

Nanoparticle Albumin–Bound Paclitaxel for Metastatic Breast Cancer

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The taxanes, paclitaxel and docetaxel, are among the most important drugs in the modern treatment of metastatic breast cancer. By the mid 1990s, several phase II trials had demonstrated both agents to have considerable activity in the metastatic setting.¹⁻⁵ Phase III trials were then conducted to compare these agents with the then reference agent, doxorubicin.

In 1999, a large randomized trial comparing docetaxel with doxorubicin found an improved response rate in patients who received docetaxel (48% v 33%; $P = .008$), though differences in time to progression (26 v 21 weeks) and survival (15 v 14 months) were not statistically significant.⁶ A similar study that compared paclitaxel at a dose of 200 mg/m² given over 3 hours, with doxorubicin 75 mg/m², showed paclitaxel to have an inferior response rate (25% v 41%; $P = .003$) and time to progression (3.9 v 7.5 months; $P < .001$) but again, overall survival was not statistically different between the two arms (15.6 v 18.3 months), possibly as a result of the preplanned cross-over on progression.⁷

Both agents, however, were rapidly adopted for the treatment of metastatic breast cancer, especially for the many women who had received an anthracycline in the adjuvant setting. Trials were subsequently launched to examine taxane combinations in advanced disease, and while some have demonstrated improved efficacy compared with single agents, this benefit has to be balanced against the excess toxicities seen with some of these regimens.^{8,9}

This encouraging activity of taxanes in advanced disease led investigators to examine their role in addition to anthracyclines in the adjuvant setting. The first to be reported was CALGB (Cancer and Leukemia Group B) 9344 and the final analysis of this trial showed improvements in 5-year disease-free and overall survival with the addition of four cycles of paclitaxel to four cycles of doxorubicin + cyclophosphamide (disease-free survival [DFS] 70% v 65%, $P = .0023$; overall survival [OS] 80% v 77%, $P = .0064$).¹⁰

Other paclitaxel adjuvant studies have shown less convincing benefits.¹¹ Docetaxel has also been evaluated in several adjuvant trials. In the Breast Cancer International Research Group study (BCIRG 001), six cycles of doxorubicin, docetaxel, and cyclophosphamide (TAC) were found to be associated with superior DFS and OS compared with doxorubicin, fluorouracil, and cyclophosphamide (FAC; DFS 75% v 68%; $P = .001$; OS 87% v 81%, $P = .008$).¹² Taxanes are now commonly used in adjuvant regimens for women with high-risk disease.

Parallel to these studies, major advances have been achieved for women with HER-2–overexpressing breast cancer by employing schedules combining taxanes plus trastuzumab in advanced disease¹³ and in the adjuvant setting.^{14,15}

Despite their widespread use, both docetaxel and paclitaxel are associated with significant toxicities, including alopecia, fatigue, myalgia, nail changes, myelosuppression, neuropathy, and hypersensitivity reactions. Although these adverse effects are manageable for the majority of patients, it has meant there are limitations on the duration of therapy and on combining the taxanes with other agents with overlapping toxicity profiles.

Paclitaxel and docetaxel are highly hydrophobic, and therefore have to be delivered in synthetic vehicles. In the case of paclitaxel the vehicle is polyoxyethylated castor oil (Cremophor EL) and ethanol, whereas the combination of polysorbate 80 and ethanol are used for docetaxel. It has become increasingly recognized that the vehicles may be responsible for some of the “taxane-associated toxicity,” particularly fluid retention and hypersensitivity.¹⁶ The experiences from the early phase I and II trials of these drugs found that the incidence of such reactions could be reduced to acceptable levels with the use of premedication schedules containing antihistamines together with moderate to high doses of corticosteroids.¹⁷⁻²⁰

It is in large part because of the toxicities associated with the current formulations of taxanes that strategies to

enhance the therapeutic index of these agents have been developed. These can be broadly divided into those that change the scheduling of the conventional agents, and those that change the formulation or vehicle. Giving paclitaxel weekly seems to be associated with less myelosuppression and alopecia, and may even improve efficacy.²¹ A large ongoing United Kingdom study is comparing equivalent total doses of paclitaxel given either weekly or every three weeks (three-weekly) for women with metastatic breast cancer (Anglo Celtic IV; <http://www.angloceltic.org.uk>). Weekly docetaxel also seems to be an effective regimen associated with less myelosuppression, neurotoxicity, and stomatitis than three-weekly dosing, but onycholysis, fatigue, and hyperlacrimation are more frequent toxicities.²²

Several companies have developed new taxane formulations. These include conjugation of paclitaxel to docosahexaenoic acid²³, the use of polymeric micelle-formulated paclitaxel,²⁴ as well as modifications to the taxoid structure itself.²⁵⁻²⁷ Another approach to improving the therapeutic index of paclitaxel has been the development of ABI-007, in which paclitaxel is bound to nanoparticles of the naturally occurring vehicle for hydrophobic molecules, albumin. After preclinical, animal, and phase I studies had been performed,^{28,29} a phase II study of the compound in patients with metastatic breast cancer was conducted that demonstrated an encouraging overall response rate of 48% (64% in the subgroup of patients who received ABI-007 as first-line therapy). In this study, time to progression was 26.6 weeks, and median overall survival 63.6 weeks—figures that compare very favorably with the original phase II studies of docetaxel and paclitaxel.³⁰ Perhaps most intriguingly in this phase II study, myelosuppression and peripheral neuropathy were less frequent and less severe than would have been expected with the parent compounds. Hypersensitivity reactions were very rare, despite the drug being given without premedication.

In this edition of the *Journal of Clinical Oncology*, Gradishar et al³¹ report the results of a phase III trial comparing ABI-007 to conventional paclitaxel in cremophore/ethanol (Taxol; Bristol Myers-Squibb, Princeton, NJ) for women with metastatic breast cancer. Polyoxyethylated castor oil-based paclitaxel was given at its licensed dose of 175 mg/m² every 3 weeks, and ABI-007 at a dose of 260 mg/m². The authors state that they selected this dose, which is lower than that used in the phase II study, so that toxicity would be on a par with standard paclitaxel at 175 mg/m².

The study was conducted in five countries at 70 centers, inclusion criteria were standard, and patients were either taxane-naïve or to had received a taxane only as part of adjuvant therapy more than 12 months before study entry. Standard paclitaxel was given with corticosteroid plus antihistamine premedication in 99% of cycles, and ABI-007 was given without premedication in 98% of cycles. Four hun-

dred sixty patients were enrolled onto the study; ABI-007 was administered in less than an hour in more than 99% of patients, and paclitaxel was given over 3 hours.

Overall response rate, the primary end point of the trial, was found to be superior for patients randomly assigned to receive ABI-007 compared with paclitaxel (33% v 19%; $P = .001$). This advantage was maintained in the subgroups who were receiving the taxane as first-line therapy (42% v 27%; $P = .029$) and those who were receiving it as second- or third-line treatment (27% v 13%; $P = .006$) as well as the groups with differing degrees of prior anthracycline exposure. The secondary end point of time to progression was also superior in the nanoparticle paclitaxel group (23.0 v 16.9 weeks; $P = .006$). Overall survival was not found to be significantly different in the intent-to-treat population (65.0 v 55.7 weeks; $P = .374$), but there was a difference in the subgroup who received therapy as second or third line (56.4 v 46.7 weeks; $P = .024$).

Perhaps the most important aspect of the study was the difference seen in the toxicity profiles of the two drugs. Grade 4 neutropaenia was seen in 9% of the ABI-007 group compared with 22% of the patients receiving standard paclitaxel ($P < .001$). There were no severe (grade 3/4) hypersensitivity reactions reported in the patients who received ABI-007, compared with five of the 225 patients who received standard paclitaxel despite premedication, and mild reactions were rare in both groups (< 1% and 2%, respectively). Although the incidence of grade 3 sensory peripheral neuropathy was higher in patients who had received ABI-007 (10% v 2%, $P < .001$), the interruption of treatment and subsequent dose reduction allowed for return to grade 1 or II levels, with a median time of 22 days. The number of patients with persistent grade 3 neuropathy after 28 days was the same in each arm (< 2%). Some degree of alopecia was seen in most patients in both groups. The quality-of-life analysis showed no differences between the two arms.³¹

Compared with three-weekly polyoxyethylated castor oil-based paclitaxel, ABI-007 would seem to have several advantages. First, efficacy with respect to response and time to progression seems superior. Second, and arguably most importantly, this is a taxane that can be given three-weekly, in 30 minutes, and without premedication. For patients with a contraindication to steroids, this is a major advantage. In addition, the lower incidence of myelosuppression favors ABI-007, and although sensory neuropathy was more common, this was reversible and relatively short lived for the majority of patients. However, before a change in practice is considered as a result of this study, a key question needs to be asked:

Is paclitaxel 175 mg/m² three-weekly really the gold standard with which new taxanes should be compared? Firstly, is the dose adequate? Previously, one might have argued that the dose of paclitaxel was suboptimal, as the

Table 1. Study Characteristics

Study	ORR (%)	TTP (weeks)	OS (weeks)	Grade III/IV Neutropenia (%)	Febrile Neutropenia (%)
Jones et al, 2004 ³³					
Docetaxel 100 mg/m ²	32	24.7*	66.7*	93.3*	15*
Paclitaxel 175 mg/m ²	25	16*	55*	54.5*	2*
Gradishar et al, 2005 ³¹					
ABI-007 260 mg/m ²	33*	23	65	30*	< 2
Paclitaxel 175 mg/m ²	19*	16.9	55.7	46*	< 2

Abbreviations: ORR, overall response rate; TTP, time to progression; OS, overall survival.
*Denotes statistically significant difference.

phase II studies had often used doses in excess of 200 mg/m². However, the CALGB 9342 study that examined dose of paclitaxel failed to demonstrate any superiority for paclitaxel doses of 175, 210, and 250 mg/m² with response rates of 23%, 26%, and 21% respectively. There was, however, a very marked increase in paclitaxel-related neuropathy and myelosuppression with the higher doses.³²

Secondly, is the schedule optimal? As we have alluded to here, there seems, in terms of response rate and some toxicities, to be an advantage emerging for weekly taxane schedules.

Thirdly and most importantly, is paclitaxel the reference taxane? There has been one randomized trial that has compared paclitaxel with docetaxel in the first-line setting for metastatic breast cancer. Docetaxel at a dose of 100 mg/m² was compared with paclitaxel at 175 mg/m². In this trial, docetaxel was found to have a superior time to progression (5.7 v 3.7 months; *P* = .0001) and OS (15.4 v 12.7 months; *P* = .03), and there was also a trend toward a superior response rate (32% v 25%; *P* = .10). This trial, however, did show docetaxel to be associated with a significantly higher rate of neutropaenia and febrile neutropenia (Table 1).³³

Probably as a consequence of this head-to-head comparison and the randomized trials against doxorubicin, it is docetaxel, rather than paclitaxel, that has become the taxane of choice for most oncologists when selecting a drug for the first-line therapy of metastatic disease. The efficacy of ABI-007 seen in the trial reported by Grandishar et al would seem to be on par with docetaxel 100 mg/m², and certainly ABI-007 seems to be a less myelosuppressive drug (Table 1).

Fourthly, is a taxane alone good enough? For the vast majority of women with HER-2–overexpressing breast cancer, the standard treatment for metastatic disease will include trastuzumab. Therefore, for ABI-007 to be considered the new standard taxane for all patients with metastatic breast cancer, both efficacy and safety data need to be obtained for combination therapy for this agent. Likewise, its combinability with other cytotoxics such as gemcitabine and capecitabine needs to be tested in the metastatic setting.

In a situation in which a single-agent three-weekly taxane is being considered for metastatic breast cancer, this trial would certainly suggest that ABI-007 could be used. The other formulations and schedules of taxanes that are being developed must also be tested in the phase III setting and it is encouraging to think that this class of cytotoxics will now be available in more effective, less toxic, and more convenient regimens.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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REFERENCES

- Gianni L, Munzone E, Capri G, et al: Paclitaxel in metastatic breast cancer: A trial of two doses by a 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 87:1169-1175, 1995
- Wilson WH, Berg SL, Bryant G, et al: Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: A phase I/II trial of 96-hour infusion. *J Clin Oncol* 12:1621-1629, 1994
- Reichman BS, Seidman AD, Crown JP, et al: Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 11:1943-1951, 1993
- Valero V, Holmes FA, Walters RS, et al: Phase II trial of docetaxel: A new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol* 13:2886-2894, 1995
- ten Bokkel Huinink WW, Prove AM, Piccart M, et al: A phase II trial with docetaxel (Taxotere) in second line treatment with chemotherapy for advanced breast cancer: A study of the EORTC Early Clinical Trials Group. *Ann Oncol* 5:527-532, 1994
- Chan S, Friedrichs K, Noel D, et al: Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 17:2341-2354, 1999
- Paridaens R, Biganzoli L, Bruning P, et al: Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: A European Organization for Research and Treatment of Cancer Randomized Study with cross-over. *J Clin Oncol* 18:724-733, 2000
- Albain K, Nag S, Calderillo-Ruiz G: Global phase III study of gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. *Proc Am Soc Clin Oncol* 22:5s, 2004 (abstr 510)
- O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated

patients with advanced breast cancer: Phase III trial results. *J Clin Oncol* 20:2812-2823, 2002

10. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes form adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 21:976-983, 2003

11. Mamounas E, Bryant J, Fehrenbacher L, et al: Paclitaxel following doxorubicin/cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer. Results from NSABP B-28. *Proc Am Soc Clin Oncol* 22:4, 2003 (abstr 12)

12. Martin M, Pienkowski T, Mackey J, et al: Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 352:2302-2313, 2005

13. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001

14. Romond EH, Perez EA, Bryant J, et al: Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer: Combined analysis of NSABP-B31/NCCTG-N9831, Advances in monoclonal antibody therapy for breast cancer. American Society of Clinical Oncology Scientific Symposium, Orlando, FL, May 13-17, 2005

15. Piccart M: First results of the HERA trial: Advances in monoclonal antibody therapy for breast cancer. American Society of Clinical Oncology Scientific Symposium, Orlando, FL, May 13-17, 2005

16. Weiss RB, Donehower RC, Wiernik PH, et al: Hypersensitivity reactions from taxol. *J Clin Oncol* 8:1263-1268, 1990

17. Bookman MA, Klothe DD, Kover PE, et al: Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Ann Oncol* 8:611-614, 1997

18. Markman M, Kennedy A, Webster K, et al: An effective and more convenient drug regimen for prophylaxis against paclitaxel-associated hypersensitivity reactions. *J Cancer Res Clin Oncol* 125:427-429, 1999

19. Micha JP, Rettenmaier MA, Dillman R, et al: Single-dose dexamethasone paclitaxel premedication. *Gynecol Oncol* 69:122-124, 1998

20. Parikh B, Khanolkar S, Advani SH, et al: Safety profile of single-dose dexamethasone premedication for paclitaxel. *J Clin Oncol* 14:2189-2190, 1996

21. Perez EA, Vogel CL, Irwin DH, et al: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 19:4216-4223, 2001

22. Taberero J, Climent MA, Lluch A, et al: A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol* 15:1358-1365, 2004

23. Wolff AC, Donehower RC, Carducci MK, et al: Phase I study of docosahexaenoic acid-paclitaxel: A taxane-fatty acid conjugate with a unique pharmacology and toxicity profile. *Clin Cancer Res* 9:3589-3597, 2003

24. Kim TY, Kim DW, Chung JY, et al: Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin Cancer Res* 10:3708-3716, 2004

25. Hidalgo M, Aylesworth C, Hammond LA, et al: Phase I and pharmacokinetic study of BMS-184476, a taxane with greater potency and solubility than paclitaxel. *J Clin Oncol* 19:2493-2503, 2001

26. Sessa C, Cuvier C, Caldiera S, et al: Phase I clinical and pharmacokinetic studies of the taxoid derivative RPR 109881A administered as a 1-hour or a 3-hour infusion in patients with advanced solid tumors. *Ann Oncol* 13:1140-1150, 2002

27. Kurata T, Shimada Y, Tamura T, et al: Phase I and pharmacokinetic study of a new taxoid, RPR 109881A, given as a 1-hour intravenous infusion in patients with advanced solid tumors. *J Clin Oncol* 18:3164-3171, 2000

28. Sparreboom A, Scripture CD, Trieu V, et al: Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res* 11:4136-4143, 2005

29. Ibrahim NK, Desai N, Legha S, et al: Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res* 8:1038-1044, 2002

30. Ibrahim NK, Samuels B, Page R, et al: Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol* 23:6019-6026, 2005

31. Gradishar WJ, Tjulandin S, Davidson N, et al: Superior efficacy of nanoparticle albumin-bound paclitaxel (Abraxane, ABI-007) compared with cremophor-based paclitaxel (Taxol) in women with metastatic breast cancer: Results of a phase III trial. *J Clin Oncol* 23: 10.1200/JCO.2005.04.937

32. Winer EP, Berry DA, Woolf S, et al: Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and Leukemia Group B trial 9342. *J Clin Oncol* 22:2061-2068, 2004

33. Jones S, Erban J, Overmoyer B: Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 23:5542-5551, 2005