating the efficacy and safety of ixabepilone added to capecitabine in patients with metastatic breast cancer previously treated with anthracyclines and taxanes. In both trials (CA163046 and CA163048), patients were randomly assigned to receive ixabepilone administered at 40 mg/m^2 on Day 1 of a 21-day cycle plus capecitabine 1,000 mg/m^2 twice daily on Days 1–14, or capecitabine 1,250 mg/m^2 twice daily on Days 1–14 of a 21-day cycle.[6,7] The primary endpoint was TTP in the 046 trial and OS in the 048 trial.

Both phase III trials demonstrated a significant improvement in PFS with ixabepilone plus capecitabine versus capecitabine alone; the median PFS was 5.3 months versus 3.8 months (P=.001) in one trial and 6.2 vs 4.4 months in the other trial (P=.0005).[6,7] Ixabepilone was also associated with an increase in ORR. However, neither trial demonstrated a significant improvement in OS with ixabepilone.

In the 048 trial, a secondary analysis adjusted for prognostic factors yielded a significant OS improvement with the addition of ixabepilone to capecitabine (HR, 0.85; 95% CI, 0.75–0.98; P=.023).[7] An exploratory analysis also suggested a survival benefit with ixabepilone among patients with a Karnofsky performance status (KPS) of 70–80. An exploratory analysis of the 046 trial also showed a significant OS benefit with ixabepilone only in patients with a KPS of

Table 3. Ixabepilone in Metastatic Breast Cancer: Phase II Data

Metastatic Breast Cancer Patient Population	N	Dose	Partial Response (%)	Stable Disease (%)
No previous taxane in adjuvant or metastatic setting[1]	23	6 mg/m^2 days 1–5, q3w	57	26
Anthracycline-, taxane-, and capecitabine-resistant[2]*	126	40 mg/m^2 q3w	11.5	50
Previous treatment with adjuvant anthracycline[3]	65	40 mg/m^2 q3w	42	35
Taxane-resistant[4]	49	40 mg/m^2 q3w	12	41

*Responses were independently evaluated. Only H1 and H2 blockers were used as premedication in phase 2.

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70–80.[8] In a preplanned pooled exploratory analysis of the 2 trials, ixabepilone was not associated with a significant OS improvement in patients with a KPS of 90–100 (*P*=.81), but it was associated with a significant OS difference in patients with a KPS of 70–80 (*P*=.0015).[9]

Adverse effects associated with ixabepilone are similar to those observed with other microtubule-targeting agents, including cytopenias and peripheral neuropathy, with approximately 23% of patients developing grade 3/4 neuropathy with ixabepilone plus capecitabine.[7,10] Moreover, toxicities were serious enough to warrant an amendment to the protocol to ensure that patients had adequate liver function. This issue is not unique to ixabepilone; microtubule-targeting agents, particularly epothilones, require careful assessment of liver function and caution regarding the degree of hepatic insufficiency.

In summary, ixabepilone has demonstrated single-agent activity in patients with previously treated metastatic breast cancer, although no phase III data have been published evaluating single-agent ixabepilone. The addition of ixabepilone to capecitabine is associated with an improvement in response rate and an extension of PFS, but not an improvement in OS. Ixabepilone is associated with peripheral neuropathy and cytopenias, which appear to be more severe when ixabepilone is combined with capecitabine.

Novel Microtubule-Targeting Agents: Eribulin

Eribulin is a synthetic analog of halichondrin B that potently inhibits microtubule growth.[10] Several phase II trials demonstrated the efficacy of eribulin in patients with heavily pretreated metastatic breast cancer. In patients who had received a median of 4 prior regimens, single-agent eribulin was associated with an ORR of 9–14% and a median response duration of 4–6 months.[11] The clinical benefit rate of eribulin was 17–20%, which is also notable, given that stabilization of disease benefits patients in regard to both quality of life and symptom improvement.

The safety and efficacy of single-agent eribulin were further assessed in the global, randomized, open-label,

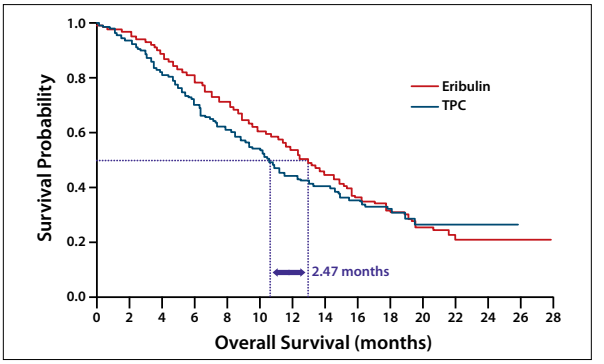

Figure 6. Overall survival in the EMBRACE trial in the intent-treat population. EMBRACE=Eribulin Monotherapy Versus Treatment of Physician's Choice in Patients With Metastatic Breast Cancer. *HR Cox model including geographic region, HER2/neu status, and prior capecitabine therapy as stratification factors. †*P* value from stratified log-rank test (predefined primary analysis); HR, hazard ratio; CI, confidence interval; TPC=treatment of physician's choice. Data from Cortes J et al. *J Clin Oncol.* 2010;28:3922-3928.

phase III EMBRACE (Eribulin Monotherapy Versus Treatment of Physician's Choice in Patients With Metastatic Breast Cancer) trial.[12] The trial enrolled 762 women with locally recurrent or metastatic breast cancer who had previously received between 2 and 5 chemotherapy regimens, with at least 2 regimens specifically for advanced disease, including an anthracycline and a taxane. Patients had to have had disease progression within 6 months of the last chemotherapy regimen, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Neuropathy of grade 3 or higher at baseline was an exclusion criterion.

Patients were randomly assigned 2:1 to receive eribulin, administered at 1.4 mg/m^2 as a 2-5–minute infusion on Days 1 and 8 of a 21-day cycle (508 patients), or treatment of physician's choice (254 patients). Stratification factors included geographic region, prior capecitabine, and HER2/neu status. The control treatment (physician's choice) was designed based on a lack of available therapies

for this patient population. In the control arm, 96% of patients received chemotherapy, and no patient received best supportive care or biologic therapies only.

The investigators reported a significant improvement in median OS with eribulin versus treatment of physician's choice (13.1 vs 10.7 months; HR, 0.81; 95% CI, 0.66–0.99; *P*=.041; Figure 6).[13] A recent update of the survival outcomes showed similar findings.[14]

In regard to secondary endpoints, eribulin was associated with a nonsignificant improvement in median PFS over treatment of physician's choice in an independent review (3.7 vs 2.2 months; HR, 0.87; *P*=.14) and a significant improvement in median PFS in the investigators' review (3.6 vs 2.2 months; HR, 0.76; *P*=.002).

The most frequent grade 3/4 toxicities associated with eribulin were neutropenia (45%; 4.2% febrile neutropenia), leukopenia (14%), fatigue (8.8%), and peripheral neuropathy (8.2%). Hand-foot syndrome was more common in the control arm. The toxicity rates were low, considering the lines of therapy that the patients had already received. Additional analyses are evaluating the reversibility of eribulin-associated peripheral neuropathy and its incidence after a longer-term follow-up.

Subset analyses did not identify a patient population that appeared to derive a greater or lesser benefit from eribulin. Although the small group of patients with HER2-positive disease also appeared to benefit from eribulin, it is now recognized that HER2-positive disease is generally managed best with ongoing HER2 blockade. An exploratory analysis suggested a weaker benefit with eribulin in more heavily pretreated patients, but this was not a preplanned analysis.

An important ongoing trial is Study 301, which is comparing eribulin versus capecitabine in patients with locally advanced or metastatic breast cancer who have received 2 or fewer chemotherapy regimens for advanced disease, and who have received an anthracycline and a taxane in the adjuvant or neoadjuvant setting or for locally advanced or metastatic disease.[15] This study will compare OS and PFS as will as quality of life, ORR, duration of response, pain intensity, analgesic consumption, toxicity, and pharmacokinetic/pharmacodynamic relationships for eribulin. This study will help elucidate whether one therapy is better used earlier or later in the course of disease, based on both efficacy and toxicity factors.

In summary, eribulin is clearly active in patients with heavily pretreated breast cancer, demonstrating an improvement in median OS of more than 2 months compared with treatment of physician's choice. Note that this is the median, and some patients will gain a greater benefit. Eribulin is associated with an ORR of approximately 10–12% and a trend toward a longer PFS. Severe peripheral neuropathy is not common, occurring in approximately 8% of patients. An important ongoing phase III trial is comparing eribulin versus capecitabine in previously treated patients.

Future Directions in Microtubule-Targeting Therapy

The future of metastatic breast cancer treatment will likely include a growing number of targeted therapies; novel targeted therapies are currently being evaluated, and additional candidates for therapeutic targets continue to be identified. However, cytotoxic chemotherapy remains the backbone of treatment for metastatic breast cancer. A critical issue in metastatic breast cancer is defining the optimal use of the currently available therapies, including in the adjuvant setting. Another important area is the identification and validation of biomarkers—perhaps gene profiles, proteins, or protein isoforms—that predict responsiveness to different therapies or the likelihood of developing different toxicities.

Acknowledgment

Dr. Tripathy has no real or apparent conflicts of interest to report.

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New Treatment Paradigms for Optimizing Survival in Advanced and Metastatic Breast Cancer

CME Post-Test: *Circle the correct answer for each question below.*

1. The majority of breast cancer deaths occur in the setting of:

   a. Initial human epidermal growth factor receptor 2 (HER2)-positive disease
   b. Initial hormone receptor–positive disease
   c. Initial hormone receptor–negative disease
   d. Initial triple-negative disease

2. What type of treatment is the mainstay of therapy for triple-negative breast cancer?

   a. Anthracyclines
   b. Chemotherapy
   c. Microtubules
   d. Targeted agents

3. In a meta-analysis of 8 randomized trials involving 817 breast cancer patients with estrogen receptor (ER)-positive disease, which treatment significantly increased overall survival?

   a. Chemotherapy
   b. Endocrine therapy
   c. Targeted therapy
   d. There was no significant difference in overall survival

4. For patients with HER2-positive metastatic breast cancer, the addition of _____ to chemotherapy has demonstrated a significant improvement in response rate and progression-free survival compared with chemotherapy alone in several randomized trials.

   a. Bevacizumab
   b. Capecitabine
   c. Lapatinib
   d. Trastuzumab

5. The phase III RIBBON-2 trial showed an improvement in progression-free survival with the addition of _____ to chemotherapy in the second-line treatment of patients with HER2-negative metastatic breast cancer.

   a. Bevacizumab
   b. Capecitabine
   c. Lapatinib
   d. Trastuzumab

6. Microtubules are heterodimers that each contain:

   a. 1 subunit of α-tubulin and 1 subunit of β-tubulin
   b. 1 subunit of α-tubulin and 2 subunits of β-tubulin
   c. 2 subunits of α-tubulin and 1 subunit of β-tubulin
   d. 3 subunits of α-tubulin and 1 subunit of β-tubulin

7. Which microtubule-targeting agent binds in the middle of the microtubule, along the inner surface of the hollow structure?

   a. Eribulin
   b. Paclitaxel
   c. Vinblastine

8. Which agent is a microtubule destabilizer?

   a. Docetaxel
   b. Nab-paclitaxel
   c. Ixabepilone
   d. Vinorelbine

9. In phase II studies, single-agent ixabepilone demonstrated activity in patients with previously treated metastatic breast cancer, yielding an overall response rate of:

   a. 7.8%
   b. 9.7%
   c. 11.5%
   d. 13.1%

10. In the EMBRACE trial, eribulin was associated with a median overall survival of:

    a. 7.8 months
    b. 9.7 months
    c. 11.5 months
    d. 13.1 months

Evaluation Form: New Treatment Paradigms for Optimizing Survival in Advanced and Metastatic Breast Cancer

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Incorporate new clinical trial data in the management of patients with advanced or metastatic breast cancer	1 2 3 4 5
2. Develop individualized management strategies for patients with advanced or metastatic breast cancer	1 2 3 4 5
3. Explain the mechanisms of action of novel agents in breast cancer	1 2 3 4 5
4. Identify future research directions in the management of patients with advanced or metastatic breast cancer	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:

❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 8851**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit (*required fields)

Name*_____ Degree*_____

Organization_____ Specialty*_____

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Telephone_____ Fax_____ Email*_____

Signature*_____ Date*_____

For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.