

Abraxane (nanoparticle albumin-bound paclitaxel) in metastatic breast cancer

Novel formulation permits higher-dose taxane therapy with greater safety

In January of this year, the US Food and Drug Administration approved an albumin-bound, nanoparticle-sized form of paclitaxel for injectable suspension (Abraxane) for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline agent unless clinically contraindicated.

Abraxane is a polyoxyethylated castor oil (Cremophor)-free nanoparticle albumin-bound (*nab*) paclitaxel formulation designed to improve paclitaxel tumor cell penetration and reduce the frequency of adverse reactions associated with Cremophor use. Cremophor is an excipient in many drug formulations used to overcome poor water solubility. It is associated with leaching of plastic from standard IV tubing, hypersensitivity reactions, complement activation, axonal swelling, and demyelination and may interact with paclitaxel to cause myelosuppression; it may also contribute to reduced cell penetration by encapsulating the drug. Use of *nab* paclitaxel produces higher tumor drug concentrations, with potential mechanisms including selective tumor vessel permeability, albumin-receptor-mediated transport, and increased cell permeability. Premedication with dexamethasone or antihistamines to prevent hypersensitivity reactions is not required with *nab* paclitaxel.

Comparison with Cremophor-based paclitaxel

In the phase III trial providing support for its regulatory approval,¹ an Abraxane regimen of 260 mg/m² given by 30-minute infusion with-

out premedication every 3 weeks was compared with Cremophor-based paclitaxel (175 mg/m²), given by 3-hour infusion with routine premedication every 3 weeks, in 454 patients with metastatic breast cancer. One or more prior chemotherapy regimens had been received by 59% of patients, and 77% had received prior anthracycline treatment. The primary objective of the trial was to demonstrate non-inferiority/superiority of *nab* paclitaxel versus Cremophor-based paclitaxel based on best confirmed response after six cycles of treatment. Median numbers of treatment cycles were six in the *nab* paclitaxel group and five in the paclitaxel group, with 28% and 20% of patients, respectively, receiving more than six cycles. Outcomes were assessed by investigators and by independent review of a blinded radiology team.

In the investigator data set, *nab* paclitaxel treatment was associated with a greater response rate (33% vs 19%, $P < 0.001$) and longer time to tumor progression (21.9 vs 16.1 weeks, $P = 0.029$). In the independent review data set, *nab* paclitaxel was also associated with a greater response rate (24.0% vs 11.1%, $P < 0.001$) and prolonged time to tumor progression (21.0 vs 15.4 weeks, $P = 0.014$). Among all patients, median survival was 65.0 weeks in the *nab* paclitaxel arm and 55.3 weeks in the conventional paclitaxel arm, with the 2.5-month difference not being statistically significant ($P = 0.322$). Among patients receiving paclitaxel as second-line or subsequent therapy, however, median survival was 56.4 weeks in the *nab* paclitaxel arm and 46.7 weeks

in the conventional paclitaxel arm, with the 2.5-month difference being significant (hazard ratio, 0.73; 95% CI: 0.55–0.95, $P = 0.02$).

Grade 4 neutropenia was significantly less common with *nab* paclitaxel (7% vs 19%, $P < 0.001$). Grade 3 sensory neuropathy was significantly more common with *nab* paclitaxel (10% vs 2%, $P < 0.001$), but neuropathy was manageable. No grade 3 or 4 hypersensitivity reactions were observed in *nab* paclitaxel-treated patients. Nail changes and severe fluid retention were infrequent, and no septic deaths occurred.

Use in taxane-refractory metastatic breast cancer

In a phase II clinical trial, 106 patients with taxane-refractory disease received *nab* paclitaxel (100 mg/m²) via 30-minute infusion on days 1, 8, and 15 every 28 days without premedication.² Patients were considered to have taxane-refractory disease if their disease progressed while they were receiving paclitaxel or docetaxel or a relapse occurred within 12 months of adjuvant taxane treatment.

In all, 91% of the women had visceral predominant disease, 65% had more than three lesions that were being followed to assess response, 88% had progression of metastatic disease while on a taxane, and 12% developed metastatic disease within 12 months of adjuvant taxane treatment. Responses were seen in 16 women (15%; 95% CI: 8.3%–21.9%) and disease control (partial responses +

Summary by Matt Stenger, MS; reviewed by Joanne L. Blum, MD, PhD, Baylor Charles A. Sammons Cancer Center, Texas Oncology, PA, and US Oncology, Dallas, TX.

stable disease \geq 16 weeks) in 32 patients (30%; 95% CI: 21.4%–38.9%). Responses and clinical benefit were seen in women who had received prior treatment with paclitaxel, docetaxel (Taxotere), or both. Grade 4 treatment-related neutropenia was seen in 1% and grade 3 sensory neuropathy was observed in 4% of the patients. Ninety-one percent of the women were able to receive full doses of therapy (100 mg/m²).

The long-term disease control and remarkably good safety profile seen in these patients prompted amendment of the study to enroll additional patients to be treated at an increased dose of 125 mg/m².

In the higher dose *nab* paclitaxel study, 75 patients received 125 mg/m² via 30-minute infusion on days 1, 18, and 15 every 28 days without premedication.³ Women (median

age, 53 years) had a median of three prior chemotherapy regimens for metastatic disease; most had visceral predominant disease. Responses were seen in 12%, including one patient who achieved a complete response. Clinical benefit (complete responses + partial responses + stable disease \geq 16 weeks) was seen in 39% (95% CI: 28%–50%) of these patients.

Overall, 19 patients (26%) had dose reductions, primarily for sensory neuropathy and neutropenia. Treatment-related toxicities were more pronounced with the higher dose (125 mg/m²): grade 4 neutropenia occurred in 3% of patients; grade 3 sensory neuropathy in 17%; grade 3 fatigue in 9%; and grade 3 nausea, diarrhea, and anorexia in 3%.

Response rates were comparable with those achieved in patients who

received the 100 mg/m² dose, but side effects were more commonly seen, requiring dose modification in 25% of women, compared with 9% of women who received the 100 mg/m² dose.

References

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3. O'Shaughnessy JA, Blum JL, Sandbach JF, et al. Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer. Paper presented at the 27th Annual San Antonio Breast Cancer Symposium; December 8–11, 2004. Abstract 1070.

Clinical implications of using *nab* paclitaxel in metastatic breast cancer

Joanne L. Blum, MD, PhD

Baylor Charles A. Sammons Cancer Center, Texas Oncology, PA, and US Oncology, Dallas, TX

NANOPARTICLE ALBUMIN-bound paclitaxel (*nab* paclitaxel, Abraxane) represents an important advance for patients with metastatic breast cancer. Although originally designed as a non-inferiority study, the pivotal phase III trial comparing paclitaxel given in a dose of 175 mg/m² every 3 weeks with *nab* paclitaxel, given in a dose of 260 mg/m² every 3 weeks, showed superiority in response rate and time to disease progression when compared with paclitaxel. Neutropenia was less frequent with *nab* paclitaxel than with paclitaxel, and although sensory neuropathy was more frequent with *nab* pa-

clitaxel, it was of shorter duration.¹

We conducted two phase II trials of weekly *nab* paclitaxel, given in a dose of 100 or 125 mg/m² per week over 3 weeks, followed by a week off, among breast cancer patients whose disease had progressed despite use of a taxane, which could have been either paclitaxel or docetaxel (Taxotere). In both of these studies, responses were seen among 12%–15% of the patients, and clinical benefit, defined as a complete or partial response or stable disease for 16 weeks or longer, was observed in 30%–39% of these women. Responses and clinical benefit were observed even in women who had received prior weekly paclitaxel or docetaxel, suggesting that the

response to weekly *nab* paclitaxel was independent of schedule.^{2,3}

Cancer and Leukemia Group B (CALGB) study 9342 demonstrated that increasing the dose of paclitaxel from 175 to 210 or 250 mg/m², administered over 3 hours every 3 weeks, failed to increase efficacy but did increase toxicities, both sensory neuropathy and neutropenia.⁴ One hypothesis for the lack of dose response of paclitaxel may be because of entrapment by Cremophor micelles. Another hypothesis currently being tested is that the albumin receptor gp60 facilitates the uptake of *nab* paclitaxel, so that more paclitaxel is available to tumor cells.⁵

Encouraging results prompt further studies

In light of the encouraging and, in some cases, durable responses to *nab* paclitaxel when given weekly to women with taxane-refractory metastatic breast cancer, and in conjunction with data from CALGB study 9840, which showed that weekly paclitaxel at a dose of 80 mg/m² is more effective than giving paclitaxel at a dose of 175 mg/m² every 3 weeks,⁶ current studies are being planned or are under way to examine giving *nab* paclitaxel weekly at higher doses even earlier in the treatment of metastatic breast cancer and in combination with other active agents in women with metastatic disease. Additional studies are being planned or are under way to study *nab* paclitaxel in the neoadjuvant and adjuvant settings. Until these studies are completed, *nab* paclitaxel should be considered instead of Cremophor-based paclitaxel as a single agent for the treatment of metastatic breast cancer. Its shorter duration of administration (30 minutes), lack of need for special tubing or dexamethasone and antihistamine premedication, and de-

creased risk of hypersensitivity reactions are all important advantages for patients with metastatic breast cancer. Insurance reimbursement is available for Abraxane when administered at a dose of 260 mg/m² every 3 weeks or when given at a dose of 100–125 mg/m² on days 1, 8, and 15 of a 28-day cycle.

Taxanes, both paclitaxel and docetaxel, are a valuable treatment option for women with metastatic breast cancer. However, toxicities and inconvenience of administration have limited the utility of these agents. New formulations such as *nab* paclitaxel may allow paclitaxel to be given safely at higher doses, either alone or in combination with other agents, thereby increasing efficacy and safety. The availability of *nab* paclitaxel represents an important practice-changing advance for breast cancer patients with metastatic disease.

References

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Dr. Blum can be reached at Joanne.Blum@USOncology.com.