

CCR 20th Anniversary Commentary: Setting the Stage for Nanoparticle Albumin-Bound Paclitaxel—How Far Science Has Come

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In this phase I pharmacokinetic study of ABI-007, which was published in the May 1, 2002, issue of *Clinical Cancer Research*, Ibrahim and colleagues provided the framework needed for subsequent studies to confirm the benefits of ABI-007 over solvent-based formulations. Since the study's publication, experiments have

highlighted the importance of drug-delivery systems, the immune system in cancer biology, and immunoregulatory properties of taxane compounds. *Clin Cancer Res*; 21(9); 1975-7. ©2015 AACR.

See related article by Ibrahim et al., *Clin Cancer Res* 2002;8(5) May 2002;1038-44

Since their initial isolation from extracts of Pacific yew trees in 1971, taxane compounds have been used in the treatment of numerous cancers. By inhibiting mitosis and blocking cells in the G₂ and M phases of the cell cycle, taxanes have been shown to induce programmed cell death. Paclitaxel and docetaxel made up this category of chemotherapeutic agents; however, their relative water insolubility limited their initial clinical utility until they could be remodeled into solvent-based formulations. By adding Cremophor EL (BASF) and dehydrated ethanol to paclitaxel, as well as using Tween 80 as a solvent base for docetaxel, taxanes were developed into viable parenteral chemotherapeutic agents. Nonetheless, the use of such solvents limited the maximum tolerated dose (MTD) of the parent compound secondary to added toxicities, including but not limited to peripheral neuropathy, neutropenia, and hypersensitivity reactions. In early clinical trials, hypersensitivity reactions due to Cremophor EL and Tween 80 (Sigma-Aldrich) were reported in as many as 30% of patients receiving paclitaxel or docetaxel without premedication. However, even after premedication with glucocorticoids and histamine 1 and 2 blockers severe, life-threatening reactions are still seen in 2% to 4% of patients (1, 2). Furthermore, to limit drug-related toxicity, these formulations of paclitaxel and docetaxel had to be administered in various dosing schedules to modify the frequency or the severity of side effects. Besides, the use of Cremophor EL, ethanol, and Tween 80 presented additional complexities due to leaching plasticizers from polyvinyl chloride (PCV) bagging and infusion sets, thus requiring careful preparation and administration using glass bottles or non-PVC bags and tubing.

ABI-007, also known as nanoparticle albumin-bound paclitaxel (nab-paclitaxel), is an injectable, Cremophor-free paclitaxel formulation developed to decrease solvent-associated side effects (hypersensitivity, and hematologic or nonhematologic toxicities), avoid the need for special tubing, and allow for faster drug administration. Based on their findings in a phase I and pharmacokinetic study of ABI-007, Ibrahim and colleagues (3) reported that not only were hypersensitivity reactions eliminated with nab-paclitaxel use, obviating premedication with antihistamines or steroids, but also faster infusion times were possible (30 minutes with nab-paclitaxel vs. 3-hour to 24-hour infusion rates with traditional paclitaxel formulation). Moreover, because taxanes exhibit a dose-response curve, and because the solvents used to improve solubility may limit dose escalation of paclitaxel or docetaxel, substituting the Cremophor EL, ethanol, and Tween 80 with human albumin was thought to allow for an increase in the MTD. As expected, a higher MTD with ABI-007 was documented, when compared with the solvent-based paclitaxel formulations (300 mg/m² vs. 175 mg/m²), thus initiating widespread interest in this novel drug formulation.

Importantly, albumin not only served as a solvent for novel paclitaxel and docetaxel formulations, but served as a vehicle for drug transport and delivery into malignant cells as well. Present in malignant endothelial cells is a 60-kDa cell-surface glycoprotein receptor (gp60), which has a high affinity for albumin. Once bound to albumin, gp60 combines with an intracellular protein, calveolin-1, leading to the invagination of the cell membrane and the formation of a transcytotic vesicle. By this mechanism, albumin facilitates receptor-mediated endothelial transcytosis and allows albumin-bound antineoplastic agents to be selectively cotransported into the extravascular space of tumors. Once in the interstitium of the tumor, transport into the malignant cell is further facilitated by secreted protein, acidic, and rich in cysteine (SPARC, or osteonectin), an extracellular matrix glycoprotein. The ability of albumin to bind to SPARC is due to sequence homology with gp60 and is considered to be responsible for the accumulation of albumin in some tumors. Thus, because SPARC is expressed in 50 to 60 distinct tumor cell types, but underexpressed in normal cells, this binding represents one mechanism of targeted drug

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delivery into tumor cells (4). Furthermore, by means of passive diffusion, albumin enhances drug permeability and retention in malignant tissue. As a tumor grows, the resulting angiogenesis leads to defective vascularity and deficient lymphatic drainage. Consequently, particles with a diameter of roughly 300 nanometers (nm) or less can accumulate in the vascular bed of tumor cells. With an average size of 130 nm, ABI-007 penetrates leaky capillaries of cancerous tissues more readily, compared with the larger micelles formed by Cremaphor-EL paclitaxel of 200 nm. In addition, while the working lymphatic system of normal tissues continues to dissipate excessive buildup of antineoplastic agents, the deficient lymphatic drainage of tumor beds increases drug accumulation in tumor extracellular tissue.

Breast cancer is a multifaceted disease with modern, receptor-targeted therapies that have greatly improved survival. Nevertheless, it remains second only to lung cancer as the most common cause of cancer-related death in women in the United States. As such, taxane-based treatment regimens continue to be first-line options for many patients, especially those with aggressive or metastatic breast cancer. Phase I–III studies have demonstrated improved safety, tolerability, and clinical efficacy in metastatic breast cancer, as well as showing that nab-paclitaxel may play a promising role in the management of triple-negative breast cancer (TNBC). Phase II trials of patients with metastatic TNBC have demonstrated overall response rates as high as 85%, and studies on other histologically aggressive disease subtypes suggest increased therapeutic activity when nab-paclitaxel is combined with gemcitabine or carboplatin (5, 6).

As heterogeneous as breast cancer, lung cancer is a collection of various histopathologic diseases. Unfortunately, the diagnosis also imparts a significantly poor prognosis, with 5-year survival rates as low as 16% in patients older than 65. Currently, taxanes combined with platinum compounds comprise one of the most common first-line treatment options for patients with lung cancer, and great interest in the discovery of more efficacious treatment regimens has included nab-paclitaxel-based clinical trials. Significant improvements in overall response rates have been documented in patients with advanced non-small cell lung cancer when nab-paclitaxel plus carboplatin is compared with solvent-based paclitaxel combined with carboplatin treatment regimens. Of great importance, however, is the demonstration of improved drug efficacy in patients older than 70, and in those with squamous histology, two factors that have traditionally imparted worse outcomes and limited treatment options (7).

Interest in nab-paclitaxel for the treatment of pancreatic cancer started when enhanced SPARC expression was found to be associated with poorer prognosis. Gemcitabine plus FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) has been the cornerstone treatment regimen in patients with pancreatic cancer, but toxicities from FOLFIRINOX are significant and, often times, limit its utility. Unfortunately, in those perceived unable to receive or tolerate FOLFIRINOX, treatment with gemcitabine alone greatly reduces survival outcomes. Thus, by binding to SPARC, nab-paclitaxel was hypothesized to improve clinical outcome, while simultaneously enhancing treatment tolerability. Nab-paclitaxel, in combination with gemcitabine, has been shown to significantly increase survival rates, median progression-free survival, and response rates when compared with gemcitabine alone (8). Despite increased side effects with this combination therapy compared with gemcitabine

alone, most of the side effects are reversible. Therefore, this novel treatment regimen fills a great clinical need in patients with pancreatic cancer. In those unable to tolerate FOLFIRINOX, nab-paclitaxel is an accepted alternative, added to gemcitabine, without much compromise of treatment outcome.

In addition to developing drugs capable of targeting malignant cells, renewed interest in anticancer agents has been based on findings that show certain compounds may contain immunomodulatory properties. Once thought to have a minor role in tumor growth, the immune system is now recognized as a key player in eliminating or promoting malignancy. The primary mechanism by which the immune system identifies and targets cancer cells is through the recognition of MHC class I-protein complexes by cytotoxic T lymphocytes (CTL). Once activated, CTLs target and destroy these cancer cells. Unfortunately, by downregulating MHC class I molecular expression, tumor cells are able to evade the host's immune system and replicate without recognition. Thus, murine models showing that paclitaxel reverses cancer-related immune system downregulation have elicited great interest. Despite lacking any structural similarity to bacterial lipopolysaccharide, paclitaxel induces an immune response that mimics the effects of lipopolysaccharide, activating murine macrophages and dendritic cells through the Toll-like receptor 4 and myeloid differentiation primary response gene 88-dependent pathway. Secondary to this immune upregulation, cytokine production leads to the recruitment of antitumor cells, such as CTLs and natural-killer cells, to overcome this immune system evasion and destroy malignant cells (9).

Interestingly, multiple immune cell types, which act to suppress the immune system, have been identified. Regulatory T cells, myeloid-derived suppressor cells (MDSC), and alternatively activated macrophages have emerged as the major suppressors of antitumor immune responses, with studies reporting correlations between elevated MDSC levels and increased metastatic tumor burden (10). Given the immunosuppressive effects of such cell lines, drug efficacy is no longer based solely on direct tumor cytotoxicity. Drugs capable of eliminating regulatory T cells, activated macrophages, or MDSCs may prove to enhance antitumor response rates and significantly increase survival. In tumor-bearing mice, docetaxel was found to significantly inhibit tumor growth, decrease MDSC levels in splenocytes, selectively increase CTL responses, and induce cell death in certain MDSC cell lines (11). Nonetheless, current immunoregulatory studies are largely based on murine models, and whether such processes will translate into significant clinical efficacy, reduce recurrence rates, or improve long-term survival in human subjects has yet to be established.

Continued research into nab-paclitaxel's mechanism of action is proving to be beneficial, as this novel formulation with a novel drug-delivery mechanism (albumin), along with its enhanced ability to target tumor cells, explains, at least partly, its superiority over other drugs of its class. In addition, the potential immunomodulatory role of nab-paclitaxel, in contrast with that of paclitaxel and docetaxel, remains unaddressed. As this nanoparticle albumin-bound technology is developed, drugs previously shown to be ineffective or not tolerated can be remodeled and reevaluated, potentially adding innovative therapeutic options to disease treatment strategies. Of possibly greater practical importance still, however, is the fact that future nab-based products may be administered not only through intravenous access, but via oral,

pulmonary, and nasal routes as well, broadening both the scope of clinical medicine and the utility of such compounds.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Archived Drug Label: TAXOL (Paclitaxel) Injection; [about 25 screens]. [cited 2014 Nov 7]. Available from: <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=27377#s11>.
2. Sanofi Prescription Products: Taxotere Package Insert; [PDF on the Internet]. [cited 2014 Nov 7]. Available from: <http://products.sanofi.us/Taxotere/taxotere.pdf>.
3. Ibrahim NK, Desai N, Legha S, Soon-Shiong P, Theriault RL, Rivera E, et al. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res* 2002;8:1038–44.
4. Young BA, Wang P, Goldblum SE. The counter adhesive protein SPARC regulates an endothelial paracellular pathway through protein tyrosine phosphorylation. *Biochem Biophys Res Comm* 1998;251:320–32.
5. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, et al. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. *Clin Breast Cancer* 2013;13:416–20.
6. Lobo C, Welsh C, Higgins C, Ferrell A, Castellon A, Baez O, et al. Final results of a phase II study of nab-paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. *Breast Cancer Res Treat* 2010;123:427–35.
7. Socinski MA, Iglesias JL, Bondarenko I, Renschler MF, Zhang H, Bhar P, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055–62.
8. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703.
9. Javeed A, Ashraf M, Riaz A, Ghafoor A, Afzal S, Mukhtar MM. Paclitaxel and immune system. *Eur J Pharm Sci* 2009;38:283–90.
10. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol Immunother* 2009;58:49–59.
11. Kodumudi KN, Woan K, Gilvary DL, Sahakian E, Wei S, Djeu JY. A novel chemoimmunomodulating property of docetaxel: suppression of myeloid-derived suppressor cells in tumor bearers. *Clin Cancer Res* 2010;16:4583–94.

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