MANAGING PATIENTS WITH HEAVILY PRETREATED METASTATIC BREAST CANCER: BALANCING EFFICACY AND SAFETY

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Christopher J. Twelves, MD, MB ChB, FRCP, RCPS, and Monica N. Fornier, MD

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“No fixed algorithm exists to guide chemotherapy treatment selection in patients with heavily-pretreated metastatic breast cancer...”
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“[Study] data will help guide treatment selection, which is based on many factors, including prior therapies, toxicities, performance status, and patient preference.”
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Jointly sponsored by:

In affiliation with:

Global Academy for Medical Education
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This educational activity is supported by an educational grant from Eisai Inc.
About This CME Activity

Managing Patients With Heavily Pretreated Metastatic Breast Cancer: Balancing Efficacy and Safety

Educational Need
Breast cancer is the most commonly diagnosed malignancy in women in the United States, and up to 30% of women diagnosed with early breast cancer will eventually develop advanced disease. Women with metastatic breast cancer (MBC) are increasingly likely to have been exposed to an anthracycline and a taxane in different treatment scenarios, making subsequent use of these options less likely to be effective. Thus, there is a need for effective, alternative cytotoxic therapies in patients with prior exposure to anthracycline- and taxane-based therapy. This series of articles examines chemotherapy selection for women with heavily pretreated MBC through a review of the evidence for the use of FDA-approved and off-label cytotoxic agents in this setting.

Learning Objectives
After completing this educational activity, participants should be able to:
• Discuss the approaches to the treatment of heavily pretreated MBC, including sequential versus combination chemotherapy
• Describe the efficacy and toxicity of newer chemotherapy agents and combinations for the treatment of patients with heavily pretreated MBC
• Devise evidence-based treatment plans for patients with advanced breast cancer that has progressed following treatment with taxanes and anthracyclines

Target Audience
This activity has been developed for medical oncologists.

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Acknowledgment
This educational activity is supported by an educational grant from Eisai Inc.

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Date of original release: May 1, 2012
Date of expiration: May 1, 2013
Course code: CEE77511
Estimated time to complete: 2 hours

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COMMUNITY ONCOLOGY (ISSN 1548-5315) is published monthly by International Medical News Group, LLC, 60B Columbia Road, Morristown, NJ 07960.

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Breast cancer is the most commonly diagnosed malignancy in women in the United States. In 2011, an estimated 230,480 new cases of breast cancer were diagnosed in women—approximately 30% of all new cases of cancer among women—and 39,520 died from breast cancer, second only to lung cancer.\(^1\) Up to 30% of women diagnosed with early breast cancer will eventually develop advanced disease.\(^2\)

Retrospective evidence suggests that survival rates for women with metastatic breast cancer have been improving during the past several decades. For example, in an analysis of 834 patients treated for recurrent breast cancer at M.D. Anderson and stratified from time of disease recurrence, the estimated risk of death was reduced by approximately 1%/y from 1974-2000.\(^3\) Improvement in overall survival (OS) of women with a diagnosis of metastatic breast cancer was observed in a large population-based study that compared patients diagnosed in early, and also middle or latter years of the 1990s; survival improved 30% for those diagnosed late in the decade compared with those diagnosed in the early or middle parts of the decade. This improvement was associated with use of newer, more effective systemic therapy for metastatic breast cancer.\(^4\)

Mauri et al reviewed trials comparing different chemotherapeutic regimens and/or targeted therapy in advanced breast cancer from 1973-2007 and found that stepwise improvements in treatment efficacy cumulatively have achieved major improvements in survival. Use of anthracycline regimens resulted in relative risk reductions in mortality of 22%-33% compared with older, single-agent nonanthracyclines. Further reductions in risk were achieved by use of newer regimens, such as single-agent taxanes or combinations of an anthracycline and a taxane.\(^5\)

The majority of women who develop metastatic disease do so following previous treatment of early breast cancer. Those women with hormone receptor-positive metastatic breast cancer are likely to initially receive endocrine therapy; cytotoxic therapy is, however, recommended for disease that is refractory or has become resistant to endocrine therapy, and for patients with rapidly progressive visceral disease. Chemotherapy also is recommended for most women diagnosed with hormone receptor-negative metastatic breast cancer.\(^6\)

Patients with metastatic breast cancer in whom chemotherapy is being considered are more and more likely to have been exposed to an anthracycline and/or a taxane in different treatment scenarios. Anthracyclines, and increasingly taxanes, are widely used in the adjuvant setting. Alternatively, these agents may have been administered as a first- or second-line treatment for metastatic disease alone or occasionally in combination. Therefore, selection of chemotherapy for women with metastatic disease is influenced by treatment history for which significant heterogeneity exists.\(^7\) The increasing population of patients with anthracycline/taxane-resistant metastatic disease highlights the need to identify effective cytotoxic treatment in this setting.
Chemotherapy drug resistance is believed to cause treatment failures in >90% of patients with metastatic cancer, micrometastatic disease resistance also likely limits the efficacy of chemotherapy in the adjuvant setting. Extensive use of the taxanes and anthracyclines as adjuvant therapy potentially contributes to resistance in those patients who subsequently relapse. Even where there is no history of prior exposure, de novo resistance to chemotherapy may be present before treatment. Mechanisms of resistance to anticancer drugs include reduced apoptosis, altered cell cycle checkpoints, increased metabolism of drugs, increased or altered targets, increased repair of damage, and intracellular drug compartmentalization. Resistance also can occur due to variations in microtubular structure, affecting interaction of the drug with its target. Tumors may overexpress a particular isoform of tubulin; acquired and intrinsic mutations can affect tubulin binding sites, and altered expression of microtubule-associated proteins can occur.9,10

Despite population-based findings of improved outcomes, which are partially attributable to earlier detection and use of more effective systemic therapies, median survival in patients with metastatic breast cancer is 18–24 months,11 and the disease remains incurable.11 The primary goals of treatment focus on prolonging survival, alleviation or prevention of tumor-related symptoms, and maximizing quality of life.

OS is the recognized “gold standard” endpoint in evaluating clinical benefits of cancer therapies. However, studies that use OS for evaluation of clinical benefit require large numbers of patients, longer follow-up periods, and may be confounded by subsequent therapies.12 A review of phase III randomized trials in the setting of advanced breast cancer from January 1998–December 2007 found OS was used infrequently as the primary endpoint.13 Moreover, in those trials with OS as the primary endpoint, none had a positive outcome with respect to OS. Improved OS as a secondary endpoint was achieved in 15 trials, a finding that was observed more frequently in larger trials and those conducted in second- or third-line settings.

Progression-free survival (PFS) frequently is used as a surrogate for OS; however, the relationship between the 2 endpoints is disputed. Interestingly, in a review of data from recent phase III trials in advanced breast cancer, PFS accounted for approximately one-third of OS; nearly two-thirds of patient survival was attributed to duration of survival after the disease had progressed.13 When postprogression survival is longer than PFS, many more patients are required to show statistically superior OS than improved PFS.14

Lack of correlation between PFS and OS was noted by Cortazar et al, who reviewed US Food and Drug Administration (FDA) submission data for 14 randomized clinical trials in 9,819 patients with metastatic breast cancer for which first-line or second- and third-line indications were being sought. PFS was the primary or secondary endpoint. Using a linear regression model, each trial was weighted by sample size and the relationship between PFS and OS investigated. No association between PFS and OS was observed. The variation in PFS explained <10% of the variation in OS, suggesting the relationship between PFS and OS is weak, especially for second- and third-line therapies for metastatic breast cancer.15 This may be explained in part by post-trial lines of therapy, especially where a substantial proportion of patients in the control arm are able to receive the “experimental” therapy at progression.

Case Study: Is this a common clinical scenario in your practice?

A 62-year-old woman diagnosed 7 years ago with a 24 mm, grade II, 1 node positive (stage IIb), estrogen receptor (ER)/progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer was treated with breast-conserving surgery, followed by whole breast irradiation and adjuvant chemotherapy with doxorubicin and cyclophosphamide (AC) and 5 years of tamoxifen. One year ago, she presented with radiologic evidence of bone metastases. Following 2 lines of single-agent endocrine therapy, and development of visceral disease (liver), the patient received single-agent paclitaxel as first-line chemotherapy for advanced disease followed by single-agent capecitabine following disease progression. Her Eastern Cooperative Oncology Group (ECOG) performance status is 1 and her most recent CT scan indicates further progression of disease.

Commentary: When patients have metastatic disease progression following 2 lines of endocrine therapy, it may be reasonable to consider additional lines of endocrine therapy, especially where the patient appeared to benefit from the most recent hormonal agent. Development of visceral disease, however, as illustrated by the liver metastases observed in this patient, often provides a tipping point from endocrine therapy to chemotherapy. Three chemotherapeutic agents currently have US Food and Drug Administration (FDA) approval for patients with heavily pretreated breast cancer, including prior exposure to an anthracycline and a taxane: capecitabine, ixabepilone (as a single agent or in combination with capecitabine), and eribulin. Lower level evidence provides some support for use of a variety of other cytotoxic agents in this setting. Decision making regarding cytotoxic therapy selection should be individualized according to a number of patient-, disease-, and treatment-related factors. The aim of this supplement is to review existing evidence to provide guidance on developing treatment plans for patients with advanced breast cancer that has progressed following treatment with taxanes and anthracyclines.
No established standard of care

No standard of care exists in selecting cytotoxic therapy for patients with heavily pretreated metastatic breast cancer. This conclusion is supported by results from a recent retrospective cohort study evaluating treatment patterns in patients with advanced breast cancer previously exposed to an anthracycline, a taxane, and capecitabine. Although 61.8% of these patients received ≥ 1 additional lines of chemotherapy, a variety of agents were used in this setting. In this context, it is also important to note that clinical outcome measures, such as response rate and time to disease progression, typically decline as the line of cytotoxic therapy increases. For example, typical outcomes with single-agent first-line chemotherapy for advanced breast cancer are response rates of 25%-45%, with time to progression of 5-8 months. For second- and third-line therapy, response rates decrease from 15%-30% to 0%-20%, respectively, and time to progression declines from 2-5 months to 1-4 months. Few data are available for patients treated with ≥ 4 lines of therapy.

Single-agent chemotherapy options for the treatment of metastatic breast cancer are included in the National Comprehensive Cancer Network (NCCN) guidelines as “preferred” or “other” agents. “Preferred” single agents are summarized by class and include anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel), antimetabolites (capecitabine and gemcitabine), and other microtubule inhibitors (vinorelbine and eribulin). Other single agents recommended are cyclophosphamide, mitoxantrone, cisplatin, oral etoposide, vinblastine, fluorouracil (continuous infusion), and ixabepilone. However, the guidelines do not include recommendations on the order in which these agents should be administered across multiple lines of cytotoxic therapy.

NCCN guidelines also include lists of chemotherapy combination regimens: cyclophosphamide/doxorubicin/fluorouracil; fluorouracil/epirubicin/cyclophosphamide; doxorubicin/cyclophosphamide; epirubicin/cyclophosphamide; doxorubicin/docetaxel or doxorubicin/paclitaxel; cyclophosphamide/methotrexate/fluorouracil; docetaxel/capecitabine; gemcitabine/paclitaxel; and ixabepilone plus capecitabine. Most trials comparing combination chemotherapy to single-agent cytotoxic therapy in advanced breast cancer have been conducted in the first-line setting and generally have demonstrated increased rates of objective response and longer time to progression with greater toxicity but no improvement in OS in the combination arm. The benefits of sequential single-agent therapy may be comparable to combination therapy with fewer side effects.

Treatment selection factors

Considerations in optimal timing of initiation of cytotoxic therapy and continuation are individualized due to biologic variability of patients and their disease, including likelihood of resistance to particular cytotoxic agents. Risk assessment and treatment choices are guided by a number of factors, which can be classified as disease-related or patient-related. Disease-related factors include disease-free interval since primary diagnosis and completion of adjuvant therapy, previous therapies and response to them, hormone receptor status and human epidermal growth factor receptor 2 (HER2) status of the primary tumor and/or metastatic lesion, tumor burden (location and extent of metastases), and need for rapid disease and/or symptom control. Patient-related factors include patient’s preferences, age, menopausal

FIGURE 1 Symptoms and side effects, social functioning, physical functional status, and psychological status are the 4 primary domains of quality of life that should be reviewed for potential effect of treatment selection. Reprinted from Murphy CG, et al. Copyright 2009, with permission from Elsevier.

FIGURE 2 FDA drugs approved in second- and third-line metastatic breast cancer. Cytotoxic agents are in bold.
Review

status, comorbidities and performance status, anticipated side effects of treatment, socioeconomic and psychological factors, and availability and access to treatment. The quality of life issues that may have an impact on treatment selection are illustrated in Figure 1.7

In 2009, the Central European Cooperative Oncology Group (CECOG) published its third consensus on medical treatment of metastatic breast cancer.22 The consensus statement acknowledges that few effective treatment options are available to women with metastatic breast cancer who have failed to respond or relapsed after pre-treatment with anthracyclines and taxanes. Based on studies of agents that have shown activity, consensus treatment recommendations state, “... capcitabine, gemcitabine, liposomal doxorubicin, ixabepilone or vinorelbine, all administered as either monotherapy or in combination with other cytotoxic agents may be beneficial after failure of anthracyclines and taxanes.” Consecutive cytotoxic chemotherapy is worth considering in women who have responded to previous regimens, but no definitive guidance can be given regarding the optimal agents or the order they should be administered.”22

Newer approaches
Newer approaches for treatment of patients with advanced breast cancer include new drug classes and formulations to overcome drug resistance. Newer formulations of existing classes of agents are represented by nab-paclitaxel and pegylated liposomal doxorubicin, whereas the epothilones and halichondrins represent new drug classes. Although numerous chemotherapeutic options are available for women with heavily pretreated, advanced breast cancer, only a handful of cytotoxic agents have been FDA-approved as second- or third-line treatment options for patients with metastatic breast cancer (Figure 2). The next 2 articles address criteria to guide selection of cytotoxic agents for patients with HER2-negative metastatic breast cancer previously exposed to an anthracycline and a taxane; HER2-targeted therapy is outside the purview of this review. Most of the studies cited in these articles involve single-agent cytotoxic therapy, although several combination chemotherapy regimens will be discussed. No fixed algorithm exists to guide treatment selection, a process based on many factors, including prior therapies, cytotoxic toxicities, patient performance status, and patient choice and preference.

Acknowledgments
Writing assistance was provided by Debra Hughes. The authors retained full editorial control of the manuscript.

References
Approved chemotherapy agents for patients with metastatic breast cancer previously exposed to taxanes and anthracyclines

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Patients with metastatic breast cancer whose disease progresses after treatment with anthracycline and taxane therapy have limited approved treatment options. Currently, 3 cytotoxic agents are US Food and Drug Administration (FDA)-approved for the treatment of patients with heavily pretreated metastatic breast cancer: capecitabine, ixabepilone (as monotherapy in patients resistant to capecitabine, and in combination with capecitabine), and eribulin mesylate. This article reviews the efficacy and toxicity data for each of these agents and regimens.

Capecitabine
The antimetabolite capecitabine is a fluoropyrimidine carbamate, an orally administered pro-drug of 5-fluorouracil (5-FU) designed to mimic continuous infusion of 5-FU and deliver drug preferentially to tumor tissue. Capecitabine inhibits thymidylate synthase and interferes with DNA and RNA synthesis.¹ Capecitabine monotherapy often is considered a treatment of choice in patients with metastatic breast cancer with prior exposure to an anthracycline and a taxane due to its activity as well as its good overall safety profile and oral route of administration.² Additional support for the use of this agent is the negligible risk of capecitabine-associated alopecia,³ an adverse effect of chemotherapy that has a detrimental impact on quality of life for many patients with breast cancer.⁴

Efficacy data for 3 phase III trials and 7 phase II trials of capecitabine in patients with metastatic breast cancer previously treated with anthracyclines and taxanes are summarized in Table 1.⁵-¹⁴ The capecitabine dose was 1,250 mg/m² or 1,255 mg/m² twice daily for 14 days every 3 weeks in all these studies, which have shown overall response rates (complete response [CR] + partial response [PR]) ranging from 9%-32% and disease control rates of 30%-78% in this heavily pretreated population. Range in median time to progression (TTP) was 3.1-4.9 months and median progression-free survival (PFS) was 2.8-5.9 months for those studies reporting these endpoints. Median overall survival (OS) ranged from 9.3-18.1 months.

A systematic review of response and survival data for patients with metastatic breast cancer treated with capecitabine as second-line agent or later (after treatment with anthracyclines and/or taxanes) from the studies listed in Table 1 reported weighted mean values for disease control rate of 57%; for median TTP, 3.9 months; and for median OS, 13.5 months.³

Capecitabine generally is well tolerated. The most frequently reported grade 3/4 nonhematologic adverse events were hand-foot syndrome (weighted mean of 16%), and diarrhea (weighted mean of 10%).³ Other reported adverse effects included stomatitis, nausea, and vomiting. Grade 3/4 hematologic adverse effects were uncommon.
reported in one review to occur in 4% of patients. Cape-
citabine is less well tolerated in US patients, and many
clinicians routinely use capecitabine at a dose of 1,000
mg/m² twice daily. According to guidelines from the
National Comprehensive Cancer Network (NCCN),
capecitabine is listed as a “preferred” single agent for the
treatment of recurrent or metastatic breast cancer.
The capecitabine dosing schedule recommended by NCCN
guidelines in the setting of metastatic breast cancer is
1,000-1,250 mg/m² twice daily, days 1-14, cycled every 21
days. A novel dosing schedule that has been pro-
posed as a strategy to increase the tolerability of capecit-
abine involves use of a 7-day on/7-day off schedule.

Ixabepilone
Ixabepilone is an epothilone analog that binds to a
different site on the microtubule than the taxanes. By
binding directly to the beta-tubulin structure, the mi-
crotubule is stabilized, which promotes polymerization
and increases microtubule polymer mass in cells. Re-
sults of clinical trials of 1,973 patients with metastatic
breast cancer and prior exposure to anthracyclines and
taxanes, 527 of whom had triple-negative disease, found that ixabepilone, whether as monotherapy or in
combination with capecitabine, showed promising ef-
ficacy and good tolerability.

Single-agent ixabepilone
The efficacy of ixabepilone as monotherapy in patients with
heavily pretreated metastatic breast cancer has been
explored in several phase II studies (Table 2) using the
currently approved FDA dose of 40 mg/m² infused
intravenously over 3 hours every 3 weeks. Activity was
demonstrated, with response rates higher in less heavily
pretreated patients. In routine practice, other doses and
schedules have been used.

Ixabepilone plus capecitabine
Thomas et al conducted a phase III randomized trial of
ixabepilone plus capecitabine vs capecitabine alone, the
results of which led to FDA approval of ixabepilone
plus capecitabine for patients with metastatic breast

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### Table 1: Phase II/III studies of capecitabine in anthracycline-/taxane-pretreated metastatic breast cancer

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CR = complete response; NR = not reported; PFS = progression-free survival; PR = partial response; SD = stable disease; TTP = time to progression.

* Overall response rate by independent review = 9.0%; overall response rate by investigator review = 19%.

### Table 2: Phase II studies of single-agent ixabepilone in pretreated metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ORR (all PR) (%)</th>
<th>SD (%)</th>
<th>Disease control rate (%)</th>
<th>Median response duration (mo)</th>
<th>Median TTP (mo)</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez et al 2007</td>
<td>113</td>
<td>11.5</td>
<td>50</td>
<td>61.5</td>
<td>5.7</td>
<td>3.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Roche et al 2007</td>
<td>65</td>
<td>41.5</td>
<td>35</td>
<td>76.5</td>
<td>8.2</td>
<td>4.8</td>
<td>22.0</td>
</tr>
<tr>
<td>Thomas et al 2007</td>
<td>49</td>
<td>12.0</td>
<td>41</td>
<td>53.0</td>
<td>10.4</td>
<td>2.2</td>
<td>7.9</td>
</tr>
</tbody>
</table>

ORR = objective response rate; PR = partial response; SD = stable disease; TTP = time to progression.

* Prior exposure to anthracycline, taxane, and capecitabine; † Prior exposure to adjuvant anthracycline; ‡ Prior exposure to a taxane in the metastatic setting; § Independent radiologic assessment.
cancer resistant to anthracyclines and taxanes. In this pivotal trial, 752 patients were randomized to ixabepilone 40 mg/m² intravenously over 3 hours, day 1 plus oral capecitabine 2,000 mg/m²/day, days 1-14, every 3 weeks, or to single-agent oral capecitabine 2,500 mg/m²/day, days 1-14, every 3 weeks. Prior treatment must have included an anthracycline-based regimen, and patients must have also received docetaxel-based or paclitaxel-based chemotherapy and experienced disease progression during therapy or within 4 months of the last dose in the metastatic setting or within 12 months in the adjuvant setting. The primary endpoint was PFS. Patients were stratified for distant metastasis (liver or lung), anthracycline resistance, prior chemotherapy for metastatic disease, and study site.

For the ixabepilone plus capecitabine arm, an independent review committee determination of median PFS was 5.8 months compared with 4.2 months for those receiving capecitabine alone (Table 3). Again, the combination arm had significantly improved PFS, 6.2 months compared with 4.2 months for capecitabine alone (HR, 0.79; \( P = 0.0005 \) objective response rate (CR + PR), 43% vs 29%, respectively (\( P = .0001 \)).

Grade 3/4 treatment-related adverse events commonly reported in both studies are summarized in Table 4. In the pivotal trial, all 33 deaths within 30 days of last dose in patients receiving ixabepilone plus capecitabine were related to neutropenia. The risk was greatest in those with baseline elevation grade 2 in liver biochemistry; 5 of 16 such patients (31%) died, compared with 7 of 353 patients (2%) with baseline 1 liver dysfunction, leading to a study protocol amendment excluding those with baseline grade 2 liver dysfunction. In the confirmatory study, fewer deaths occurred in the group receiving ixabepilone plus capecitabine (3%; attributed to sepsis) than capecitabine alone (7%).

Peripheral neuropathy, which commonly occurred in the ixabepilone plus capecitabine group in both studies, was managed by dose reduction and delay. Compared with the taxanes, treatment interruption of ixabepilone appears to result in more rapid and complete symptom resolution, suggesting the nature of peripheral neuropathy may be different with the epothilones. Vahdat et al conducted a retrospective review of phase II and III clinical trials of ixabepilone as monotherapy or in combination with capecitabine (\( n = 1,540 \)). Pre-existing peripheral neuropathy was a significant risk factor for increased grade 3/4 peripheral neuropathy (HR, 1.44; \( P = .007 \)), whereas prior therapy with taxanes appeared to decrease this risk (HR, 0.35; \( P = .018 \)). Patients with grade 2 peripheral neuropathy resulting from prior taxane use were excluded from the ixabepilone studies, suggesting a selection bias.

### Table 3: Pivotal and confirmatory trials of ixabepilone plus capecitabine vs capecitabine alone: OS and PFS

<table>
<thead>
<tr>
<th></th>
<th>Pivotal (N = 752)</th>
<th>Confirmeratory (N = 1,221)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capecitabine + ixabepilone (n = 375)</td>
<td>Capecitabine (n = 377)</td>
</tr>
<tr>
<td>Median OS* (mo)</td>
<td>12.9</td>
<td>11.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.90 (0.77, 1.05)</td>
<td>0.90 (0.78, 1.03)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.1936</td>
<td>0.1162</td>
</tr>
<tr>
<td>Adjusted Cox regression†</td>
<td>HR (95% CI)</td>
<td>0.75 (0.64, 0.88)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.0003</td>
<td>0.0005</td>
</tr>
<tr>
<td>Median PFS‡ (mo)</td>
<td>5.8</td>
<td>4.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.64, 0.88)</td>
<td>0.79 (0.69, 0.90)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.0003</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

* Primary endpoint in confirmatory trial; † Baseline prognostic factors: performance status, age, number of organ sites, visceral disease, estrogen receptor status; ‡ Primary endpoint in pivotal trial.

Hortobagyi GN, et al; Sparano JA, et al. *S* Primary endpoint in confirmatory trial; † Baseline prognostic factors: performance status, age, number of organ sites, visceral disease, estrogen receptor status; ‡ Primary endpoint in pivotal trial.
A subgroup analysis of efficacy and safety data from the pivotal and confirmatory trials was conducted to determine a more precise estimate of benefits of ixabepilone plus capecitabine vs capecitabine alone in patients with poor Karnofsky performance status (KPS). Although analyses of subsets characterized by KPS scores were stipulated in the original study protocols, no formal statistical comparisons adjusted for multiple testing were planned. In those women with KPS 70-80 (n = 606), median OS months for those in the ixabepilone plus capecitabine group was better than that for capecitabine alone (12.3 vs 9.5 months, respectively; HR, 0.75; P = .0015) as was median PFS (4.6 vs 3.1 months; HR, 0.76; P = .0021) and objective response rate (35% vs 19%, respectively). For those with KPS 90-100 (n = 1,349), there was no difference in median OS between the combination and capecitabine alone arms (16.7 months vs 16.2 months, respectively; HR, 0.98; P = .8111), although PFS and response rates were both superior with the combination of ixabepilone and capecitabine. These results suggest the combination of ixabepilone plus capecitabine, which had a similar safety profile between subgroups, may have superior efficacy compared with capecitabine alone, and a possible OS benefit in those with a poorer KPS.

According to NCCN guidelines, single-agent ixabepilone and the combination of ixabepilone and capecitabine are listed as “other” single-agent therapy and “other” combination therapy for treatment of recurrent or metastatic breast cancer.

**Eribulin mesylate**

Eribulin mesylate, a nontaxane synthetic derivative of halichondrin B, has a novel mode of action that inhibits microtubule growth, causing sequestration of tubulin into nonfunctional aggregates. This suppresses microtubule polymerization and causes irreversible mitotic block, cell cycle arrest, and apoptosis. In preclinical studies, eribulin retained activity against paclitaxel-resistant cell lines, and in phase I studies, eribulin was active, with predictable myelosuppression the principle toxicity. The efficacy and tolerability of eribulin was evaluated in 2 phase II single-arm multicenter studies in patients with metastatic breast cancer pretreated with an anthracycline and a taxane and, if present, pre-existing neuropathy ≤ grade 2.5,36 Vahdat et al enrolled 103 patients who had received a median of 4 prior therapies (range, 1-11) and had disease progression on or within 6 months of the last dose of chemotherapy. Eribulin was administered initially at a dose of 1.4 mg/m² as a 2- to 5-minute intravenous infusion days 1, 8, and 15 every 28 days. The schedule subsequently was changed to days 1 and 8 every 21 days due to neutropenia at day 15 leading to omission of therapy. The primary endpoint was overall response rate. In the 28-day cohort, 59 patients were evaluable for response, as were 28 in the 21-day cohort. The independently reviewed overall response rate was 11.5%. The clinical benefit rate, defined as PR plus stable disease 6 months was 17.2%. Median duration of response was 171 days (5.6 months); median PFS, 79 days (2.6 months); and median OS, 275 days (9.0 months). Commonly occurring grade 3/4 hematologic adverse events included neutropenia, 64%; febrile neutropenia, 4%; and leukopenia, 18%; nonhematologic events were peripheral neuropathy (5%) and fatigue (5%).

In the phase II study by Cortes et al, patients were required to have had previous treatment with an anthracycline, a taxane, and capecitabine. A total of 291 patients who received a median of 4 prior regimens (range, 2-5) received eribulin 1.4 mg/m², day 1 and 8 every 21 days. The primary endpoint, objective response rate by independent review, was 9.3% (all PRs) among the 269 patients evaluable for response. The investigator-reported objective response rate was 14.1%; stable disease was 46.5% and clinical benefit rate was 17.1%. Median duration of response was 4.1 months; PFS, 2.6 months; and

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**TABLE 4**  Grade 3/4 adverse events in the pivotal and confirmatory trials of ixabepilone plus capecitabine vs capecitabine alone

<table>
<thead>
<tr>
<th>Grade 3/4 adverse event (%)</th>
<th>Pivotal</th>
<th></th>
<th>Confirmatory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Capecitabine + ixabepilone (n = 369)</td>
<td>68</td>
<td>Capecitabine (n = 368)</td>
<td>11</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>22.8</td>
<td>0</td>
<td>24.7</td>
<td>1.2*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9*</td>
<td>3.3</td>
<td>11.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>18*</td>
<td>17*</td>
<td>21*</td>
<td>20*</td>
</tr>
</tbody>
</table>

Thomas E, et al²³; Sparano JA, et al.²⁶
* No grade 4.
median OS, 10.4 months. Grade 3/4 toxicities included neutropenia (54%; febrile neutropenia, 5.5%), leukopenia (14%), and asthenia/fatigue (10%; no grade 4). A total of 6.9% of patients had grade 3 neuropathy (no grade 4). Similar results, albeit with higher rates of hematologic toxicities, were obtained in a single-arm, open-label phase II study in 80 Japanese patients receiving 1.4 mg/m² eribulin on a 21-day cycle who had a median of 3 prior regimens (range, 1 to 5), including an anthracycline and a taxane. The primary endpoint, overall response rate by independent review, was 21.3%. An additional 30 patients (37.5%) had stable disease and the clinical benefit rate (ie, CR + PR + stable disease ≥ 6 months) was 27.5%. Median duration of response was 3.9 months; PFS was 3.7 months; and OS, 11.1 months. Grade 3/4 neutropenia (95.1%; febrile neutropenia, 13.6%) and leukopenia (74.1%) were the most frequently occurring adverse events; grade 3 peripheral neuropathy was observed in 3.7% of patients (no grade 4). The open-label, multicenter, randomized phase III Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice versus E7389 (EMBRACE) study enrolled 762 patients with locally recurrent or metastatic breast cancer who received between 2 and 5 previous regimens that included an anthracycline and a taxane, at least 2 of which were for advanced disease. Patients needed to have disease progression on or within 6 months of the last chemotherapy regimen and neuropathy ≤ grade 2.

Patients were randomly assigned 2:1 to eribulin mesylate 1.4 mg/m² as a 2- to 5-minute intravenous bolus on days 1 and 8 of a 21-day cycle or the control group, treatment of physician’s choice (TPC), a discretionary selection of any monotherapy (ie, cytotoxic, hormonal, or biologic therapy) approved for the treatment of cancer and administered according to local practice, if applicable, or supportive care only (palliative treatment or radiotherapy). Patients were stratified by geographic region, prior capecitabine treatment, and human epidermal growth factor receptor (HER)2 status. The primary endpoint was OS in the intent-to-treat population; secondary endpoints were PFS, objective response rate, response duration, and safety.

The treatment arms were well balanced, the majority of the patients being white (92%), and having a good performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1, 91%). Median age was 55 years; 16% had HER2-positive disease, 19% had triple-negative metastatic breast cancer, and 84% had ≥ 2 organs involved, including metastases to the liver, lung, and bone. Ninety-nine percent of the patients had received taxanes and anthracyclines and 73% had also received capecitabine.

TPCs represented “real-world” selections (Figure 1), with 96% of patients treated with cytotoxics typically used in the metastatic breast cancer setting; the remainder received endocrine therapy and none received biologic therapy or best supportive care alone. Fifty-nine percent of patients in the eribulin arm received 5 or more cycles of therapy.

The primary endpoint was achieved with median OS significantly longer in the eribulin than in the TPC arm (13.1 vs 10.7 months, respectively; P = .041; HR, 0.81; 95% CI, 0.66, 0.99). An updated OS analysis, requested by European and US regulatory authorities, confirmed the rates observed initially: median OS was 13.2 months with eribulin and 10.6 months for TPC (P = .014) (Figure 2). The 1-year survival rates in the updated analysis were 54.5% and 42.8%, respectively.

For patients evaluable for response, best objective response rate in the eribulin group by independent review was 12% compared with 5% in those receiving TPC (P = .005); the clinical benefit rate was 23% vs 17%, respectively. By independent review, median PFS for eribulin and TPC was 3.7 vs 2.2 months, respectively (HR, 0.87; 95% CI, 0.71, 1.05; P = .14). A similar difference by investigator review with fewer patients censored reached statistical significance (P = .002). Median duration of response was 4.2 months for eribulin vs 6.7 months for TPC (P = .159).

Predefined exploratory subgroup analyses by molecular markers (estrogen receptor [ER] and/or progesterone receptor [PR] positive; HER2-positive, and triple-negative), number of organs involved, sites of disease, and prior capecitabine therapy demonstrated a similar pattern consistent with significant improvement in OS with er-
Eribulin; no individual subgroup was identified that appeared not to benefit from eribulin. For patients with ER/PR-positive (n = 528) and ER/PR-negative (n = 187) disease, relative risk reduction was 27% and 34%, respectively, for HER2-positive (n = 123) and HER2-negative (n = 565) disease, it was 24% and 19%, respectively. For patients in the triple-negative subgroup (n = 144), risk reduction was 29%.41

Two additional exploratory analyses of the patients in the EMBRACE trial were conducted to determine the influence of number of prior regimens and age on OS among those treated with eribulin. The first compared OS, PFS, overall response rate, clinical benefit rate, and toxicity in 4 age cohorts; analyses were stratified by geographic region, HER2 status, and prior capecitabine use. Results suggested survival outcomes with eribulin are independent of age; therefore, age alone should not preclude use of this agent. Toxicity was similar in older vs younger patients.42 In the second analysis, the OS benefit with eribulin compared with TPC appeared to be greater for patients who had received fewer previous treatment regimens for locally recurrent or metastatic disease; those receiving ≤ 3 regimens (n = 571) had a relative risk reduction of 33%, compared with those who had > 3 regimens (n = 190); relative risk reduction, 10%.43

Regarding toxicity, there was little difference in the frequency of adverse events and serious adverse events between the eribulin and TPC arms.38 In the eribulin group, neutropenia was the most frequently reported grade 3/4 adverse event (45%), but febrile neutropenia occurred in only 5% of patients and hematologic toxicities resulted in discontinuation of < 1% of patients. Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin (5%); for those who developed grade 3/4 peripheral neuropathy but continued treatment, this improved to grade 2 or better in later cycles following delays and dose reductions. Asthenia/fatigue occurred at a similar level with eribulin (grade 3, 8%; grade 4, 1%) and TPC (grade 3, 10%; no grade 4).

Ongoing trials involving eribulin mesylate in the treatment of metastatic breast cancer include a phase III study of eribulin vs capecitabine as second-line therapy with coprimary endpoints of PFS and OS,44 a phase II study of eribulin vs ixabepilone with a primary endpoint of rates of occurrence of peripheral neuropathy,45 and a phase Ib/II trial of eribulin in combination with capecitabine.46 According to the NCCN Breast Cancer Guidelines, eribulin is listed as a “preferred” single agent for the treatment of women with recurrent or metastatic breast cancer.16

**Conclusions**

The FDA-approved single agents, capecitabine, ixabepilone, and eribulin, and the combination of capecitabine with ixabepilone, represent advances in the treatment of patients with heavily pretreated metastatic breast cancer. In phase II studies, overall response rates ranged from 9%-32% for capecitabine, 12%-42% for ixabepilone, and 9.3%-12% for eribulin. In these studies, the most common nonhematologic grade 3/4 adverse effects for the single agents are hand-foot syndrome and diarrhea for capecitabine; peripheral neuropathy and asthenia/fatigue for ixabepilone; and asthenia/fatigue and peripheral neuropathy for eribulin.

A pivotal phase III trial of capecitabine plus ixabepilone compared to capecitabine alone, with PFS as the primary endpoint, did not show improved OS (12.9 months, P = .19), but median PFS was superior (5.8 months, P = .0003); a confirmatory trial, with OS as the primary endpoint, had similar findings. By contrast, in the EMBRACE study, eribulin significantly improved OS (13.1 months, P = .041 in the initial analysis; 13.2 months, P = .014 in updated analysis) compared with TPC with benefit also in PFS (3.7 months, P = .14 [by independent review] or 3.6 months, P = .002 [by investigator review]).

In the setting of prior exposure to an anthracycline and a taxane, the EMBRACE trial for the first time presents evidence of increased survival in women treated with eribulin compared with the “real-world” TPC, which included agents typically used in the metastatic breast cancer setting. These data will help guide treatment selection, which is based on many factors, including prior therapies, toxicities, performance status, and patient preference.
Acknowledgments
Writing assistance was provided by Debra Hughes. The authors retained full editorial control of the manuscript.

References


Choosing chemotherapy for patients with metastatic breast cancer previously exposed to taxanes and anthracyclines: other agents

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Many options exist for the treatment of patients with heavily pretreated metastatic breast cancer. In addition to the 3 agents—capecitabine, ixabepilone (single agent and with capecitabine), and eribulin mesylate (discussed in the previous article)—approved by the US Food and Drug Administration (FDA) for use in patients with metastatic breast cancer previously treated with a taxane and an anthracycline, a number of other agents have shown efficacy in this population. These cytotoxic agents include vinorelbine, gemcitabine, pegylated liposomal doxorubicin, nab-paclitaxel, pemetrexed, irinotecan, and platinum salts (ie, carboplatin, cisplatin).* Of these single agents, only gemcitabine and nab-paclitaxel are FDA-approved for use in patients with breast cancer, although neither is specifically indicated for the treatment of women with metastatic breast cancer and prior exposure to both an anthracycline and a taxane.1-8

Lack of a standard of care and the wide variety of cytotoxic options used in the treatment of women with heavily pretreated metastatic breast cancer are well illustrated by the control arm of the Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice versus E7389 (EMBRACE) trial, which evaluated single-agent eribulin vs the single-agent choice of the treating physician.9 In the treatment of physician’s choice (TPC) arm of the study, vinorelbine, gemcitabine, taxanes, anthracyclines, and other chemotherapies were administered to 25%, 19%, 15%, 10%, and 10% of patients, respectively. While all these agents or classes of agents have demonstrated activity as first-line treatment for metastatic breast cancer, the data for patients with prior exposure to both an anthracycline and a taxane are less robust.

A recent systematic review evaluated efficacy and safety data from phase II and phase III clinical studies of the single agents, capecitabine, gemcitabine, vinorelbine, and liposomal doxorubicin in the setting of heavily pretreated breast cancer.10 A critical criterion for inclusion in the review was that at least 80% of patients enrolled in the study had previous exposure to both an anthracycline and a taxane. The agents and studies included in this systematic review as well as additional agents/studies also meeting this inclusion criterion are the focus of this article. Despite inclusion in the systematic analysis of Oostendorp et al,10 data on the efficacy and safety of some of these agents, particularly gemcitabine and liposomal doxorubicin, in the setting of heavily pretreated metastatic breast cancer are limited, with evidence more scarce for agents not included in the systematic review. Also mentioned here are studies of other agents that are often used in the setting of heavily pretreated metastatic breast cancer, but do not meet the strict inclusion criterion regarding pretreatment history. Hence, the lower level of evidence for the use of these latter cytotoxic therapies, especially as single agents, in the setting of anthracycline/taxane-pretreated metastatic breast cancer is emphasized.

*All of the agents discussed herein are used off-label for treatment of patients with metastatic breast cancer previously treated with anthracyclines and taxanes.

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Disclosures: Dr Fornier has nothing to disclose. Dr Twelves has received grant research support from Roche. He has also been a consultant for Eisai Inc. and Roche and a speaker for Eisai Inc.
Single-agents studied in the setting of prior anthracycline- and taxane-exposed metastatic breast cancer

Gemcitabine

Gemcitabine, an analogue of cytidine, is an antimetabolite prodrug that is activated through intracellular phosphorylation and involved in the inhibition of DNA synthesis.11 Three phase II studies of gemcitabine in patients with anthracycline- and taxane-resistant breast cancer reported response rates of 17% to 22.6% at doses of 800 to 1,000 mg/m² days 1, 8, and 15 every 28 days.12-14 However, in another phase II study of this population, the overall response rate was 0% following administration of gemcitabine at a 1,200 mg/m² dose on the same schedule, although the disease-control rate and median time to progression (TTP) were 26% and 1.9 months, respectively.15

In a systematic review including 3 of these studies,13-15 weighted mean values for disease-control rate (ie, overall response rate plus stable disease rate) and overall survival (OS) were 35% and 9.8 months, respectively.10 Serious nausea and/or vomiting were reported in 14% of patients in 1 study,15 and serious fatigue in 5%-9% of patients in 2 studies.14,15 Rates of grade 3/4 neutropenia ranged from 12%-18%. Although guidelines from the National Comprehensive Cancer Network (NCCN) list gemcitabine as a “preferred” single agent for the treatment of recurrent or metastatic breast cancer,16 the authors of the systematic review “found only limited evidence for the effectiveness of gemcitabine” in this specific setting.10

Vinorelbine

Vinorelbine is an antimicrotubule agent that interferes in cellular replication by causing abnormalities in microtubule formation, although its mechanism of action is distinct from other agents, such as the taxanes, which target microtubules.17 In 9 clinical studies of single-agent vinorelbine conducted in patients with advanced breast cancer pretreated with an anthracycline and a taxane, overall response rates were 13%-35%.10,18-26 Representative results were observed in the most recently conducted study where vinorelbine was administered at a dose of 25 mg/m² on days 1, 8, 15, and 22 every 4 weeks to 26 patients previously treated with anthracyclines and taxanes.18 The overall response rate, median TTP, and median OS were 20.8%, 3.7 months, and 10.4 months, respectively.

In a systematic review of all 9 studies, weighted mean values for disease-control rate and OS were 49% and 12.6 months, respectively.10 Serious fatigue was reported in 13% of patients in 1 study25 and 16% of patients were reported to experience serious alopecia in another.26 High rates of grade 3/4 neutropenia (eg, > 50%) have been reported. According to guidelines from the NCCN, vinorelbine is listed as a “preferred” single agent for the treatment of recurrent or metastatic breast cancer.16

Pemetrexed

Pemetrexed is an antifolate metabolite that interferes with the synthesis of DNA and RNA by interfering with the nucleotide synthesis.27 Two phase II studies of pemetrexed in patients with refractory metastatic breast cancer conducted in the past decade have shown overall response rates of 8% to 9% at a dose of 500 mg/m² every 3 weeks,28,29 with manageable toxicities including fatigue, dyspnea, anorexia, nausea, chest pain, and grade 3/4 neutropenia.17

O’Shaughnessy et al enrolled 80 patients with metastatic breast cancer previously treated with ≥ 3 regimens containing anthracyclines, taxanes, and capecitabine and administered intravenous pemetrexed 500 mg/m² on day 1 of a 21-day cycle. Following a protocol amendment, 60 patients received concurrent folic acid and vitamin B₁₂ supplements to minimize toxicity related to pemetrexed. Overall response rate was 8% and stable disease, 36%. Median TTP was 2.9 months, and median OS, 8.2 months. Grade 3/4 toxicities were primarily hematologic; grade 4 neutropenia occurred in 10% of patients, and grade 3 neutropenia and leukopenia in 29% and 21% of patients, respectively. The effect of supplementation on toxicity was not clear.28

Another study of pemetrexed 500 mg/m² administered as a 10-minute intravenous infusion on day 1 every 21 days in 79 patients who had experienced progressive disease following treatment with anthracycline and a taxane had a response rate of 9%; 43 received folic acid and vitamin B₁₂ supplementation. A median of 4 cycles was administered. The median duration of response was 5.5 months. Median PFS was 3.1 months, and median survival was 10.5 months. Grade 3/4 toxicities included neutropenia (36.4%). Toxicity appeared to be ameliorated with vitamin supplementation.29

Taxane or anthracycline retreatment in patients with metastatic breast cancer previously exposed to an anthracycline and a taxane

Although many patients with early-stage breast cancer receive adjuvant anthracycline-taxane-based chemotherapy, evidence is limited for rechallenging those patients who experience a prolonged disease-free survival interval following completion of adjuvant chemotherapy with 1 or both of these agents following diagnosis of metastatic disease.30 Most of the available data are from single-center cohort studies, or subgroup analyses and retrospective reviews of phase III studies. Only 1 phase III trial examined the strategy of anthracycline rechallenge, and
nearly all of the patients in that study were not “heavily-pretreated” as the majority had not received prior cytotoxic therapy for advanced disease. Nevertheless, the cumulative dose of anthracycline in standard adjuvant chemotherapy regimens is below the 450-550 mg/m² and 800-900 mg/m² for doxorubicin and epirubicin, respectively, and liposomal anthracycline formulations are associated with a reduced risk of cardiotoxicity. Potential options for rechallenge with a taxane include using the same agent, a different member of the drug class, or an alternative formulation such as albumin-bound paclitaxel, with the caveat that cumulative toxicity may be an issue.

**Pegylated liposomal doxorubicin**

The mechanisms of action of pegylated liposomal doxorubicin and conventional doxorubicin are the same; they both interfere with DNA replication through multiple processes, including DNA intercalation and inhibition of the enzyme topoisomerase II. The encapsulation of conventional doxorubicin in a polyethylene glycol (pegylated) liposomal formulation was developed to improve the therapeutic index of doxorubicin. Uptake of this agent by the reticuloendothelial system is impaired and the serum half-life of the drug is prolonged. Pegylated liposomal doxorubicin is less cardiotoxic than conventional doxorubicin. Due to wider tissue distribution, this formulation is associated with lower rates of myelotoxicity, alopecia, and gastrointestinal toxicity, although rates of hand-foot syndrome and mucositis are increased.

Keller et al conducted a phase III study in which 301 women with advanced breast cancer were randomly assigned to 1 of 3 treatment arms: pegylated liposomal doxorubicin (50 mg/m² every 28 days); vinorelbine (30 mg/m² weekly); or mitomycin C (10 mg/m² day 1 and every 28 days) plus vinblastine (5 mg/m² day 1, 14, 28, and 42) every 6 to 8 weeks. One hundred fifty patients received pegylated liposomal doxorubicin. All patients in the study had been previously treated with a taxane and 83% of patients had prior exposure to an anthracycline. Disease-control rate, median PFS, and median OS for patients in the pegylated liposomal doxorubicin arm were 10%, 2.9 months, and 10.4 months, respectively. Similar PFS and OS results were observed for patients in the comparator arm (ie, patients receiving vinorelbine or mitomycin plus vinblastine). The toxicity profile of pegylated liposomal doxorubicin in this study included an increased incidence of nausea, vomiting, fatigue, hand-foot syndrome, and stomatitis. According to guidelines from the NCCN, pegylated liposomal doxorubicin is listed as a “preferred” single agent for the treatment of recurrent or metastatic breast cancer. Nevertheless, the authors of the systematic review “found only limited evidence for the effectiveness of liposomal doxorubicin” in this specific setting.

**Nab-Paclitaxel**

The mechanism of action of nab-paclitaxel is the same as paclitaxel; it interferes with cellular replication by stabilizing microtubules. However, in the nab-paclitaxel formulation, paclitaxel is coated with nanoparticles of albumin to increase its solubility and enhance its delivery to the tumor. Compared with the conventional formulation of paclitaxel, nab-paclitaxel is solvent-free and has a shorter infusion time. Blum et al conducted a phase II study involving nab-paclitaxel 100 mg/m² days 1, 8, and 15 every 28 days in 106 women with metastatic breast cancer who had undergone a median of 3 prior regimens (range, 0-7) whose disease had progressed during treatment with taxanes or had relapsed within 12 months of adjuvant taxane therapy. Seventy-five percent of these patients had received an anthracycline in the adjuvant setting. Objective partial responses were observed in 14% of patients, and stable disease of at least 16 weeks in duration was observed in 12%. Median PFS was 3 months and median OS, 9.2 months. Survival probability at 12 months was 39%. Rate of OS was similar in those who responded or had stable disease.

**Nab-paclitaxel** was well tolerated without steroids or granulocyte colony-stimulating factor prophylaxis. Grade 3 neutropenia occurred in 14% of patients and grade 4, 4%. Grade 3 sensory neuropathy was observed in 8% of patients. For those who developed treatment-limiting peripheral neuropathy, a treatment delay of 1-2 weeks was recommended prior to reintiating treatment with nab-paclitaxel at a reduced dose. Other reported adverse events included fatigue, nausea, and alopecia. According to guidelines from the NCCN, nab-paclitaxel is listed as a “preferred” single agent for the treatment of recurrent or metastatic breast cancer.

**Other single agents studied in the setting of heavily pretreated metastatic breast cancer**

**Irinotecan**

Irinotecan is an inhibitor of topoisomerase I, an enzyme involved in the cleavage and rescaling of DNA strands during the DNA replication process. To assess the efficacy and tolerability of 2 schedules of irinotecan, women with metastatic breast cancer whose disease had progressed after 1 to 3 chemotherapy regimens were randomized in a multicenter phase II study to 100 mg/m² for 4 weeks followed by a 2-week rest (n = 52; the “weekly” arm) or 240 mg/m² every 3 weeks (n = 51, the “every-3-weeks” arm), both in 6-week cycles. In this study, approximately 60% of patients received prior treatment...
with both a taxane and an anthracycline. In the weekly arm, objective response rate (1 complete plus 11 partial regressions) was 23%. The median duration of response was 4.9 months, and median OS was 9.7 months. Patients in the every-3-weeks arm had 7 partial regressions for an objective response rate of 14%. Median response duration was 4.2 months, and median OS was 8.6 months. Irinotecan tolerability was good, especially in the weekly arm; grade 3/4 neutropenia was 29%; and diarrhea, 17%. In the every-3-weeks arm, grade 3/4 neutropenia was 36%; vomiting, 20%; dyspnea, 18%; nausea, 16%; and diarrhea, 12%. With respect to emerging irinotecan-based therapy, an objective response rate of 29% was observed in a phase II trial of 70 patients with metastatic breast cancer and prior anthracycline/taxane exposure when they were treated with a novel polymer conjugate of irinotecan, NKTR-102. Dose-limiting toxicity was primarily grade 3 diarrhea occurring in approximately 20% of patients.41

Platinum salts (carboplatin, cisplatin)

Platinum salts function by binding to DNA and causing formation of DNA crosslinks.42 Several studies conducted in the 1970s and 1980s with single-agent cisplatin in patients with previously treated metastatic breast cancer at varying doses and regimens reported response rates from 0%-21% (Table 1).43-48 According to guidelines from the NCCN, cisplatin is listed as an “other” single agent for the treatment of recurrent or metastatic breast cancer.16

The efficacy of carboplatin studied in this population in the 1980s and 1990s at varying doses in primarily 4-week treatment regimens demonstrated response rates of 0% to 16% (Table 2).49-53 Most of the studies on platinum-based single agents were conducted before FDA approval of docetaxel or paclitaxel.

The combinations of cisplatin plus gemcitabine and carboplatin plus gemcitabine have been evaluated in the setting of anthracycline-/taxane-exposed breast cancer in 2 recent phase II studies. Somali et al investigated the safety and efficacy of gemcitabine (1,000 mg/m²) plus cisplatin (30 mg/m²) both administered on days 1 and 8 every 3 weeks in 33 patients with metastatic breast cancer that progressed following anthracycline- and taxane-based chemotherapy. The objective response and disease-control rates were 25.8% and 45.2%, respectively, with a median TTP of 4 months and a median OS of 9.5 months.54 In this study, the only grade 3 nonhematologic toxicity was nausea and vomiting at a rate of 9.6%. No grade 4 nonhematologic toxicities were reported. Reported rates of grade 3 (3.2%) and grade 4 (3.2%) neutropenia also were low.

Another phase II study evaluated the efficacy and safety of the combination of gemcitabine (1,000 mg/m²) on days 1 and 8) and carboplatin (AUC 4 IV on day 1) every 3 weeks in 39 patients with advanced breast cancer previously exposed to an anthracycline and a taxane.55 The reported clinical outcomes included: overall response rate, 31%; disease-control rate, 62%; median TTP, 5.3 months; median OS, 13.2 months. However, rates of grade 3/4 hematologic toxicity were high; grade 3/4 he-

### Table 1: Single-agent cisplatin in patients with previously treated metastatic breast cancer

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (N)</th>
<th>Dosage</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bull et al 1978</td>
<td>16</td>
<td>70 mg/m² every 3 weeks</td>
<td>13</td>
</tr>
<tr>
<td>Samal et al 1978</td>
<td>23</td>
<td>15 mg/m²/day x 5 days every 4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>Yap et al 1978</td>
<td>14/12</td>
<td>100 mg/m² every 3-4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>Ostrow et al 1980</td>
<td>17</td>
<td>100 mg/m² every 3-4 weeks</td>
<td>12</td>
</tr>
<tr>
<td>Forastiere et al 1982</td>
<td>18</td>
<td>60 mg/m² every 3 weeks</td>
<td>0/21</td>
</tr>
<tr>
<td>Martino et al 1984</td>
<td>15/13</td>
<td>15 mg/m²/day x 5 days every 4 weeks</td>
<td>0/15</td>
</tr>
</tbody>
</table>

**RR** = response rate.

### Table 2: Single-agent carboplatin in patients with previously treated metastatic breast cancer

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (N)</th>
<th>Dosage</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmo-Pereira et al 1989</td>
<td>19</td>
<td>400 mg/m² every 4 weeks</td>
<td>16</td>
</tr>
<tr>
<td>O’Brien et al 1993</td>
<td>13</td>
<td>AUC 7 mg/mL/minute every 4 weeks</td>
<td>8</td>
</tr>
<tr>
<td>Vermoken et al 1993</td>
<td>30</td>
<td>450 mg/m² every 5 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Booth et al 1985</td>
<td>14</td>
<td>280-320 mg/m² every 4 weeks</td>
<td>0</td>
</tr>
<tr>
<td>Martin et al 1991</td>
<td>14</td>
<td>400 mg/m² every 4 weeks</td>
<td>0</td>
</tr>
</tbody>
</table>

**AUC** = area under the curve; **RR** = response rate.
matologic toxicity included leukopenia (59%/5%), thromboctopenia (26%/23%).

There is some preclinical and retrospective evidence that platinum-based chemotherapy may be particularly active in the treatment of patients with triple-negative breast cancer. Nevertheless, prospective data in support of this hypothesis are lacking. A phase II trial investigating the efficacy and safety of cisplatin or carboplatin for the treatment of triple-negative metastatic breast cancer is underway.57

Ongoing research and future options

A number of new cytotoxic agents are being investigated in the setting of metastatic breast cancer. For example, the new vinca alkaloid, vinflunine, was shown to be active and well tolerated as a single agent in third-line treatment of women with metastatic breast cancer following failure of an anthracycline and a taxane. Other agents include a novel epothilone, patupilone, which is thought to penetrate the blood–brain barrier;60 new taxane therapies such as oral tesetaxel61 and larotaxel62 and indibulin, a novel antimitotic agent. Selected studies of some of these investigational agents in the setting of pretreated metastatic breast cancer are described in Table 3.64-68

Conclusions

Cytotoxic agents remain the mainstay of treatment for many patients with metastatic breast cancer, with the goals of therapy focusing on prolongation of survival and improvement in quality of life. However, the development of chemotherapy resistance and the toxicities associated with cytotoxic therapy are major limitations in the treatment of patients with metastatic breast cancer. Most, if not all, of the agents discussed in this article have shown activity in the setting of metastatic disease. Nevertheless, data in heavily-pretreated patients with prior exposure to both a taxane and an anthracycline are very limited. Research is ongoing to improve outcomes in this patient population.

Acknowledgments

Writing assistance was provided by Debra Hughes. The authors retained full editorial control of the manuscript.

References


Self-Assessment Questions

1. A “tipping point” in moving from endocrine therapy to chemotherapy is:
   b. ER/PR status.
   c. HER2 status.
   d. Nodal status.

2. The percentage of women diagnosed with early breast cancer who will eventually develop advanced disease is estimated to be up to:
   a. 10%.
   b. 30%.
   c. 45%.
   d. 50%.

3. Median survival in patients with metastatic breast cancer is:
   a. 12-15 months.
   b. 12-18 months.
   c. 15-24 months.
   d. 18-24 months.

4. All of the following are mechanisms of resistance to anticancer drugs except:
   a. Reduced apoptosis.
   b. Decreased drug metabolism.
   c. Altered cell cycle checkpoints.
   d. Altered drug targets.

5. The 2 newest drug classes for the treatment of patients with advanced breast cancer are:
   a. Taxanes and anthracyclines.
   b. Epothilones and halichondrins.
   c. Halichondrins and taxanes.
   d. Epothilones and anthracyclines.

6. All of the following statements about the treatment of women with metastatic breast cancer are TRUE except:
   a. Data on the use of cytotoxic agents in heavily pretreated patients with prior exposure to both a taxane and an anthracycline are limited.
   b. A fixed treatment algorithm should be followed for best results.
   c. Retrospective evidence suggests survival rates have been improving over the past several decades.
   d. Overall survival should be considered the gold standard for evaluating clinical benefits of therapies.

7. The 3 chemotherapeutic agents that have FDA approval for patients with heavily pretreated breast cancer, including prior exposure to an anthracycline and a taxane are:
   a. Docetaxel, ixabepilone, trastuzumab.
   b. Paclitaxel, capecitabine, eribulin mesylate.
   c. Capecitabine, ixabepilone, eribulin mesylate.
   d. Lapatinib, nab-paclitaxel, ixabepilone.

8. The range of median survival times observed in phase II/III studies of capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane were:
   a. 8.5-15.3 months.
   b. 9.3-18.1 months.
   c. 6.9-12.3 months.
   d. 6.3-15.9 months.

9. Use of capecitabine results in a negligible risk of:
   a. Diarrhea.
   b. Nausea.
   c. Vomiting.
   d. Alopecia.

10. The most common nonhematologic grade 3/4 adverse effect in patients treated with capecitabine is:
    a. Hand-foot syndrome.
    b. Peripheral neuropathy.
    c. Asthenia/fatigue.
    d. Nausea.

11. The principal difference between the pivotal and confirmatory randomized trials of ixabepilone plus capecitabine vs capecitabine alone was:
    a. Baseline prognostic factors.
    b. Median PFS.
    c. Median OS.
    d. Primary endpoint.

12. The most common nonhematologic grade 3/4 adverse effect in patients treated with ixabepilone plus capecitabine is:
    a. Hand-foot syndrome.
    b. Peripheral neuropathy.
    c. Asthenia/fatigue.
    d. Nausea.

13. Asthenia/fatigue, one of the most common nonhematologic grade 3 adverse effects observed in the eribulin arm of the EMBRACE trial, occurred at a frequency of:
    a. 3%.
    b. 8%.
    c. 15%.
    d. 35%.

14. In the EMBRACE trial, the chemotherapeutic agent most often selected as a TPC was:
    a. Anthracycline.
    b. Capecitabine.
    c. Gemcitabine.
    d. Vinorelbine.

15. The updated OS results for patients in the eribulin arm vs the TPC arm of the EMBRACE trial were:
    a. 13.2 vs 12.1 months.
    b. 13.2 vs 11.6 months.
    c. 13.2 vs 11.0 months.
    d. 13.2 vs 10.6 months.

16. The 2 cytotoxic agents that are FDA-approved for use in breast cancer but not in women with metastatic breast cancer and prior exposure to an anthracycline and a taxane are:
    a. Gemcitabine and nab-paclitaxel.
    b. Nab-paclitaxel and irinotecan.
    c. Pemetrexed and vinorelbine.
    d. Pegylated liposomal doxorubicin and irinotecan.

17. The characteristic of pegylated liposomal doxorubicin that is shared with conventional doxorubicin is:
    a. Cardiotoxicity.
    b. Mechanism of action.
    c. Therapeutic index.
    d. Myelotoxicity.

18. When a patient has previously received a taxane, all of the following are potential options when rechallenging with a taxane except use of:
    a. The same agent.
    b. A different member of the same drug class.
    c. An alternative formulation.
    d. An anthracycline beyond maximum cumulative dose.

19. The characteristic of nab-paclitaxel that is similar to paclitaxel is:
    a. Infusion time.
    b. Microtubule stabilizer.
    c. Solubility.
    d. Solvent-free administration.

20. In a phase II study, the primary adverse effect of treatment with irinotecan was:
    a. Diarrhea.
    b. Dyspnea.
    c. Neutropenia.
    d. Vomiting.
1. As a result of this session, I am better able to:
   a. Discuss the approaches to the treatment of heavily pretreated metastatic breast cancer, including sequential versus combination chemotherapy.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

   b. Describe the efficacy and toxicity of newer chemotherapy agents and combinations for the treatment of patients with heavily pretreated metastatic breast cancer.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

   c. Devise evidence-based treatment plans for patients with advanced breast cancer that has progressed following treatment with taxanes and anthracyclines.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

2. The objectives were related to the purpose of the activity.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

3. The content of this learning activity was clearly written.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

4. Did you perceive any commercial bias in this activity?  
   Yes  No

   If you answered Yes for Question 4, please explain:______________________________

5. My level of knowledge about managing patients with heavily pretreated breast cancer prior to this activity was adequate.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

6. My level of knowledge about managing patients with heavily pretreated breast cancer was enhanced by this activity.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

7. My overall competence in managing patients with heavily pretreated breast cancer prior to this activity was adequate.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

8. My overall competence in managing patients with heavily pretreated breast cancer was enhanced by this activity.  
   (5 = Strongly Agree, 1 = Strongly Disagree)
   5  4  3  2  1

9. I would recommend this activity to others.  
   Yes  No

   If you answered No for Question 9, please explain:______________________________

10. This activity will assist in the improvement of my (check all that apply):  
    1. Competence
       2. Performance
       3. Patient outcomes

11. I plan to make changes to my clinical practice as a result of this activity.  
    Yes  No

   Yes. Please give 1 example:______________________________

   No. Please explain:______________________________

12. If you answered Yes to Question 11, what is your level of commitment to making the changes stated above?  
    1. Very committed
       2. Somewhat committed
       3. Not very committed

13. What are the barriers you face in your current practice setting that may impact patient outcomes? (check all that apply)  
    1. Lack of evidence-based guidelines
       2. Guidelines not applicable to my current practice/patients
       3. Lack of time
       4. Organizational/institutional
       5. Patient adherence
       6. Treatment-related adverse events
       7. Other

   If Other, please explain:______________________________

14. Please rank each of the educational formats below in order of preference from 1 (highest) to 8 (lowest).  
    1. Association Meetings
       2. Grand Rounds
       3. Home Study (CD-ROM)
       4. Home Study (printed)
       5. Internet-Based Case Studies
       6. Symposiums
       7. Teleconferences
       8. Webinars

15. Please indicate topics for future activities:______________________________

   __________________________

   __________________________

I certify that I have completed this activity and the actual time I spent was:  
1.5 hours  2.0 hours  2.5 hours

Other (fill in number of minutes): ______