Improved Paclitaxel Formulation Hints at New Chemotherapy Approach


APP’s drug reformulation ambitions go beyond paclitaxel. At the symposium, the company also unveiled a provocative theory to explain why its albumin nanoparticle-based formulation performed so much better than Taxol. The theory, involving a novel transport mechanism that preferentially targets tumors, could have broad implications for delivery of other cancer drugs. APP’s theory “is really going to fire the imagination, I think, of the oncology community,” said trial investigator Joyce O’Shaughnessy, M.D., of the Baylor-Charles A. Sammons Cancer Center in Dallas.

The successful results were badly needed by APP. The company has seen its stock roller-coaster in the last few months, and shareholders have filed seven different lawsuits accusing APP of over-hyping its results. The business press has been critical, with Barron’s raising questions about the clinical trials and Forbes detailing the history of Soon-Shiong’s failed foray into diabetes therapy in the early 1990s, an episode that led to bitter and expensive legal battles with his brother. More recently, APP’s parent company was accused of conspiring with Bristol-Myers Squibb to keep generic paclitaxel off the market. (See News, Vol. 94 No. 5, p. 324-6.) In July the company was cleared of wrongdoing by a California court.

In San Antonio, all that mattered was ABI-007’s performance against Taxol. The new formulation was clearly superior: in a randomized, open-label trial of 454 patients with metastatic breast cancer, the overall response rate for ABI-007 was 33%, compared with 19% for Taxol. Median time to progression was 21.9 weeks for ABI-007 versus 16.1 weeks for Taxol. Overall side effects were fewer for ABI-007, even though it delivered a 50% higher dose of the active agent, paclitaxel. “ABI-007 has significant advantages over Taxol,” concluded principal investigator William Gradishar, M.D., of Northwestern University, Chicago.

These results also impressed several breast cancer experts with no connection to the trial or the company. “I certainly hope that regulatory agents … make a decision regarding the possibility of this drug being approved, so that it is available for patient use,” Edith Perez, M.D., director of the breast cancer program at the Mayo Clinic, said at the meeting.

Making a Better Taxol

ABI-007 has been long in development. Soon-Shiong and chemist Neil Desai, Ph.D., conceived the drug after attending a 1992 National Cancer Institute-organized meeting on Taxol, which had just received marketing approval. Taxol was amazingly effective, but the meeting revealed some serious problems, mainly with toxicity. That is because the drug is formulated with the castor oil derivative Cremophor to make it water soluble. “It was clear to the scientists of the world that Cremophor was not a safe material,” said Soon-Shiong. Cremaphor often leads to hypersensitivity reactions in patients, who must be pretreated with steroids.

Soon-Shiong and Desai created a Cremaphor-free paclitaxel formulation by fusing the compound with albumin, a natural protein used by the body to transport water-insoluble compounds. The resulting drug, ABI-007, is a suspension of albumin nanoparticles, each of which contains a tiny bit of active drug. No steroid pretreatment is needed. Clinical trials, begun in 1998, were promising, but the head-to-head trial with Taxol has now clinched ABI-007’s clinical superiority. “There’s no question in my mind that this drug will eventually make it for use,” said Daniel Von Hoff, M.D., director of the Arizona Health Science Center’s Cancer Therapeutics Program.

ABI-007 even works for some patients who have progressed on standard Taxol. A phase II trial for such patients with metastatic breast cancer is well under way, with five responders among the first 28 patients. “That’s what I’m excited about,” said Von Hoff, who helped design the trial. “When you’ve got your clinical team running down the hall saying, ‘Look at this, look at this X-ray, Dan. My God, this is really something—and she progressed on Taxol!’ that’s pretty impressive.” Several patients have gone more than a year without progressing, said trial principal investigator Joanne Blum,

Dr. William Gradishar
M.D., Ph.D., of the Baylor University Medical Center in Dallas.

Nevertheless, in terms of clinical results, ABI-007 is evolutionary, not revolutionary. “From an incrementalism point of view I think that the Abraxane data represent an important advance,” said Clifford Hudis, M.D., of the Memorial Sloan-Kettering Cancer Center. “[But] it’s not curing more patients than conventional paclitaxel. And that’s the important limit.” Only 2% to 3% of ABI-007 patients in the phase III trial had a complete response, O’Shaughnessy reported, and Hudis pointed out that APP has yet to report survival data for its phase III patients. (Not enough patients have died yet to enable an analysis.) “What I want to sound is upbeat, but not over the top about this,” said Hudis. “These are important advances, but they are not the last word on how to improve therapy for patients.”

**Hitchhiking Into Tumors**

But the clinical results are only half the story, said Soon-Shiong. “We are excited about the next potential leap,” he said in an interview with the *Journal*. “Why are we seeing this phenomenon of a doubling of response rate?” The answer, said Soon-Shiong, has much wider implications for cancer therapy. To begin with, he said, the Cremophor in Taxol not only leads to toxicity, but keeps paclitaxel from reaching the tumor. That’s because Cremophor paclitaxel becomes entrapped in micelles, tiny hydrophobic droplets in plasma. This entrapment phenomenon, said Soon-Shiong, explains earlier studies showing no effect on tumors from increasing Taxol dose. “By trapping the drug in plasma and increasing the dose, you really have no opportunity to achieve a dose response,” he said. ABI-007 avoids that pitfall and frees paclitaxel to pass from the vascular system into tumors. “When you were giving a higher dose of Taxol, you were giving a higher dose of Cremophor,” said Soon-Shiong. “We’ve been able now to drive the drug into the tumor and maximize the potential of this tubulin poison.”

Keeping the drug in contact with the tumor is another problem with current chemotherapy. High intratumoral pressure, a phenomenon first described by Rakesh Jain, M.D., of Harvard Medical School in 1996, tends to push conventional drugs out of the tumor interstitial space. “A drug in solution gets kicked right out,” said Soon-Shiong. “If it’s in a nanoparticle, it gets in via the leaky tumor vasculature and gets entrapped.”

In San Antonio, APP presented data showing a 33% greater tumor penetration into mouse xenografts by ABI-007 compared with Taxol. Based on a series of preclinical tests by APP (and recent cell biology work by others), Soon-Shiong believes that the drug reaches the tumor by a novel mechanism. Some ABI-007 penetrates the tumor via leaky junctions in tumor vasculature and stays there because of the tumor’s impaired lymphatic system. More of the drug engages albumin receptors—gp60 receptors—inside the tumor blood vessel. The receptors, in turn, fold into sacs called caveolae that then empty the drug into the tumor interstitial space, where the freed paclitaxel subsequently penetrates tumor cells and kills them via microtubule binding. “The molecules are literally pulled through” the blood vessel walls via the albumin receptors, Soon-Shiong explained. Thus ABI-007 is able to take advantage of albumin’s normal molecular machinery, which facilitates macromolecule transport to cells—especially tumor cells, which presumably have evolved to maximize nutrient delivery.

**New Hope for High Dose?**

This explanation for ABI-007’s clinical potency is still theoretical. “The exact relevance to the clinical situation we don’t know,” cautioned O’Shaughnessy. But if formulating paclitaxel with albumin can help get it to tumors, the same strategy should work for other chemotherapy drugs. This might get around one of the biggest obstacles in chemotherapy for solid tumors: the failure of high doses to achieve better kill rates. “What’s important is not how much drug you give the patient, but how much drug gets to the tumor,” said Craig Henderson, M.D., of the University of California at San Francisco. “So [ABI-007] then becomes a tool for us to begin to get proof of principle of this concept, that it’s the dose of drug that’s at the tumor that’s the important endpoint.”

Soon-Shiong said his company plans to formulate other water-insoluble chemotherapy drugs, possibly including docetaxel and the camptothecins, with albumin nanoparticles. Other cytotoxic molecules, shelved because of delivery problems, are also candidates. “These molecules are active, we want to get them to the tumor,” Soon-Shiong said. “We have a potential way. It may be as simple as that.”

Whether Soon-Shiong’s “Nanoparticle Albumin Bound” (NAB) technology becomes a general platform for anticancer agents—and other water-insoluble drugs—remains to be seen. But the maverick ex-transplant surgeon appears to have won over the medical community to ABI-007. “I’m damn glad he was able to get this agent available for patients,” said Von Hoff. “Because, I will tell you, without question, that this has helped a lot of people already.”

—Ken Garber