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■ Article

Evolution of Taxanes in the Treatment of Metastatic Breast Cancer

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Taxanes have become effective therapies for patients with metastatic breast cancer (MBC); however, understanding the differences among them is important. Each of the taxanes currently approved for treating MBC has a unique formulation, which translates to differences in toxicity profiles and administration considerations. In this article, the rationale for the development of the taxanes paclitaxel, docetaxel, and *nab*-paclitaxel is reviewed from a historical perspective. The mechanisms of action, formulations, and indications of taxanes also are discussed. The impact of their formulations on clinical practice and patient care, particularly solvent-based versus novel solvent-free formulations, will be reviewed from the nursing perspective.

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Many approaches to the treatment of metastatic breast cancer (MBC), including surgery, radiation, chemotherapy, and biologic therapies, have been investigated with varying degrees of success. Although each of these approaches has modestly improved outcomes for some patients, no one treatment has been optimized with respect to providing a cure or reducing toxicity or disfigurement. Limited effective treatment options exist for most patients with MBC. Consequently, the five-year survival rate for patients with MBC is about 24% compared to almost 100% in patients with localized breast tumors (Howlader et al., 2012). Therefore, the importance of improving outcomes in patients with MBC is clear. In the evolution of treatment for MBC, the taxane family of chemotherapy drugs was found to contribute to the improvement in outcomes for many patients with MBC. This article provides an overview of the rationale for the development of paclitaxel, docetaxel, and *nab*-paclitaxel, as well as a comparison of the formulations, dosing schedules, efficacy, and toxicity profiles of each taxane.

Paclitaxel

In 1969, the first taxane, paclitaxel, was isolated from the bark of *Taxus brevifolia* (Pacific yew tree) (Kingston, 2007). In the late 1970s, as part of a program initiated by the National Cancer Institute, paclitaxel demonstrated activity against colon and mammary tumors in mice (Kingston, 2007). It was later shown that paclitaxel's mechanism of action—stabilization of microtubules—was different than that of previously identified anticancer compounds that affect DNA/RNA or destroy microtubules (Kingston, 2007; Wilson, Creswell, & Chin, 1975). Microtubules are dynamic (see Figure 1). During the nongrowth stage, microtubules are continually built on one end (plus end) by the addition of tubulin dimers (polymerization), whereas tubulin dimers are continually removed (depolymerization) on the other end of the microtubule (minus end) (Alberts et al., 2002). This process is referred to as treadmilling (Lodish et al., 2000). During phases of lengthening and shortening, microtubule depolymerization can occur at the plus end as well (Lodish et al., 2000). The balance between polymerization and depolymerization is tightly regulated and affects the length of the microtubules (Lodish et al., 2000). The varying lengths of the microtubules are important for cellular structure and processes such as mitosis (Lodish et al., 2000). Taxanes bind to the inner surface of microtubules and function by affecting polymerization and depolymerization (Lodish et al., 2000). Paclitaxel was the first anticancer compound observed to promote microtubule assembly and inhibit depolymerization (Kingston, 2007;

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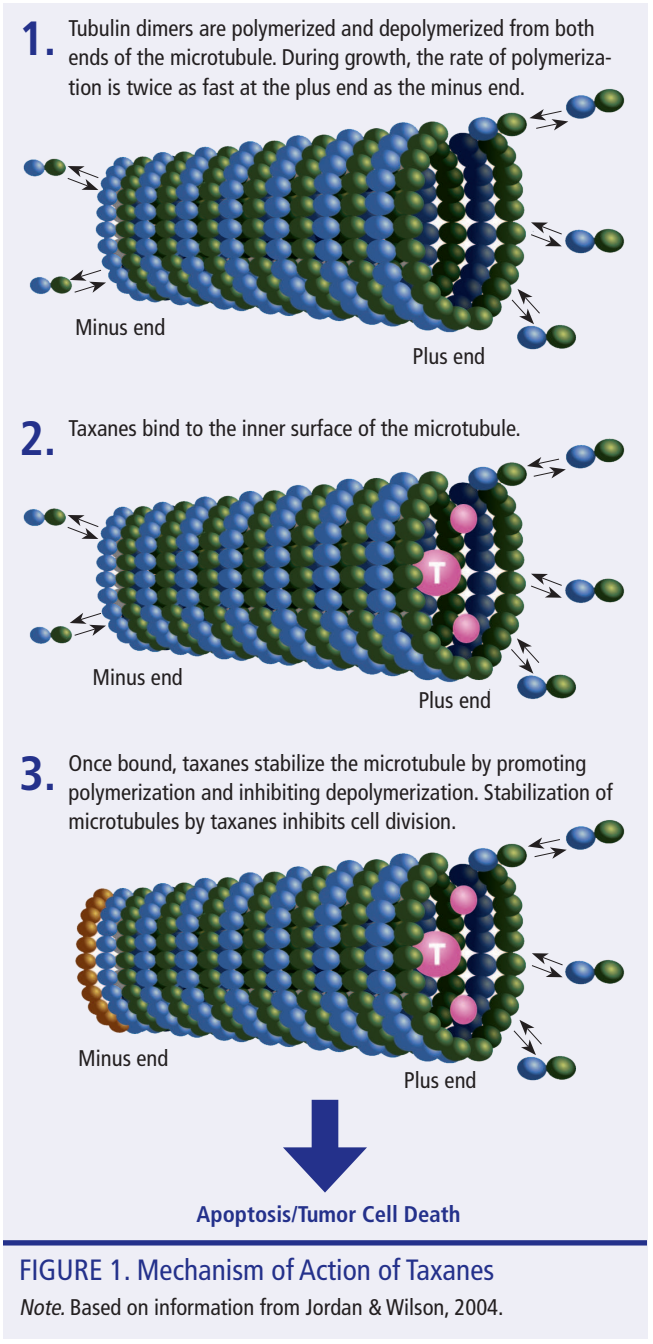


FIGURE 1. Mechanism of Action of Taxanes

Note. Based on information from Jordan & Wilson, 2004.

Rowinsky & Donehower, 1995; Schiff, Fant, & Horwitz, 1979). This results in inhibition of cell division and leads to cell death or apoptosis (Bettelheim, Brown, Campbell, & Farrell, 2010).

The discovery of a potential anticancer compound with a unique mechanism of action caused significant interest in drug development; however, difficulties with developing a sustainable source and formulation slowed the clinical development of paclitaxel (Kingston, 2007). The yield of paclitaxel from the Pacific yew tree is extremely low because only the bark contains enough paclitaxel to isolate usable quantities. In addition, the isolation process kills the tree (Bettelheim et al., 2010; Kingston, 2007). Therefore, the supply from the Pacific yew tree was, and still is, very limited. Numerous methods were tried to produce paclitaxel from other sources, but, to date, manufacturing mainly comes from plant tissue cultures (Kingston, 2007; Malik et al., 2011). Despite those efforts, paclitaxel still is on the American Society of Health-System Pharmacists' drug shortage list (American Society of Health-System Pharmacists, 2013).

The inability to easily dissolve paclitaxel in water for parenteral administration was another obstacle in its clinical development (Kingston, 2007). After much effort, Cremophor® EL (now renamed Kolliphor® EL), a castor oil derivative, and dehydrated ethanol were determined to be the most appropriate solvents for paclitaxel (Kingston, 2007; ten Tije, Verweij, Loos, & Sparreboom, 2003). The final formulation consists of a 1:1 solution of paclitaxel to Cremophor EL and dehydrated ethanol to arrive at solvent-based paclitaxel (Bristol-Myers Squibb, 2011). Cremophor EL is not an inert solvent because it can produce a range of biologic effects, some of which have important clinical implications (Gelderblom et al., 2002). Its use has been associated with severe anaphylactic hypersensitivity reactions, hyperlipidemia, abnormal lipoprotein patterns, aggregation of erythrocytes, and peripheral neuropathy (Adams, Flora, Goldspeil, Wilson, & Arbuck, 1993; Huttel, Olesen, & Stoffersen, 1980; Kongshaug, Cheng, Moan, & Rimington, 1991; Watkins, Ward, & Appleyard, 1997; Windebank, Blexrud, & de Groen, 1994; Woodburn & Kessel, 1994). Although the exact mechanisms behind these phenomena are not well understood, several theories exist, such as Cremophor EL-induced complement activation and histamine release in the case of hypersensitivity reactions (Gelderblom et al., 2002).

In 1994, paclitaxel received approval from the U.S. Food and Drug Administration (FDA) for the treatment of MBC after failure of combination chemotherapy or relapse within six months of adjuvant anthracycline-containing chemotherapy (Bristol-Myers Squibb, 2011; Cortazar et al., 2012; Rowinsky & Donehower, 1995). The FDA approval was based on the findings from a randomized study comparing the therapeutic index of paclitaxel given at 175 mg/m^2 or 135 mg/m^2 every three weeks (Cortazar et al., 2012). In that study, the higher dose of paclitaxel demonstrated an encouraging overall response rate (29%) and median overall survival (11.7 months) in 235 patients with MBC whose tumors did not respond to previous chemotherapy (Nabholtz et al., 1996). Of note was the fact that the response achieved in patients previously exposed or resistant to anthracyclines (n = 303) was similar to the response in those without such prior exposure (n = 147) (Nabholtz et al., 1996). The most common severe adverse event in the high- and low-dose arms was neutropenia (67% and 50%, respectively), and 7% and 3% of patients in the high- and low-dose arms, respectively, developed severe neuropathy (Nabholtz et al., 1996).

The approved dose and schedule of paclitaxel for the treatment of breast cancer is 175 mg/m^2 given every three weeks (Bristol-Myers Squibb, 2011). A three-hour infusion of paclitaxel is recommended for patients with breast cancer; however, a 24-hour infusion is recommended for patients with other tumor types (Bristol-Myers Squibb, 2011). Subsequently, paclitaxel also was approved for administration after standard doxorubicin-containing combination chemotherapy for the adjuvant treatment of node-positive breast cancer (Bristol-Myers Squibb, 2011).

One limitation of paclitaxel is the increased risk of potentially life-threatening hypersensitivity reactions and peripheral neuropathy (both of which can be associated with the Cremophor

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EL excipient) (Authier, Gillet, Fialip, Eschalier, & Coudore, 2000; de Groen, Aksamit, Rakela, Forbes, & Krom, 1987; ten Tije et al., 2003; Windebank et al., 1994). Efforts to reduce the risk of hypersensitivity reactions, including lengthy infusion protocols and premedication with corticosteroids and antihistamines, have resulted in reduced frequency and severity of hypersensitivity reactions (Bristol-Myers Squibb, 2011; Kingston, 2007). Another limitation of paclitaxel related to its formulation is that Cremophor EL can entrap paclitaxel in micelles when in contact with the blood, which reduces the bioavailability of the drug (Sparreboom et al., 1999). This entrapment may result in nonlinear paclitaxel pharmacokinetics (i.e., fluctuations in blood paclitaxel concentration) (Gianni et al., 1995; Sparreboom et al., 1999; ten Tije et al., 2003). Entrapment of other agents used in combination with Cremophor EL-based paclitaxel also can occur, affecting their pharmacokinetic profile as well (Gianni et al., 1995; Sparreboom et al., 1999). Because paclitaxel has nonlinear pharmacokinetics, it can be difficult to predict responses with changes in dosing (Gianni et al., 1995; ten Tije et al., 2003). The formulation of paclitaxel also has an impact on nursing practice as specialized polyethylene-lined IV administration sets are required because of the risk of chemical leaching caused by Cremophor EL (Bristol-Myers Squibb, 2011). To improve the efficacy and safety profile of paclitaxel, studies have examined different schedules for paclitaxel and demonstrated that weekly paclitaxel was more effective than the every-three-weeks schedule (Seidman et al., 2008; Sparano et al., 2008). Although the weekly schedule was associated with a greater incidence of severe neurosensory toxicities, generally the rates of most other severe toxicities were not significantly different between the schedules (Seidman et al., 2008; Sparano et al., 2008).

Docetaxel

During the process of searching for alternate sources of paclitaxel, docetaxel (a semisynthetic analog of paclitaxel) was developed (Malik et al., 2011). Docetaxel is slightly different than paclitaxel in chemical structure and solubility (Kingston, 2007). Docetaxel is slightly more soluble in water than paclitaxel and is formulated using the solvent polysorbate 80 (ten Tije et al., 2003). The mechanism of action of docetaxel on microtubules, however, is the same as paclitaxel (Kingston, 2007; Malik et al., 2011).

Polysorbate 80, like Cremophor EL, can form micelles in aqueous solutions (ten Tije et al., 2003); the pharmacokinetic profile of docetaxel appears to be linear but may vary in certain individuals and at doses higher than those generally administered (Kearns, 1997; McLeod, Kearns, Kuhn, & Bruno, 1998). In addition, polysorbate 80 has been linked to hypersensitivity reactions (Coors, Seybold, Merk, & Mahler, 2005); therefore, premedication with steroids is required for docetaxel (sanofi-aventis, 2010). As with paclitaxel, specialized polyethylene-lined IV administration sets are required for docetaxel to prevent the leaching of chemicals from typical infusion bags and tubing (sanofi-aventis, 2010). Docetaxel received accelerated approval from the FDA for MBC in 1996 based on the results of six single-arm trials that demonstrated an overall response rate of about 38% in patients who were anthracycline resistant (Cortazar et al., 2012). Additional results from the randomized phase III TAX 304 trial of docetaxel (100 mg/m^2 every three weeks) in patients with anthracycline-resistant MBC confirmed the efficacy of docetaxel, with an overall response rate of 30% and a median overall survival of 11.4 months (Nabholtz et al., 1999). Of the 203 patients receiving docetaxel in the trial, 93% experienced grade 3 or 4 neutropenia. The results of the TAX 304 trial were the basis for the regular approval of docetaxel in 1998 (Cortazar et al., 2012). Docetaxel administered sequentially with doxorubicin and cyclophosphamide is currently indicated for the treatment of MBC after failure of prior chemotherapy and for the adjuvant treatment of node-positive breast cancer (sanofi-aventis, 2010). Docetaxel at a dose of 60–100 mg/m^2 typically is administered over one hour every three weeks (sanofi-aventis, 2010).

A phase III trial directly comparing every-three-weeks schedules of docetaxel and paclitaxel demonstrated improved efficacy of docetaxel compared with paclitaxel in patients with MBC (Jones et al., 2005). The median overall survival in the intent-to-treat population was significantly longer for docetaxel compared with paclitaxel (15.4 versus 12.7 months, $p = 0.03$). However, subsequent studies demonstrated that the weekly schedule of paclitaxel was more effective than the every-three-weeks schedule in patients with breast cancer in terms of response and survival outcomes (Seidman et al., 2008; Sparano et al., 2008). The less favorable toxicity profile of docetaxel observed in the Jones et al. (2005) study suggested the need to further improve taxane-based therapy.

nab-Paclitaxel

nab-Paclitaxel was developed based on a need to improve on the efficacy and safety profiles of the initially developed taxanes. *nab*-Paclitaxel consists of paclitaxel formulated with albumin (Gardner et al., 2008). Albumin facilitates the transport of poorly soluble molecules in the blood, such as hormones, fatty acids, and certain types of drugs (Prajapati, Sharma, & Roy, 2011). Therefore, *nab*-paclitaxel was designed to exploit the natural properties of albumin to facilitate delivery of paclitaxel to the tumor. In a pharmacokinetic study of *nab*-paclitaxel versus solvent-based paclitaxel (formulated in Cremophor EL and ethanol), a higher systemic exposure of free paclitaxel (active drug) was observed in patients receiving *nab*-paclitaxel (Gardner et al., 2008); this was likely caused by the differences in formulation between the drugs. Preclinical studies have demonstrated that *nab*-paclitaxel is better at reaching tumors than solvent-based paclitaxel (i.e., a significantly higher intratumoral paclitaxel accumulation) and that

Exploration on the Go

The development of paclitaxel from the Pacific yew tree was not without controversy. To find out more, open a barcode scanner on your smartphone, take a photo of the code, and your phone will link automatically. Or visit http://toxipedia.org/display/toxipedia/Taxanes+-+History.

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Implications for Practice

- Paclitaxel and docetaxel are formulated with solvents, requiring premedication to prevent hypersensitivity reactions, as well as polyethylene-lined IV administration sets.
- Because *nab*-paclitaxel is formulated with albumin, it does not require premedication to prevent hypersensitivity reactions or special IV administration sets.
- For patients with metastatic breast cancer, the taxanes differ in length of infusion (attributable to their formulations): 30 minutes for *nab*-paclitaxel, one hour for docetaxel, and three hours for paclitaxel.

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Cremophor EL and ethanol inhibited the binding of paclitaxel to endothelial cells (Desai et al., 2006; Gardner et al., 2008).

Although the precise mechanism for the unique albumin delivery of *nab*-paclitaxel to tumors remains under investigation, several hypotheses have been developed. One proposed mechanism is that *nab*-paclitaxel may use albumin-specific receptors on endothelial cells of blood vessels to facilitate its delivery to the tumor microenvironment (John, Vogel, Tiruppathi, Malik, & Minshall, 2003; Simionescu, Gafencu, & Antohe, 2002). A second hypothesis suggests that vasculature around tumors is leaky, allowing small molecules such as albumin to escape the circulation and collect in the tumor microenvironment (Maeda, Wu, Sawa, Matsumura, & Hori, 2000; Matsumura & Maeda, 1986). Finally, tumors may actively absorb albumin from the extracellular environment as a source of nutrients (Stehle et al., 1997).

The novel formulation with albumin allows for reconstitution of *nab*-paclitaxel with a saline solution instead of solvents (Celgene Corporation, 2012). This presents several advantages over solvent-based taxanes. For example, *nab*-paclitaxel can be administered without premedication for hypersensitivity reactions (Celgene Corporation, 2012). The absence of excipients like Cremophor EL allows for a more linear and predictable pharmacokinetic profile compared with solvent-based paclitaxel, which is important when dosage is adjusted. In addition, specialized IV administration sets are not required for *nab*-paclitaxel because of its lack of chemical solvent (Celgene Corporation, 2012). In addition, the unique albumin-based formulation may allow for enhanced delivery of *nab*-paclitaxel, such that a higher dose intensity can be achieved relative to solvent-based paclitaxel (Gradishar et al., 2005).

nab-Paclitaxel was approved for the treatment of breast cancer in 2005 (Cortazar et al., 2012). A phase III trial compared *nab*-paclitaxel 260 mg/m^2 with solvent-based paclitaxel 175 mg/m^2, both every three weeks, as first-line or greater therapy in patients with MBC. *nab*-Paclitaxel demonstrated a significantly better overall response rate compared with solvent-based paclitaxel (33% versus 19%, $p = 0.001$), as well as a longer time to tumor progression (23 versus 17 weeks, $p = 0.006$) (Gradishar et al., 2005). The incidence of grade 4 neutropenia was significantly lower for *nab*-paclitaxel compared with standard paclitaxel (9% versus 22%, respectively; $p < 0.001$) despite a 49% higher paclitaxel dose. However, *nab*-paclitaxel was associated with a higher rate of grade 3 sensory neuropathy compared with solvent-based paclitaxel (10% versus 2%, respectively; $p < 0.001$). Of note, the time to improvement from grade 3 sensory neuropathy to grade 2 or lower was faster with *nab*-paclitaxel versus solvent-based paclitaxel (22 versus 79 days) (Cortes & Saura, 2010). The incidence of hypersensitivity reactions in that trial was low for both arms; however, patients receiving solvent-based paclitaxel were premedicated, whereas those receiving *nab*-paclitaxel were not. In 2009, weekly *nab*-paclitaxel (100 mg/m^2 or 150 mg/m^2, both given the first three of four weeks) demonstrated a higher overall response rate and longer median progression-free survival when compared with docetaxel (100 mg/m^2 every three weeks) in patients with MBC in a phase II trial (Gradishar et al., 2012). Overall survival trended in favor of the 150 mg/m^2 *nab*-paclitaxel schedule in comparison with docetaxel. Grade 3 or higher fatigue and neutropenia were less frequent with *nab*-paclitaxel compared with docetaxel, whereas neuropathy was most frequent with 150 mg/m^2 *nab*-paclitaxel. However, time to improvement in neuropathy from grade 3 to grade 2 or lower was shorter with *nab*-paclitaxel (all doses) versus docetaxel (20–22 versus 41 days) (Gradishar et al., 2012).

nab-Paclitaxel is currently indicated for the treatment of MBC after failure of combination therapy or relapse within six months of adjuvant chemotherapy; prior therapy should have included an anthracycline unless clinically contraindicated (Celgene Corporation, 2012). The indicated dose and schedule of *nab*-paclitaxel is 260 mg/m^2 every three weeks (Celgene Corporation, 2012). Because of its lack of solvent, *nab*-paclitaxel also has the shortest administration time of all of the taxanes, 30 minutes (Celgene Corporation, 2012).

Costs

An economic analysis by Force, Pugmire, and Culbertson (2010) reported that docetaxel had a higher mean unadjusted per-patient per-month (PPPM) cost compared with generic paclitaxel ($p < 0.05$), but a similar PPPM cost compared with *nab*-paclitaxel. Docetaxel was associated with a significantly higher cost of colony-stimulating factor (CSF) use compared with *nab*-paclitaxel and generic paclitaxel ($p < 0.05$) and a significantly higher cost of antiemetic and erythropoiesis-stimulating agent use compared with generic paclitaxel ($p < 0.05$ for both). Force et al. (2010) also reported that *nab*-paclitaxel had a significantly higher PPPM cost compared with generic paclitaxel ($p < 0.05$), but a similar PPPM cost compared with docetaxel. *nab*-Paclitaxel was associated with lower overall ancillary medication costs compared with the other taxanes (p was not significant). The expenditures for CSF use for *nab*-paclitaxel were significantly lower than for generic paclitaxel and docetaxel ($p < 0.05$). In addition, the costs were significantly lower for *nab*-paclitaxel compared with docetaxel for erythropoiesis-stimulating agent use ($p < 0.05$).

Conclusion

Although differences exist among the taxanes in formulation, administration, therapeutic benefit, and tolerability, taxanes

are an important addition to the arsenal of chemotherapeutic agents for MBC. Paclitaxel was the first new agent approved in almost 20 years, since doxorubicin in 1974, for the treatment of MBC (Cortazar et al., 2012). This class of agents has not only demonstrated a unique ability to improve outcomes and palliate the symptoms of many types of advanced cancers, it also has demonstrated effectiveness in early-stage cancer (Sparano, 2000). Docetaxel was subsequently developed to address the limited supply of paclitaxel from natural resources, and it demonstrated a treatment benefit but was slightly less tolerable than paclitaxel (Jones et al., 2005; Kingston, 2007). The need to improve on the tolerability profile of solvent-based taxanes gave rise to *nab*-paclitaxel. Several preclinical and clinical studies have shown that the unique solvent-free formulation of *nab*-paclitaxel was associated with more predictable dosing and a more tolerable safety profile compared with solvent-based paclitaxel and docetaxel. Ongoing studies continue to explore how *nab*-paclitaxel interacts differently with tumors and elucidate the mechanism of delivery and antitumor activity of *nab*-paclitaxel. In the next article, Laura M. Urquhart, MS, APRN-BC, OCN®, expands on the clinical experience of each of the taxanes in the first-line treatment of MBC.

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