

Advances in Chemotherapy for Metastatic Breast Cancer

a report by

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Despite many advances over the past few years in the adjuvant treatment of breast cancer, a significant number of patients develop metastatic disease. Furthermore, a small yet consistent percentage of women are diagnosed with *de novo* metastatic disease. Once the disease has spread outside the locoregional area of the breast and draining lymph nodes, it is considered incurable, historically with a median survival of two to three years. More recent analyses of outcomes with modern treatment regimens suggest an improvement in median survival, with patients occasionally living for a prolonged period of time with metastatic disease.^{1,2} Systemic therapy is the primary modality of treatment, given with the dual goals of prolongation of survival and palliation of symptomatology. Selection of agents, timing of initiation and discontinuation, and incorporation of novel therapies is both a science and an art. For many women, sequential use of appropriate therapy can translate into years of prolonged survival with preserved quality of life.

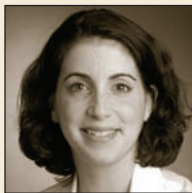
The decision of when to initiate chemotherapy for breast cancer depends on the characteristics of both the patient and the tumor. In the absence of significant symptomatology or visceral organ compromise, individuals with hormone-responsive disease are preferentially started on an appropriate endocrine therapy. Suitable agents include: aromatase inhibitors, tamoxifen, fulvestrant, or ovarian ablation (if pre-menopausal). Typically, commencement of chemotherapeutic treatment is reserved for hormone receptor-negative disease, disease refractory to further endocrine maneuvers, rapid progression, or visceral organ crisis. Concurrent use of endocrine and chemotherapy treatment is usually avoided, due to concerns regarding potential negative interactions. Historical trials comparing chemohormonal therapy with chemotherapy alone suggest that the addition of an endocrine agent does not compromise response and prolongs time to treatment failure, although it does not translate into an overall survival benefit.^{3,4} Usually, chemotherapy is administered in cycles consisting of three- to four-week units, with interval clinical and radiological

restaging to evaluate for response. Response to therapy depends on multiple factors, most importantly prior exposure to chemotherapeutic agents. Responses are significantly higher in chemotherapy-naïve patients compared with those who have received adjuvant therapy, and in the first-line metastatic setting compared with successive lines of therapy.^{5,6} Although an objective response to therapy is a goal of chemotherapeutic treatment, achieving stable disease may also be a desirable objective, as a significant proportion of patients who achieve stable disease experience improvements in cancer-related symptoms and quality of life.⁷

Variable methods of administration of chemotherapy for metastatic breast cancer exist, and multiple clinical trials have evaluated whether chemotherapy should be given in a continuous or interrupted fashion. These studies have demonstrated that although continuous 'maintenance' therapy can prolong time to progressive disease, as 'observation' patients can reinstate therapy at time of progression, no difference in survival emerges between the two methods of administration.^{8,9} In practice, chemotherapy tends to be given in a continuous fashion as long as there is demonstrated evidence of response or stable disease and the patient does not experience significant toxicity. Treatment 'holidays' can be instituted in the setting of prolonged stable disease, with resumption of prior therapy if necessary. In cases of definitive radiological or clinical progression, indicating resistance to the ongoing therapy, the regimen is changed to a different agent.

Multiple chemotherapeutic agents have demonstrated activity in the treatment of advanced breast cancer. Generally, anthracyclines and taxanes are considered the most active agents. However, as many patients have received these as part of adjuvant treatment, alternative agents are often selected in the metastatic setting, with no consensus opinion on a preferable order of therapy.¹⁰ Considerable practice variation exists in the selection and timing of agents, and decisions typically reflect previous treatment history, tumor characteristics and burden, comorbid toxicities, and patient preference. Does this variation influence patient outcome? The Cancer and Leukemia Group B (CALGB) compared first-line therapy with conventional anthracycline-based chemotherapy with treatment with an experimental agent as part of a clinical trial.¹¹ No difference in overall survival was found between the two arms, despite higher responses in the conventional therapy arm, suggesting that diversity in practice does not result in differential outcomes.

The specific data supporting the use of contemporary chemotherapy agents, including adriamycin, paclitaxel, docetaxel, capecitabine, vinorelbine, gemcitabine, liposomal doxorubicin, and epirubicin, have been reviewed extensively.¹² Although the treatment options have remained constant over



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the past few years, changes in scheduling—including the superiority of weekly paclitaxel over every-three-week dosing—have introduced small improvements.¹³ Both combination and single-agent strategies have been used in the treatment of metastatic breast cancer. In general, combination treatment leads to a higher response rate or time to progression. However, this activity typically does not translate into significant survival benefits, likely due to washout from cross-over to subsequent lines of therapy.⁴ Combination regimens also incorporate additional toxicity compared with sequential single-agent therapy, an important caveat given the goal of symptom palliation. Two combination regimens to date, paclitaxel ± gemcitabine and docetaxel ± capecitabine, have demonstrated improved overall survival in randomized trials compared with the single-agent comparator arm.^{14,15} These regimens can be useful in the setting of visceral crisis, when obtaining a rapid response to therapy is of utmost importance. Otherwise, in usual practice, sequential single-agent therapy preferably offers both improved tolerability and the ability to identify emerging resistance to treatment.

The past few years have brought two new agents into the armamentarium. Nanoparticle albumin-bound paclitaxel does not require cremaphor for preparation, thus significantly reducing the risks of hypersensitivity reaction during administration associated with other taxanes. Additionally, pre-clinical work suggests improved delivery of albumin-bound paclitaxel to tumor tissue, possibly leading to enhanced efficacy.¹⁶ In a phase III trial in the metastatic setting comparing every-three-week nanoparticle albumin-bound paclitaxel at 260mg/m² versus every-three-week paclitaxel at 175mg/m², results demonstrated a higher response rate and longer time to progression in the nanoparticle albumin-bound paclitaxel arm.¹⁷ The toxicity profile differed from traditional paclitaxel, with less hematological toxicity but more neuropathy.

Data from this study supported drug approval by the US Food and Drug Administration (FDA) in 2005 for the treatment of anthracycline-refractory metastatic breast cancer. Subsequently, weekly nanoparticle albumin-bound paclitaxel (100mg/m², three weeks on/one week off) appears to have increased activity compared with every-three-week dosing in the first-line setting.¹⁸ A phase III comparison of weekly nanoparticle albumin-bound paclitaxel and every-three-week docetaxel is expected.

The newest chemotherapeutic available for treatment of metastatic breast cancer is ixabepilone, an epothilone analog. Epothilones bind tubulin, leading to stabilization of microtubules, causing cell-cycle arrest and subsequent apoptotic cell death. Pre-clinical study of epothilones has demonstrated activity in both taxane-sensitive and taxane-refractory tumors, suggesting a role for this class of agent in refractory disease.¹⁹ Four phase II trials have examined the role of ixabepilone monotherapy in patients with metastatic breast cancer refractory to anthracyclines, taxanes, or both. Using the primary dosing schedule of 40mg/m² every three weeks, a response rate of 41.5% was observed in 65 anthracycline pre-treated patients. Similarly, this dosing schedule resulted in a response rate of 21% in a cohort of 49 taxane-refractory patients. Notably, of the six responders, five had not responded to prior taxane treatment.^{20,21}

A second dosing schedule, 6mg/m² daily for five days every three weeks, has also been explored. In the first-line metastatic setting, without prior taxane exposure, a response rate of 57% was observed in 23 patients.²² Using the same regimen in a taxane-pre-treated population, a response rate of 22%

was seen in 37 patients.²³ Finally, ixabepilone monotherapy has been evaluated at 40mg/m² every three weeks in a highly refractory population resistant to anthracycline, taxane, and capecitabine. In this phase II study of 126 patients by Perez et al., an independent radiology facility (IRF)-assessed response rate of 11.5% (18.3% for investigator assessed) was observed, with 25% having either a partial response (PR) or stable disease (SD) >6 months. All of the patients with responses had visceral metastatic disease at baseline, with a substantial number resistant to all prior chemotherapeutic treatment.²⁴ In all of these trials, the most significant toxicities seen were sensory neuropathy, fatigue, cytopenias, nausea, and myalgias. The frequency of neuropathy appears to be greater with every-three-week dosing, and in the above trials led to frequent dose reductions on the every-three-week schedule. Weekly dosing may reduce the occurrence of this toxicity and is being studied in ongoing trials. Therefore, ixabepilone monotherapy represents an attractive new chemotherapeutic option, particularly for patients with highly refractory disease.

Thomas et al. have studied the role of ixabepilone combination therapy in the phase III setting. Ixabepilone 40mg/m² every three weeks and capecitabine 2,000mg/m² was compared with capecitabine 2,500mg/m² monotherapy in 752 patients with anthracycline- and taxane-pre-treated disease. The combination arm demonstrated an improved response rate of 35 versus 14%, with a 1.6-month improvement in median progression-free survival. Both neuropathy and hematological toxicity were more significant in the combination arm, in addition to a greater number of deaths.²⁵ Based on the results of these studies, the FDA approved ixabepilone monotherapy and in combination with capecitabine for treatment of metastatic breast cancer in October 2007. Multiple ongoing studies are examining the role of ixabepilone in combination with other chemotherapeutics, with human epidermal growth factor receptor (HER)-2-directed therapy, and with angiogenesis inhibitors. Additionally, the subset of 'triple-negative' tumors—negative for estrogen receptor, progesterone receptor, and HER2—appear to derive substantial benefit from ixabepilone,²⁶ and ongoing work will further explore the role of this new agent for this tumor subset.

Another evolving paradigm in the treatment of metastatic disease is the combination of traditional chemotherapeutics with biologic therapies. Almost a decade ago, the pivotal phase III study of paclitaxel ± trastuzumab in the first-line metastatic setting heralded the entry of antibody-based targeted therapy.²⁷ Currently, the treatment paradigm for women with HER2-positive disease includes early use of trastuzumab in combination with chemotherapy. Other agents with demonstrated efficacy in combination with trastuzumab include vinorelbine, docetaxel, gemcitabine, and capecitabine.²⁸⁻³² The question of whether trastuzumab should be continued after disease progression has not been answered in clinical trials, although in general practice treatment typically consists of sequential trastuzumab/chemotherapy doublets. Lapatinib, an oral reversible HER2 tyrosine kinase inhibitor, has been evaluated in the setting of trastuzumab-refractory disease. In a phase III trial, 324 patients pre-treated with anthracycline, taxane, and trastuzumab were randomized to capecitabine alone at 2,500mg/m²/day or capecitabine 2,000mg/m²/day plus lapatinib 1,250mg/day. The trial was terminated early to report a 51% reduction in the risk of disease progression,³³ leading to FDA approval for lapatinib in March 2007. Ongoing trials will evaluate next-generation HER2-directed therapy, including irreversible tyrosine kinase inhibitors of HER2, such as HKI-272 or BIBW 2992.

Angiogenesis is thought to play an important role in the growth and dissemination of malignant tissue. Targeting angiogenesis through inhibition of vascular endothelial growth factor (VEGF) with bevacizumab—a humanized monoclonal antibody directed against VEGF—has been a successful paradigm in other solid tumor types, and is under active exploration in breast cancer. The initial phase III study in metastatic breast cancer evaluated bevacizumab and capecitabine versus capecitabine alone. Although a higher response rate was seen in the bevacizumab-containing arm, this did not translate into improvements in either progression-free or overall survival.³⁴ Subsequently, the Eastern Cooperative Oncology Group (ECOG) 2100 randomized 680 women in the first-line setting to weekly paclitaxel 90mg/m² alone or with bevacizumab at 10mg/kg every two weeks. The addition of the angiogenesis inhibitor significantly increased response to therapy and progression-free survival, although an overall survival benefit has not been observed.³⁵ Future trials will evaluate the role of bevacizumab in combination with other chemotherapeutic agents in subsequent lines of therapy. Furthermore, oral tyrosine kinase inhibitors of the VEGF receptor, such as sunitinib, represent

an alternative anti-angiogenic approach and are under investigation in phase I and II trials.

Despite the unfavorable prognosis for women with advanced breast cancer, multiple chemotherapeutic agents exist that are active and tolerable for this patient population, leading to prolongation of survival and palliation of symptoms. Research advances have refined dosing schedules to enhance efficacy and minimize toxicity, and the addition of new agents, including nanoparticle albumin-bound paclitaxel and ixabepilone, have broadened the available selection of therapies. Furthermore, the advent of biologic targeted therapies, including the addition of trastuzumab, lapatinib, and bevacizumab, has improved our ability to destroy tumor tissue while sparing the patient the traditional chemotherapy-related toxicities. Future advances will include better identification of tumor subsets, allowing improved tailoring of therapy and continued rapid development of biologic therapies. It is hoped that ongoing progress in the research laboratory will translate expediently into emerging agents that may improve patient outcomes in the clinic. ■

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