

Taxane Chemotherapy—Advances in Treatment for Breast Cancer

a report by

Debra K Frye, RN, BSN, OCN, CCRP

Research Nurse Manager, Department of Breast Medical Oncology,
University of Texas MD Anderson Cancer Center

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Debra K Frye, RN, BSN, OCN, CCRP, is Research Nurse Manager in the Department of Breast Medical Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas. She is an experienced breast cancer nurse clinician and researcher, as well as author and educator. Ms Frye has co-authored over 50 papers, six book chapters, and more than 75 abstracts on novel therapies for breast cancer and associated nursing and other clinical issues as well as developing educational materials for patients with this malignancy. She has spent her entire 30-year career in oncology nursing at the University of Texas, MD Anderson Cancer Center in Houston, Texas, where she began as an inpatient staff nurse in general oncology and progressed to outpatient clinic nurse, clinic nurse manager, senior research nurse and research nurse supervisor, all in the Department of Breast Medical Oncology.

The chance of developing invasive breast cancer sometime in a woman's life is about one in eight (13% of women). In fact, breast cancer is the most common cancer among women, except for non-melanoma skin cancer, and women living in North America have the highest rate of breast cancer in the world. In 2006, about 212,920 new cases of invasive breast cancer will be diagnosed among women in the US, and an estimated 1,720 cases of breast cancer will be diagnosed in men. Breast cancer is the second leading cause of cancer death in women, exceeded only by lung cancer. In 2006, 40,970 women and 460 men will die from breast cancer. Fortunately, death rates from breast cancer have been declining since 1990, believed to be the result of early detection and improved treatment. Two studies that explored survival of patients with recurrent breast cancer over the past two to three decades have suggested that the improvement in recent years is associated with introduction of taxane therapy.

In metastatic breast cancer, cytotoxic chemotherapy is the treatment of choice for patients with hormone receptor negative tumors, refractory to hormone therapy, or with rapidly progressive disease, regardless of hormone status. The choice of optimum chemotherapy is dependent on several factors, such as the type of previous adjuvant chemotherapy, the aggressiveness of the disease, the site(s) of metastases, the patient's age and the toxicity profile.

Initial chemotherapy choices for the treatment of newly diagnosed and metastatic breast cancer have dramatically changed over the past four decades, evolving from marginally effective non-anthracycline single agent therapies to non-anthracycline containing combinations, such as cyclo-phosphamide, methotrexate, and 5-fluorouracil (CMF) and CMF plus vincristine and prednisone (CMFVP). In the latter 1970s and throughout the 1980s, the use of anthracycline-containing regimens, such as 5-fluorouracil, adriamycin and cyclo-phosphamide, (FAC), cyclo-phosphamide, doxorubicin and 5-fluorouracil (CAF) and adriamycin and cyclo-phosphamide (AC), resulted in higher response rates and longer time-to-progression, but failed to show survival advantage in metastatic disease. During the 1980s many investigational agents were explored in clinical trials with hope of improvement in the patient's response to

therapy, duration of response and increased survival. Unfortunately, the majority of these agents failed to show benefit and/or produced unacceptable toxicities.

The taxanes are a class of anticancer agents that bind to and stabilize microtubules causing cell-cycle arrest and apoptosis (cell death). Paclitaxel, initially extracted from the bark of the Pacific yew, *Taxus brevifolia*, was identified in 1971 as part of a National Cancer Institute (NCI) program that screened medicinal plants for potential activity. Docetaxel was synthesized in 1986, using a precursor extracted from the needles of the European yew, *T. baccata*, and is similar to paclitaxel in its mechanism of action.

Results from clinical trials designed in the late 1980s have shown that taxanes are among the most active chemotherapy agents used in the management of metastatic breast cancer. Positive trials in the adjuvant and neoadjuvant setting have more recently changed practice standards. These agents may be considered the most powerful group of compounds developed in the 1990s.

Paclitaxel (Taxol®) and docetaxel (Taxotere®) are generally well tolerated. Most of the common side effects are easily reversible and largely preventable. Hypersensitivity is infrequent but potentially serious. It occurs rarely if appropriate pre-medication, such as dexamethasone, diphenhydramine and/or an H2 antagonist, is given. Hypersensitivity occurs in about 10% of patients treated with paclitaxel due to cremaphor in the paclitaxel preparation, with anaphylaxis and severe hypersensitivity reactions in 2-4% (characterized by dyspnea, hypotension, angioedema and generalized urticaria). Those with less severe reactions have been given increased corticosteroid prophylaxis, and have been successfully rechallenged with slower infusions of drug. Significantly less hypersensitivity is observed when paclitaxel is given weekly.

Patients receiving either paclitaxel or docetaxel are at risk for severe neutropenia, neutropenic fever and infections. Anemia occurs frequently but thrombocytopenia is rare.

Fatigue, malaise and generalized weakness may occur with either taxane.

Complete alopecia occurs in most patients and is reversible. Nail changes, such as hyperpigmentation and ridging, are common. A partial separation of the nail plate (onycholysis) may occur. Nausea, vomiting, anorexia, diarrhea, stomatitis, liver function test abnormalities and metallic or bitter taste sensations may occur but are usually mild. Hypotension and bradycardia during the first 3 hours of infusion have been reported but are infrequent. Significant cardiovascular events, including CHF are rare with single agent paclitaxel but patients are at increased risk if paclitaxel is combined with cisplatin, doxorubicin or trastuzumab.

Peripheral neuropathies are a common side effect of paclitaxel and may occur with docetaxel, especially if high cumulative doses are administered. Symptoms usually resolve two or months after taxane discontinuation. Symptoms may be increased in those patients with predisposed neuropathy due to diabetes or alcohol ingestion. Arthralgias and myalgias affect 60% of paclitaxel treated patients, primarily in the lower extremities, beginning two to three days after treatment, and usually resolving within 24–72 hours. Arthralgia and myalgia are infrequent and mild post docetaxel.

Colitis is a rare but serious gastrointestinal complication associated with taxane-based chemotherapy, seen more frequently seen in patients receiving docetaxel and with onset of symptoms at approximately day six of treatment. Reports by patients of acute abdominal pain could signal a potentially fatal colitis and warrant aggressive supportive care.

Fluid retention, unrelated to cardiotoxicity, is a cumulative toxicity that may occur in docetaxel treated patients and may be minimized by using the three-day regimen of dexamethasone prior to each treatment. Severe fluid retention occurs in up to 6.5% of patients. Fluid retention usually appears as peripheral edema but may present as pleural effusion and usually resolves completely within 16 weeks of the last docetaxel dose. Other docetaxel-related side effects are skin rash and/or pruritis, palmar-plantar erythrodysesthesia (hand-foot syndrome) and epiphora or hyperlacrimation (watery eyes). The latter can occur as a result of lacrimal duct stenosis in patients treated with docetaxel, appears related to cumulative dose and resolves after treatment is stopped.

In premenopausal women, the addition of a taxane to standard adjuvant anthracycline-based chemotherapy does not appear to produce a higher rate of chemotherapy-related amenorrhea compared with patients who did not receive taxanes. In fact, taxanes may decrease the risk of amenorrhea. Women with breast cancer often express initial worry that a subsequent pregnancy may increase their risk of recurrence. The

accumulated evidence at present shows that women with breast cancer treated with standard regimens do not have adverse clinical outcomes with subsequent pregnancy. The effect of the taxanes on pregnancy is being studied. Interestingly, a normal male infant was delivered post administration of paclitaxel during pregnancy per a case report from UT MD Anderson Cancer Center.

Three systematic reviews of taxane-based therapy show significant benefit in patients with metastatic and node-positive breast cancer. The available data from each of the three pooled analyses suggest that docetaxel may be more active than paclitaxel, especially when given in three-weekly schedules. Studies also indicate improved benefit in locally advanced and inflammatory breast cancer when taxanes are added to their regimen. Combinations of paclitaxel or docetaxel with doxorubicin, epirubicin, capecitabine, gemcitabine, cyclophosphamide and carboplatin in doublets or triplets have shown improvement with the addition of the taxane. Also, the addition of trastuzumab to taxane-based chemotherapy increases the efficacy of taxane-based regimens in women with stage 4 HER2-positive breast cancers.

The schedule of administration of drugs, particularly with paclitaxel, appears to have an impact on efficacy. The optimal schedule and dose for paclitaxel administration could be 80mg/m²/week, rather than the US Food and Drug Administration (FDA)-approved dose and schedule of 175mg/m² IV over three hours every three weeks. In contrast, the great majority of docetaxel studies were performed using 100mg/m² IV given over one hour every three weeks.

Significant response and survival benefits were shown in two practice-changing metastatic breast cancer taxane trials. The first compared capecitabine (2,500 mg/m² x 14 days) + docetaxel (75 mg/m² day one) with docetaxel (100mg/m² day one) every three weeks. Gastrointestinal adverse events and hand-foot syndrome were more common with the combination therapy, whereas febrile neutropenia, sepsis arthralgia and myalgia were more common with single-agent docetaxel. The second phase III trial, a gemcitabine/paclitaxel combination, showed superiority of this combination over paclitaxel in the first-line setting. Although grade 4 neutropenia was more common with the combination, the overall toxicities in both arms were manageable and a quality of life (QOL) analyses indicated better global scores for patients receiving combination therapy than for those receiving single-agent paclitaxel. In clinical practice, the taxanes are now standard therapy in metastatic cancer.

This article is continued, with references and a table, in the Reference Section on the website supporting this briefing (www.touchbriefings.com). ■