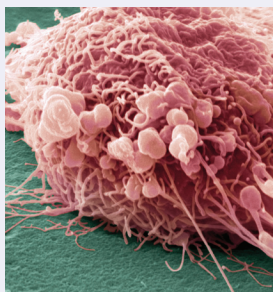


■ Introduction

Metastatic Breast Cancer Epidemiology and Management With a Focus on Taxanes

Diana Donovan, ANP



© Steve Gschmeissner/Photo Researchers

Although considerable treatment advances have been made since the early 2000s, metastatic breast cancer (MBC) continues to provide challenges for patients and healthcare providers. The responsibilities of nurses regarding the management of MBC are extensive. Among other things, nurses must provide patient education, understand treatment administration, and have the ability to perform patient assessments, as well as identify and manage symptoms. The taxanes paclitaxel, docetaxel, and *nab*-paclitaxel are a class of microtubule-stabilizing agents that are highly active against MBC but have many differences among them (e.g., formulation, administration, efficacy, tolerability profiles). Understanding those differences will aid in improving the overall patient experience. This supplement provides a historical overview of taxanes, examines the differences in their administration, and defines their efficacy and safety profiles and effects on patient quality of life. In addition, methods for assessing taxane-induced neuropathy are discussed from the nursing perspective, and treatment considerations for older adult patients with MBC are provided.

Diana Donovan, ANP, is a nurse practitioner at Weill Cornell Breast Center, New York-Presbyterian, Weill Cornell Medical Center, in New York, NY. The author received editorial support from Christopher Carter, PhD, of MediTech Media, which was funded by Celgene Corporation. The author is fully responsible for the content of and editorial decisions about this article and received no honorarium for its development. Celgene Corporation provided funding for the publication of this article and provided a medical accuracy review of content for author consideration. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff. Donovan can be reached at dianadonovannp@gmail.com, with copy to editor at CJONEditor@ons.org. (First submission October 2012. Revision submitted November 2012. Accepted for publication November 16, 2012.)

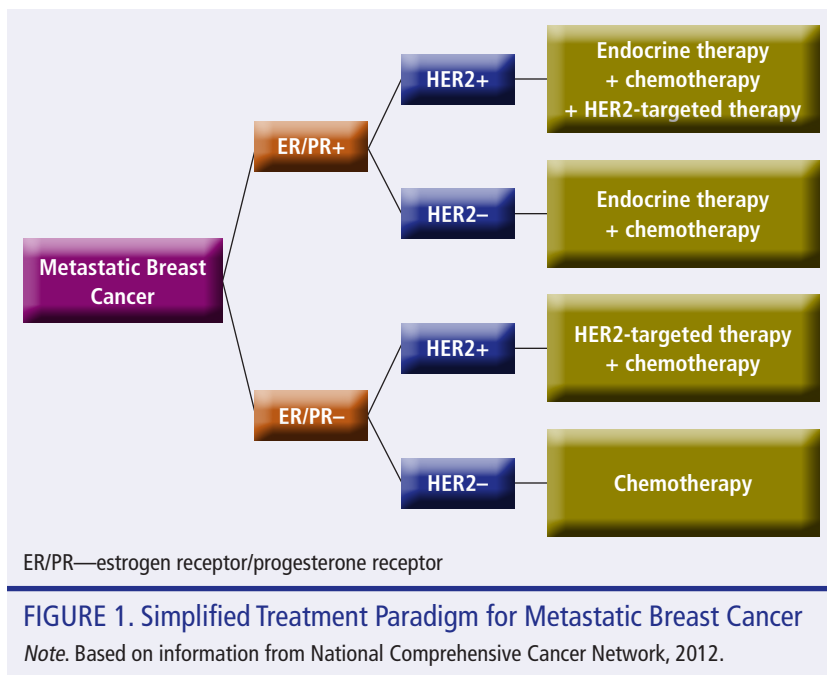
Digital Object Identifier:10.1188/13.CJON.S1.5-8

Breast cancer remains the most common cancer among women worldwide (American Cancer Society, 2011, 2012). Despite a decline in the incidence of breast cancer in the United States since the early 2000s, an estimated 226,870 new cases of breast cancer were diagnosed and 39,510 women died of breast cancer in 2012 (American Cancer Society, 2012). Since the 1990s, improved screening and methods for detection have enhanced diagnosis of early disease (Berry et al., 2005); however, about 5% of patients will be diagnosed with metastatic disease (Howlader et al., 2012). The prognosis for those patients is poor, with a five-year survival rate of 23% compared with 84%–99% for those with early-stage breast disease (American Cancer Society, 2012). In addition, disease recurrence at a distant metastatic site is common, occurring in as many as 30% of women initially diagnosed with an earlier-stage breast cancer (Early Breast Cancer Trialists' Collaborative Group [EBCTCG], 2005).

In the absence of curative treatments for patients with metastatic breast cancer (MBC), the goal of therapy remains palliative (i.e., to improve or lessen symptoms, improve qual-

ity of life, prolong survival, and delay disease progression) (O'Shaughnessy, 2005). Current management strategies must maintain a fine balance among controlling disease, prolonging survival, and maintaining quality of life. Breast cancer is a complex and heterogeneous disease composed of multiple distinct subtypes (Curtis et al., 2012). As a result, care is individualized based on tumor characteristics, including hormone receptor (HR) and HER2 status, previous therapies, patient performance status, extent of disease, presence of symptoms, and patient preference (Hurtig, 2010; O'Shaughnessy, 2005) (see Figure 1).

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, or exemestane) or antiestrogen agents (tamoxifen or fulvestrant) has demonstrated efficacy in patients with tumors positive for estrogen or progesterone expression (Bergh et al., 2012; Bonnetterre et al., 2000; Mouridsen et al., 2003; Paridaens et al., 2008). Patients who experience disease progression on hormonal therapy may benefit from additional treatment with a different class of hormonal agent (Chia et al., 2008; Pery et al., 2007).



In patients with MBC who have HER2-positive disease, agents targeting the HER2 receptor, including trastuzumab, lapatinib, and pertuzumab, have demonstrated significant clinical benefit when used in combination with systemic chemotherapy with respect to reduction of tumor burden and prolongation of overall survival (National Comprehensive Cancer Network [NCCN], 2012). As with HR-positive disease, patients who experience disease progression on anti-HER2 therapy have been shown to derive a modest benefit from additional therapy with an alternate anti-HER2 therapy. For example, patients progressing on trastuzumab may benefit from therapy with lapatinib (Von Minckwitz et al., 2011).

For patients with MBC with HR-negative disease, those with HR-positive disease with symptomatic visceral metastases, or those who are refractory to hormone therapy, current guidelines recommend systemic chemotherapy (NCCN, 2012). Systemic chemotherapy, the mainstay of management for patients with MBC, can reduce tumor burden and has been shown to prolong survival and improve quality of life (NCCN, 2012). To date, several classes of cytotoxic chemotherapy with different efficacy and tolerability profiles are recommended for the treatment of MBC (see Table 1). Of the recommended agents, taxanes (paclitaxel, docetaxel, and *nab*-paclitaxel) have well-established efficacy and safety profiles in the treatment of MBC. With the advent of taxane therapy, patients with MBC requiring chemotherapy have experienced improved outcomes compared with previous standard-of-care regimens (Bishop et al., 1999; Gradishar et al., 2005, 2009, 2011; Nabholz et al., 1993).

Taxanes for the Treatment of Metastatic Breast Cancer

Taxanes act by stabilizing microtubules, leading to inhibition of cell proliferation (Bettelheim, Brown, Campbell, &

Farrell, 2010). One of the major differences among the taxanes is formulation; docetaxel (sanofi-aventis, 2010) and paclitaxel (Bristol-Myers Squibb, 2011) are formulated with solvents, whereas *nab*-paclitaxel (Celgene Corporation, 2012) is formulated with albumin. That difference in solvents translates to differences in toxicity profiles and administration concerns (Bristol-Myers Squibb, 2011; Celgene Corporation, 2012; sanofi-aventis, 2010). Nurses play a key role in monitoring taxane-related side effects and educating patients on the signs and symptoms of toxicities. For nurses, being aware of potential taxane-related symptoms, being able to recognize them, and understanding their management in patients with MBC is critical. In addition, nurses must encourage patients to be forthcoming about any symptoms they experience. Among the key issues with taxanes and other microtubule inhibitors, sensory neuropathy is a potential toxicity that, if not monitored, can leave a patient with permanent neuronal damage (Hausheer, Schilsky, Bain, Berghorn, & Lieberman, 2006; Pachman, Barton, Watson, & Loprinzi, 2011; Ribeiro et al., 2012). In addition, comorbid conditions may place a patient at increased risk for developing peripheral neuropathy; therefore, being aware of and educating patients on these potential issues is important (Schneider et al., 2012). Symptoms such as fatigue can indicate a potential hematologic issue (e.g., taxane-induced neutropenia, anemia) (Wicklin Gillespie, 2005). Those symptoms often are indicative of many underlying issues and may not always be recognized by the healthcare provider as key taxane-related toxicity concerns. Fortunately, a number of tools exist that can be used in the assessment of patients receiving taxane therapy. Toxicities associated with taxane therapy also can affect patient quality of life; therefore, the appropriate assessment and management of patients receiving taxane therapy can help to improve quality of life for many patients.

Aim of the Supplement

The intent of this supplement is to provide an overview of taxane therapy for the treatment of MBC. The first article discusses the evolution of taxanes in the treatment of MBC, including concerns with regard to the solvent used to formulate each taxane. The second article discusses the efficacy and safety profiles of each taxane in the first-line setting, along with administration and key tolerability issues of each taxane. The third article offers insight into the assessment and management of taxane-related neuropathy, including current assessment tools. The fourth article provides a case study and a commentary on taxane-related quality-of-life considerations from a nursing perspective. This supplement concludes with special considerations in the management of older adult patients with MBC. The goal is a greatly improved patient experience through a greater understanding of the chemotherapeutic agents used in the treatment of MBC.

TABLE 1. Current Agents Recommended for the Treatment of Metastatic Breast Cancer

Microtubule Inhibitors	Vinca Alkaloids	Alkylating Agents	Anthracyclines	Targeted Therapies	Antimetabolites	Topoisomerase Inhibitors
Agents						
Paclitaxel	Vinblastine	Cisplatin	Doxorubicin	Trastuzumab	5-Fluorouracil	Etoposide
Docetaxel	Vinorelbine	Cyclophosphamide	Epirubicin	Lapatinib	Gemcitabine	Mitoxantrone
<i>nab</i> -Paclitaxel	–	Carboplatin	–	Pertuzumab	Capecitabine	–
Eribulin	–	–	–	–	–	–
Ixabepilone	–	–	–	–	–	–
Major Toxicity Concerns						
Neuropathy	Neuropathy	Nephrotoxicity	Cardiotoxicity	Cardiotoxicity	Gastrointestinal	Cardiotoxicity
Myelosuppression	Myelosuppression	Myelosuppression	Tissue necrosis if extravasation during infusion	Pulmonary toxicity	Coagulopathy	Development of secondary acute myelogenous leukemia
Hypersensitivity (solvent-based agents ^a)	Pulmonary toxicity	Hypersensitivity	Myelosuppression	Hepatotoxicity	Myelosuppression	Myelosuppression
Cardiotoxicity (eribulin)	Gastrointestinal toxicity	Urinary system toxicity (cyclophosphamide)	Infusion reactions	Infusion reactions	Nephrotoxicity	Neuropathy
Infusion reactions	Cardiotoxicity	Cardiotoxicity	–	–	–	–
–	Infusion reactions	Infusion reactions	–	–	–	–
^a Paclitaxel and docetaxel						
Note. Based on information from National Comprehensive Cancer Network, 2012; U.S. Food and Drug Administration, 2012.						

References

- American Cancer Society. (2011). *Global facts and figures* (2nd ed.). Atlanta, GA: Author.
- American Cancer Society. (2012). *Cancer facts and figures 2012*. Atlanta, GA: Author.
- Bergh, J., Jönsson, P.E., Lidbrink, E.K., Trudeau, M., Eiermann, W., Brattström, D., . . . Henriksson, R. (2012). FACT: An open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *Journal of Clinical Oncology*, *30*, 1919–1925.
- Berry, D.A., Cronin, K.A., Plevritis, S.K., Fryback, D.G., Clarke, L., Zelen, Z., . . . for the Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. (2005). Effect of screening and adjuvant therapy on mortality from breast cancer. *New England Journal of Medicine*, *353*, 1784–1792.
- Bettelheim, F.A., Brown, W.H., Campbell, M.K., & Farrell, S.O. (2010). Organic chemistry. In F.A. Bettelheim, W.H. Brown, M.K. Campbell, & S.O. Farrell (Eds.), *Introduction to organic and biochemistry* (7th ed., pp. 307–322). Belmont, CA: Brooks/Cole, Cengage Learning.
- Bishop, J.F., Dewar, J., Toner, G.C., Smith, J., Tattersall, M.H.N., Olver, I.N., . . . Canetta, R. (1999). Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. *Journal of Clinical Oncology*, *17*, 2355–2364.
- Bonnetterre, J., Thürlimann, B., Robertson, J.F.R., Krzakowski, M., Mauriac, L., Koralewski, P., . . . von Euler, M. (2000). Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *Journal of Clinical Oncology*, *18*, 3748–3757.
- Bristol-Myers Squibb. (2011). *Taxol® (paclitaxel)* [Prescribing information]. Retrieved from http://packageinserts.bms.com/pi/pi_taxol.pdf
- Celgene Corporation. (2012). *Abraxane® (nab-paclitaxel)* [Prescribing information]. Retrieved from http://www.abraxane.com/hcp/download/Abraxane_Prescribing_Information.pdf
- Chia, S., Gradishar, W., Mauriac, L., Bines, J., Amant, F., Federico, M., . . . Piccart M. (2008). Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFFECT. *Journal of Clinical Oncology*, *26*, 1664–1670. doi:10.1200/JCO.2007.13.5822
- Curtis, C., Shah, S.P., Chin, S.F., Turashvili, G., Rueda, O.M., Dunning, M.J., . . . Aparicio, S. (2012). The genomic and transcriptomic architecture of 2,000 breast tumors reveals novel subgroups. *Nature*, *486*, 346–352. doi:10.1038/nature10983

- Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*, *365*, 1687-1717. doi:10.1016/S0140-6736(05)66544-0
- Gradishar, W.J., Krasnojon, D., Cheporov, S., Makhson, A.N., Manikhas, G.M., Clawson, A., & Bhar, P. (2009). Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *Journal of Clinical Oncology*, *27*, 3611-3619. doi:10.1200/JCO.2008.18.5397
- Gradishar, W.J., Krasnojon, D., Cheporov, S.V., Makhson, A.N., Manikhas, G.M., Clawson, A., & Iglesias, J. (2011). *Nab-paclitaxel versus docetaxel for the first-line treatment of metastatic breast cancer: Final overall survival (OS) analysis of a randomized phase 2 trial* [Poster 275]. Poster presented at the American Society of Clinical Oncology Annual Meeting, Chicago, IL.
- Gradishar, W.J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., . . . O'Shaughnessy, J. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *Journal of Clinical Oncology*, *23*, 7794-7803. doi:10.1200/JCO.2005.04.937
- Hausheer, F.H., Schilsky, R.L., Bain, S., Berghorn, E.J., & Lieberman, F. (2006). Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Seminars in Oncology*, *33*, 15-49. doi:10.1053/j.seminoncol.2005.12.010
- Howlader, N., Noone, A.M., Krapcho, M., Neyman, N., Aminou, R., Altekruse, S.F., . . . Cronin, K.A. (Eds.). (2012). *SEER cancer statistics review, 1975-2009*. Retrieved from http://seer.cancer.gov/csr/1975_2009_pops09
- Hurtig, J. (2010). Managing patients with advanced and metastatic breast cancer: Taxanes and epothilones. *Clinical Journal of Oncology Nursing*, *14*, 313-323. doi:10.1188/10.CJON.313-323
- Mouridsen, H., Gershanovich, M., Sun, Y., Pérez-Carrión, R., Boni, C., Monnier, A., . . . Bhatnagar, A. (2003). Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *Journal of Clinical Oncology*, *21*, 2101-2109. doi:10.1200/JCO.2003.04.194
- Nabholtz, J.M., Falkson, C., Campos, D., Szanto, J., Martin, M., Chan, S., . . . Poulliart, P. (1993). Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial. *Journal of Clinical Oncology*, *21*, 968-975.
- National Comprehensive Cancer Network. (2012). *NCCN Clinical Practice Guidelines in Oncology: Breast cancer* [v.3.2012]. Retrieved from http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
- O'Shaughnessy, J. (2005). Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*, *10*(Suppl. 3), 20-29. doi:10.1634/theoncologist.10-90003-20
- Pachman, D.R., Barton, D.L., Watson, J.C., & Loprinzi, C.L. (2011). Chemotherapy-induced peripheral neuropathy: Prevention and treatment. *Clinical Pharmacology and Therapeutics*, *90*, 377-387. doi:10.1038/clpt.2011.115
- Paridaens, R.J., Dirix, L.Y., Beex, L.V., Nooij, M., Cameron, D., Cufer, T., . . . Therasse, P. (2008). Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: The European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *Journal of Clinical Oncology*, *30*, 4883-4890. doi:10.1200/JCO.2007.14.4659
- Perey, L., Paridaens, R., Hawle, H., Zaman, K., Nolé, F., Wildiers, H., . . . Thürlimann, B. (2007). Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: Final results of phase II Swiss Group for Clinical Cancer Research trial (SAKK 21/00). *Annals of Oncology*, *18*, 64-69. doi:10.1093/annonc/mdl341
- Ribeiro, J.T., Macedo, L.T., Curigliano, G., Fumagalli, L., Locatelli, M., Dalton, M., . . . Goldhirsch, A. (2012). Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: Back to the future? *Annals of Oncology*, *23*, 547-555. doi:10.1093/annonc/mdr382
- sanofi-aventis. (2010). *Taxotere® (docetaxel)* [Prescribing information]. Retrieved from <http://products.sanofi.us/Taxotere/taxotere.html>
- Schneider, B.P., Zhao, F., Wang, M., Stearns, V., Martino, S., Jones, V., . . . Sparano, J.A. (2012). Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *Journal of Clinical Oncology*, *20*, 3051-3057. doi:10.1200/JCO.2011.39.8446
- U.S. Food and Drug Administration. (2012). Drugs@FDA: FDA approved drug products. Retrieved from <http://www.accessdata.fda.gov/scripts/cder/drugsatfda>
- Von Minckwitz, G., Schwedler, K., Schmidt, M., Barinoff, J., Mundhenke, C., Cufer, T., . . . Loibl, S. (2011). Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *European Journal of Cancer*, *47*, 2273-2281. doi:10.1016/j.ejca.2011.06.021
- Wicklin Gillespie, T. (2005). Implementation of the NCCN practice guidelines: Anemia and neutropenia. *Advanced Studies in Nursing*, *3*, 300-309.