Breast Cancer: Basic and Clinical Research

REVIEW

Safety and Efficacy of *nab*-Paclitaxel in the Treatment of Patients with Breast Cancer

Prakash Vishnu and Vivek Roy

Division of Hematology Oncology, Mayo Clinic, Jacksonville, FL, USA. Corresponding author email: roy.vivek@mayo.edu

Abstract: Taxanes are highly active chemotherapeutic agents in the treatment of early-stage and metastatic breast cancer. Novel formulations have been developed to improve efficacy and decrease toxicity associated with these cytotoxic agents. *nab*-paclitaxel is a solvent free, albumin-bound 130-nanometer particle formulation of paclitaxel (Abraxane®, Abraxis Bioscience), which was developed to avoid toxicities of the Cremophor vehicle used in solvent-based paclitaxel. In a phase III clinical trial, *nab*-paclitaxel demonstrated higher response rates, better safety and side-effect profile compared to conventional paclitaxel, and improved survival in patients receiving it as second line therapy. Higher doses can be administered over a shorter infusion time without the need for special infusion sets or pre-medications. It is now approved in the US for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant therapy, where prior therapy included an anthracycline. Recently, several phase II studies have suggested a role for *nab*-paclitaxel as a single agent and in combination with other agents for first-line treatment of metastatic breast cancer.

Keywords: *nab*-paclitaxel, *nab*-technology, paclitaxel, metastatic breast cancer, taxanes

Breast Cancer: Basic and Clinical Research 2011:5 53–65

doi: 10.4137/BCBCR.S5857

This article is available from http://www.la-press.com.

Introduction

Taxanes (eg, paclitaxel, docetaxel) and anthracyclines (eg, doxorubicin, epirubicin) remain among the most active and widely used chemotherapy agents in breast cancer, both in adjuvant and metastatic settings.[1–3] A recent meta-analyses of 13 randomized clinical trials showed a significant improvement of disease-free and overall survival (OS) rates in high-risk early stage breast cancer with chemotherapy regimens incorporating combination of taxanes and anthracyclines.[4] However, approximately 25%–30% of early stage breast cancers will recur. There is an imperative need for agents that not only overcome resistance but also have a favorable toxicity profile. The solvents used for dissolving hydrophobic molecules, paclitaxel and docetaxel are known to be associated with significant risk of hypersensitivity reactions and neuropathy and also impair drug delivery to the tumor, limiting their clinical effectiveness.[5,6]

With the advent of nanotechnology, a novel formulation of solvent free 130-*n*anometer *a*lbumin-*b*ound paclitaxel (*nab*-paclitaxel, Abraxane®, Abraxis Bioscience) was developed for use as a colloidal suspension intravenously. Based on the pivotal phase III clinical trial results, *nab*-paclitaxel was approved in the United States by US Food and Drug Administration (FDA) in January 2005 and in Europe by European Medicines Agency (EMEA) in January 2008 for use in patients with metastatic breast cancer (MBC) who have failed combination chemotherapy or relapse within 6 months of adjuvant therapy where prior therapy included an anthracycline.

This article provides a review of pharmacology, safety and efficacy profile of *nab*-paclitaxel, and evaluates its benefit in treatment of breast cancer.

Side-Effects and Drawbacks of Solvent-Based Taxanes

Taxanes bind to the interior surface of β-microtubule chain and enhance tubulin polymerization, thereby stabilizing microtubules. This inhibits mitosis, motility and intracellular transport within (cancer) cells, leading to apoptotic cell death. Taxanes also block anti-apoptotic effects of BCL-2 gene family, induce *TP*53 gene activation with resultant mitotic arrest leading to cell death.[7]

Paclitaxel was first approved in 1992 for clinical use. It is a naturally occurring diterpinoid product extracted from bark of pacific yew. Docetaxel, another taxane, which was approved by FDA for clinical use in 2004, is a semi-synthetic esterified product of 10-deacetyl baccatin III extracted from needles of European yew. Both paclitaxel and docetaxel are highly hydrophobic. Cremaphor EL (CrEL), a non-ionic surfactant poly-oxy-ethylated castor oil mixed 1:1 with dehydrated ethanol was recognized to be the most feasible option to solubilize paclitaxel for intravenous administration. Likewise, the solvent used for Docetaxel is another poly-oxy-ethylated surfactant, polysorbate-80.[6] Being biologically and pharmacologically active, these solvents are associated with several major side effects such as hypersensitivity reactions and neuropathies. They also impair tumor penetration, limiting the clinical effectiveness of solvent-based taxanes.[5,6] CrEL-paclitaxel formulation needs special infusion set to minimize exposure to di(2-ethylhexyl)phthalate (DHEP), which may be leached from standard polyvinyl chloride sets. Prolonged infusion times and premedications with corticosteroids and antihistamine agents are required to reduce hypersensitivity reactions. However, minor reactions still occur in about 40% of all patients receiving solvent-based taxanes and nearly 3% develop potentially life-threatening reactions.[6] CrEL is also shown to cause neutropenia and prolonged peripheral neuropathy related to axonal degeneration. Fluid retention, a toxicity commonly seen with docetaxel has been attributed in part due to alteration of membrane fluidity by polysorbate-80.[6,8] Formation of large polar micelles of CrEL-paclitaxel in the plasma compartment can cause entrapment of the drug leading to non-linear pharmacokinetics.[5] This alters the pharmaco-dymanic characteristics of the solubilized drug resulting in a substantial increase in systemic exposure with concomitantly reduced systemic clearance placing patients at risk for severe systemic toxicities. This drug entrapment phenomenon which decreases the duration of drug exposure partly explains why the attempts to improve efficacy of CrEL-paclitaxel by utilizing doses higher than the standard-of-care dose (175 mg/m^2 over 3 hours every 3 weeks) have been unsuccessful.[9] More frequent dosing (such as weekly administration) which may lead to increased duration of exposure, has demonstrated improved efficacy in both adjuvant/neoadjuvant and metastatic settings.[10]

To address these limitations of solvent-based taxanes and to improve their therapeutic index, various solvent-free formulations and delivery systems such as liposomal encapsulated paclitaxel, paclitaxel vitamin E emulsion and polymer microsphere formulation of paclitaxel were investigated but with limited success.[6,8] First successful attempt to formulate a solvent-free taxane has been the development of *nab*-paclitaxel. The nano-particle protein platform utilizes the natural properties of albumin to increase drug delivery to the tumor and eliminates the need for solvents.

Nanomedicine and *nab*-Technology

Nanomedicine is the medical application of molecular *nab*-technology, a new area of science that involves working with small scale materials and devices that are at the nanometer level (10^{-9} of a meter). A few examples of the development by this discipline include liposomes, dendrimers, super paramagnetic nanoparticles and polymer-based platforms.[11] Albumin has a number of features that make it an ideal drug delivery system. It is a natural carrier of endogenous hydrophobic molecules such as vitamins, hormones and other water-insoluble plasma substances that are bound in a reversible non-covalent manner. Albumin plays an important role in endothelial transcytosis of protein-bound and unbound plasma constituents mainly by binding to a cell-surface 60 kDa glycoprotein receptor (gp60) on the endothelial cell membrane. This leads to activation of caveolin-1, a major component of membrane vesicles, resulting in receptor mediated internalization of the albumin-drug complex into caveolae (small invaginations of plasma membrane). Subsequently, caveolae transports the albumin-drug conjugate to the extracellular space, including the tumor interstitium. SPARC (*s*ecreted *p*rotein, *a*cidic and *r*ich in *c*ysteine), which is believed to be selectively secreted by the tumors, binds to albumin-drug complex with the resultant release of the drug in the vicinity of tumor cells.[11,12]

Preclinical and Clinical Evaluation of *nab*-Paclitaxel

Comparative intratumoral and antitumoral activity of *nab*-paclitaxel has been demonstrated to be greater than CrEL-paclitaxel and docetaxel in multiple tumor types using preclinical models.[12,13] Desai et al[13] using radiolabeled paclitaxel in mice with xenografts, showed that *nab*-paclitaxel was significantly less toxic; LD_{50} (lethal dose, 50%) values and maximum tolerated dose (MTD) for *nab*-paclitaxel and CrEL-paclitaxel were 47 and 30 mg/kg/day, and 30 and 13.4 mg/kg/day, respectively. At equal doses, intratumoral paclitaxel accumulation was found to be 33% higher for *nab*-paclitaxel. In live human umbilical vascular endothelial cells (HUVEC), endothelial binding and transport across the endothelial cell monolayer was significantly higher (9.9 fold and 4.2 fold respectively) with *nab*-paclitaxel and this difference was abrogated by methyl β-cyclodextrin, a known inhibitor of endothelial gp60 receptor and caveolar-mediated transport.[13] Zhou et al recently reported similar antitumoral responses with *nab*-paclitaxel in hepatocellular carcinoma (HCC) cell lines.[14] In a panel of HCC cell lines studied, *nab*-paclitaxel showed an effective IC_{50} dose at 15-fold lower than paclitaxel or docetaxel alone, and ~450-fold less compared to doxorubicin. SPARC, a type of caveolin-1 has a sequence homology with gp60, leads to its binding to albumin. It is over expressed in several tumor types including breast cancer. This interaction between SPARC and albumin has been suggested to be the reason for enhanced uptake and intra-tumoral accumulation, and also a possible role for SPARC as a bio-marker for *nab*-paclitaxel effectiveness.[12] These data provided the preclinical evidence to advance the drug to clinical studies.

Phase 1 and Pharmacokinetic Studies

Three different dose schedules of *nab*-paclitaxel have been evaluated in Phase I and pharmacokinetics studies. In a study by Ibrahim et al,[15] 19 patients with advanced solid tumors received *nab*-paclitaxel as a 30 minute infusion given every 3 weeks without premedication using doses from 135 to 375 mg/m^2. No infusion related acute hypersensitivity reactions were noted during the drug administration. Hematological toxicity was mild and not cumulative. At the highest dose studied (level 3, 375 mg/m^2), dose-limiting toxicity occurred in 3 of 6 patients and consisted of sensory neuropathy (3 patients), stomatitis (2 patients) and superficial keratopathy (2 patients). The MTD was determined to be 300 mg/m^2, substantially higher than the typical dose used with CrEL-paclitaxel. Pharmacokinetic analyses revealed whole blood

paclitaxel concentrations and area under the curve (AUC) values to increase linearly over the dose range of 135–300 mg/m^2 unlike the non-linear kinetics of solvent-based paclitaxel.

In another phase 1 trial reported by Nyman et al,[16] 39 patients with advanced non-hematological malignancies received *nab*-paclitaxel without premedication at a dose levels from 80 to 200 mg/m^2 as a 30-minute infusion once a week for 3 weeks in each monthly cycle. One third of patients received ≥6 cycles. After enrollment of the first cohort, patients were enrolled into 1 of 2 cohorts, 'lightly' and 'heavily' pretreated based on the extent of prior exposure to chemotherapy. MTDs for these two cohorts were 150 mg/m^2 and 100 mg/m^2; dose-limiting toxicities were grade 3 peripheral neuropathy and grade 4 neutropenia respectively. The pharmacokinetics was again noted to be linear and there were no dose-dependant changes in plasma clearance. Partial response (PR) was observed in patients previously treated with CrEL-paclitaxel.

A randomized cross over study comparing the pharmacokinetics of *nab*-paclitaxel and CrEL-paclitaxel was reported by Gardner et al.[17] Seventeen patients with locally advanced or metastatic solid tumors that were likely to be responsive to taxanes were randomized to receive *nab*-paclitaxel (260 mg/m^2 as a 30-minute infusion) or CrEL-paclitaxel (175 mg/m^2 as a 3 hour infusion). Patients crossed over to the alternate treatment after 1st cycle. Thereafter, patients received treatments with 260 mg/m^2 of *nab*-paclitaxel every 3 weeks. Pharmacokinetic studies were carried out for the first cycle of CrEL-paclitaxel and the first two cycles of *nab*-paclitaxel. The total drug exposure was comparable between the two formulations and the mean fraction of unbound paclitaxel was significantly higher with *nab*-paclitaxel compared to CrEL-paclitaxel (0.063 ± 0.021 vs. 0.024 ± 0.009; $P < 0.001$). This study purports that systemic exposure to unbound paclitaxel would lead to increased tumoral uptake thereby resulting in an augmented anti-tumor efficacy compared to CrEL-paclitaxel.

In a phase 1 study of three different schedules of *nab*-paclitaxel in combination with carboplatin,[18] 41 heavily pretreated patients with advanced solid tumors received *nab*-paclitaxel and carboplatin AUC of 6 on day 1. Group A received *nab*-paclitaxel at doses ranging from 220 to 340 mg/m^2 on day 1 every 21 days; group B received *nab*-paclitaxel at 100 or 125 mg/m^2 on days 1, 8, and 15 every 28 days; and group C received *nab*-paclitaxel 125 or 150 mg/m^2 on days 1 and 8 every 21 days. MTD of *nab*-paclitaxel in combination with carboplatin was 300, 100, and 125 mg/m^2 in groups A, B, and C, respectively with myelosuppression was the primary dose limiting toxicity in all the groups.

In a recent phase 1 study reported by Chien et al,[19] vascular-priming chemosensitization with 2-day pulse of high dose lapatinib followed by weekly infusion of 100 mg/m^2 *nab*-paclitaxel treatment was investigated in 25 patients with advanced solid tumors. 72% of these patients were previously taxane-refractory. Maximum tolerated dose of lapatinib was defined as 5250 mg/day in divided doses. The dose-limiting toxicities were grade 3 vomiting and grade 4 neutropenia. 65% of evaluable patients had a partial or stable response on this therapy.

Phase II Studies

Based on the results of phase 1 study,[15] Ibrahim et al investigated *nab*-paclitaxel in a multicenter phase II study to evaluate safety and antitumor activity in patients with MBC.[20] 63 women with confirmed and measurable MBC received 300 mg/m^2 of *nab*-paclitaxel over 30 minutes every 3 weeks. 48 patients had received prior chemotherapy; 39 patients had received no prior treatment for metastatic disease. Median number of treatments was 6 cycles. Overall response rate (ORR), which was the primary end point of the study, was 48% for all patients and 64% for those receiving *nab*-paclitaxel as first line treatment. Median time to progression (TTP) was 26.6 weeks and median OS was 63.6 weeks. No severe hypersensitivity reactions were reported despite lack of premedication. Toxicities noted were typical of paclitaxel and included grade 4 neutropenia (24%) and grade 3 sensory neuropathy (11%) and grade 4 febrile neutropenia (5%).

Blum et al[21] reported the benefit of weekly *nab*-paclitaxel in patients with MBC whose disease had failed conventional taxane treatment. Taxane failure was defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane therapy. Patients received 100 mg/m^2 (n = 106) or 125 mg/m^2 (n = 75) on days 1, 8, and 15 of 28 day cycle. Response rates were 14% and 16% for the 100 mg/m^2 and 125 mg/m^2 cohorts, respectively with

Table 1. nab-PACLITAXEL: AT A GLANCE[37]

***nab*-PACLITAXEL: AT A GLANCE[37]**
Mechanism of action Antimicrotubule agent, promote microtubules assembly from tubulin dimers and stabilize microtubules to prevent depolymerization. This stability causes inhibition of the normal dynamic reorganization of the microtubules which is necessary for important interphase and mitotic functions in the cells
Dosing and administration 260 mg/m^2 Intravenous infusion over 30 minutes once every 3 weeks
Pharmacokinetics Distribution: Extensive extra-vascular distribution and/or tissue binding; does not penetrate blood brain barrier Protein binding: 89% to 98% Metabolism: Hepatic; P450 (CYP2C8 and CYP3A4) Excretion: Fecal (20%); renal (4%) Elimination half life: 27 hours
Side effects Common: Cardiovascular: abnormal EKG (60%), edema (10%) Dermatologic: alopecia (90%) Gastrointestinal: diarrhea (27%), nausea (30%), Vomiting (18%) Hematologic: Anemia (33%), Neutropenia, (any grade, 80%) Hepatic: raised transaminases (39%), raised alkaline phosphatase (36%) Neurologic: asthenia/myalgia/fatigue (47%), sensory neuropathy (any grade, 71%) Ophthalmic: visual disturbance (13%) Renal: raised serum creatinine (11%) Respiratory: dyspnea (12%) Serious: Cardiovascular: cardiac arrest, cerebrovascular accident, supraventricular tachycardia, transient ischemic attack (3%) Hematologic: severe anemia (1%), bleeding (2%), febrile neutropenia (2%), neutropenia, grade 4 (9%), severe thrombocytopenia (<1%) Neurologic: severe sensory neuropathy (10%)
Special precaution Paclitaxel has been shown to be clastogenic, teratogenic and fetotoxic and should not be used in pregnancy. Men should be advised not to father a child while receiving treatment. It is not known if paclitaxel is excreted in human milk; however, it is recommended that nursing should be discontinued during therapy
Synonyms ABI-007, albumin-bound paclitaxel
Trade name ABRAXANE (Abraxis Bioscience)

an additional 12% and 21% of patients, respectively, having stable disease (SD) for ≥16 weeks. Median progression-free survival (PFS) (3 vs. 3.5 months) and median survival (9.2 vs. 9.1 months) were similar for the two dose cohorts; Survival was similar for responding patients and those with SD. No severe hypersensitivity reactions were reported and grade 4 neutropenia occurred in less than 5% of patients.

Mirtsching et al recently reported the efficacy and safety of weekly *nab*-paclitaxel as a first-line therapy of MBC.[22] *nab*-paclitaxel (125 mg/m^2) was administered by 30-minute intravenous infusion weekly for 3 of 4 weeks. Patients whose tumors overexpressed HER2 also received trastuzumab. 72 patients were enrolled; 22 patients had HER2+ breast cancer. The ORR was 42.2%; 5 patients had a CR and 22 patients had a PR. Additionally, 17 patients experienced SD, providing a disease control rate (CR + PR + SD) of 68.8%. Patients with HER2+ disease had an ORR of 52.4%; the ORR was 38.1% in the HER2- population. Median PFS was 14.5 months and survival rates at 1 year and 2 years were 69% and 62%, respectively. The most commonly observed toxicities were pain (64%), fatigue (58%), sensory neuropathy (54%), infection (46%), nausea (38%), alopecia (33%), and anemia (33%). The investigators concluded that

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.