

CED-SOS Advice Report 6 EDUCATION AND INFORMATION 2012

The Role of Albumin-bound Paclitaxel (Abraxane) in the Treatment of Metastatic Breast Cancer

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

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This particular document was developed by one clinical expert and one PEBC staff member. This document has been internally approved by PEBC management but has not been subject to a broader external review due to time constraints.

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CED-SOS Advice Report 6: Section 1 EDUCATION AND INFORMATION 2012

The Role of Albumin-bound Paclitaxel (Abraxane) in the Treatment of Metastatic Breast Cancer: Recommendations

C. Hamm and C. Walker-Dilks

Report Date: June 1, 2007

The 2007 guideline recommendation were put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

Question

What is the role of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) (Abraxane, ABI-007) in the treatment of women with metastatic breast cancer? Outcomes of interest are time to progression; time to treatment failure; objective response rate; overall survival; progression-, disease-, and event-free survival; quality of life; patient tolerance (compliance and continuation); toxicity and adverse effects; and treatment-related deaths.

Target Population

These recommendations apply to adult female patients with metastatic breast cancer.

Recommendation

- Women with metastatic breast cancer and no previous taxane chemotherapy who are candidates for first- or second-line single-agent paclitaxel could be offered *nab*-paclitaxel.

Qualifying Statement

- Evidence from a randomized phase II trial suggests that *nab*-paclitaxel may be equivalent or superior to docetaxel in terms of tumour response rate with a decrease in neutropenia and no increase in neuropathy.
- Evidence from a subgroup analysis of a randomized phase III trial shows that overall survival with *nab*-paclitaxel does not differ from paclitaxel in first-line therapy, but *nab*-paclitaxel is superior in second-line therapy.

Evidence

- Two randomized controlled trials: one phase III full report and one four-arm randomized phase II trial presented in abstract/presentation form.
- The phase III trial established the superiority of *nab*-paclitaxel over standard paclitaxel in terms of overall response rate and time to tumour progression with a lower rate of grade 4 neutropenia.
- The phase II trial showed better tumour response with *nab*-paclitaxel 100 or 150 mg/m² every three out of four weeks (qw 3/4) than with docetaxel 100 mg/m² q3w, and less grade 4 neutropenia.

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CED-SOS Advice Report 6: Section 2 EDUCATION AND INFORMATION 2012

The Role of Albumin-bound Paclitaxel (Abraxane) in the Treatment of Metastatic Breast Cancer: Systematic Review/Evidentiary Base

C. Hamm and C. Walker-Dilks

Report Date: June 1, 2007

The 2007 guideline recommendation was put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

QUESTION

What is the role of nanoparticle albumin-bound paclitaxel (Abraxane, ABI-007) in the treatment of metastatic breast cancer? Outcomes of interest are time to progression; time to treatment failure; objective response rate; overall survival; progression-free, disease-free, and event-free survival; quality of life; patient tolerance (compliance and continuation); toxicity and adverse effects; and treatment-related deaths.

INTRODUCTION

Breast cancer is the most common cancer in women. About 22 000 Canadian women are diagnosed each year, with an estimated 5300 deaths (1). Taxanes (paclitaxel and docetaxel) are among the most effective drugs available for metastatic breast cancer but are associated with substantial adverse effects and tolerability issues. Paclitaxel and docetaxel are water insoluble, requiring intravenous administration in polyethoxylated castor oil (Cremophor EL) and polysorbate 80, respectively, which are increasingly believed to be responsible for some of the increased toxicity (2,3). Premedication with histamine blockers and corticosteroids is required to avoid hypersensitivity reactions (4). Furthermore, this formulation also requires long infusion times (three hours) and special intravenous tubing (2). Approaches to enhancing the effectiveness of taxanes while reducing the associated adverse effects include altering the scheduling and changing the formulation or delivery vehicle (3).

Nanoparticle albumin-bound (*nab*) paclitaxel is a Cremophor-free formulation of paclitaxel in which paclitaxel is bound to nanoparticles of albumin. *nab*-paclitaxel requires less

volume, less time for administration, and no premedication. *nab*-paclitaxel was approved by the U.S. Food and Drug Administration in January 2005 for second-line treatment of metastatic breast cancer and was approved by Health Canada in September 2006 for treatment of metastatic breast cancer, including first-line treatment.

METHODS

This advice report was developed by the Program in Evidence-based Care (PEBC) following a request from the Committee to Evaluate Drugs (CED). This document was not formally developed by the Breast Cancer Disease Site Group (DSG) of the PEBC; however, a draft of this document was circulated to the DSG for comment. The expertise of one clinical expert was sought (CH). This expert worked with the PEBC to review the available evidence and develop recommendations that the CED could consider when making a funding decision concerning this drug. This document has been internally approved by the PEBC but has not been circulated to a broader audience in Ontario for review and approval at this time due to time constraints.

This advice report, produced by the PEBC, is a summary of the best available evidence on the role of *nab*-paclitaxel in the treatment of metastatic breast cancer developed through systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario (CCO). All work produced by the PEBC is editorially independent from its funding source.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (1950 to February, week 4, 2007) and EMBASE (1980 to week 9, 2007) were searched using the search terms shown in Table 1. Additionally, the conference proceedings from the American Society of Clinical Oncology (ASCO) (2000-2006) and the San Antonio Breast Cancer Symposium (SABCS) (1996-2006) meetings were searched for abstracts of relevant trials.

Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from those sources were searched for additional trials.

Table 1. Literature search strategy.

Search date	Database	Search terms used
8 Mar 2007	MEDLINE	Abraxane, ABI-007, (paclitaxel and [albumins or protein])
8 Mar 2007	EMBASE	
8 Mar 2007	SABCS abstracts	Abraxane, ABI-007, paclitaxel, nab-paclitaxel
8 Mar 2007	ASCO abstracts	

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports or published abstracts involving human subjects of:

1. Randomized controlled trials (RCTs) (phase II or III) comparing nab-paclitaxel as a single agent or in combination with any other intervention in women with metastatic breast cancer.

Exclusion Criteria

1. Letters, editorials, and comments were not eligible

2. Nonrandomized phase II trials were not eligible

Synthesizing the Evidence

Due to the low number of studies meeting criteria and the fact that one trial was only available in abstract, meta-analysis was not done.

RESULTS

Literature Search Results

The literature search results are in Table 2. Overall, 25 citations were considered of interest and scrutinized; two trials (reported in two abstracts and one full report) met the selection criteria (5-7).

Table 2. Literature search results.

Database	# of citations	Of interest	Met criteria
MEDLINE	144	11	1
EMBASE	73	1	0
SABCS	16	8	2
ASCO	15	5	0

ASCO = American Society of Clinical Oncology; SABCS = San Antonio Breast Cancer Symposium

The study characteristics for the two included trials appear in Table 3. Gradishar et al (5) conducted a multicentre (70 sites), randomized phase III noninferiority trial of 460 women (mean age 53 years [y]); 97% white; 83% postmenopausal) with metastatic breast cancer. Funding was provided by American BioScience, the manufacturers of Abraxane. Inclusion criteria were age ≥ 18 years, histologically or cytologically confirmed metastatic breast cancer with expected survival > 12 weeks, candidacy for single-agent paclitaxel, no previous paclitaxel or docetaxel therapy for metastatic carcinoma, no relapse with metastatic disease within one year of adjuvant paclitaxel or docetaxel, no other malignancy in the previous five years (except nonmelanoma skin cancer, cervical intraepithelial neoplasia, or in situ cervical cancer), and acceptable test results at baseline. Exclusion criteria were active brain metastasis or serious concurrent illness; Eastern Cooperative Oncology Group (ECOG) performance status > 2 ; hormone therapy in the past two weeks; chemotherapy, immunotherapy, or other investigational drug in the past four weeks; pre-existing peripheral neuropathy; or contraindication to the study drugs. Patients were allocated to *nab*-paclitaxel, 260 mg/m² intravenously over 30 minutes every three weeks without corticosteroid or antihistamine premedication or special infusion sets (n=229) or to paclitaxel, 175 mg/m² intravenously over three hours every three weeks with premedication and special infusion sets (n=225). Four hundred fifty-four patients (99%) were included in the intention-to-treat analysis. The primary outcome measure was overall response rate. Secondary outcomes were time to tumour progression, overall survival, and quality of life measures (e.g., ECOG performance status scores). An early report of this trial by O'Shaughnessy et al (6) was presented at SABCS in 2005 with outcomes reported after six cycles of treatment.

Gradishar et al (7,8) presented the planned interim results of a randomized phase II trial at SABCS 2006, comparing three different doses of *nab*-paclitaxel with docetaxel in 300 women (mean age 54 y, 73% postmenopausal) with metastatic breast cancer. Women were allocated to *nab*-paclitaxel, 300 mg/m² every three weeks (q3w); 100 mg/m² or 150 mg/m² days 1, 8, and 15 every 28 days (qw 3/4); or solvent-based docetaxel, 100 mg/m² q3w. Outcomes of interest were objective confirmed tumour response rate, toxicity, and progression-free survival. Patients were enrolled from November 2005 to June 2006 with four planned interim analyses. A slide presentation given at SABCS 2006 (available on CD-ROM) included results up to the third planned interim analysis in November 2006 (8).

Study Quality

The trials did not describe measures taken to ensure allocation concealment. O'Shaughnessy et al (6) reported that the target lesions in an independently reviewed data set were reviewed by a radiology team blinded to treatment. The randomization procedure in Gradishar et al (5) indicated 1:1 randomization stratified by anthracycline-exposed and anthracycline-naïve groups within countries. Gradishar et al (5) also used intention-to-treat analysis.

Table 3. *nab*-paclitaxel versus other interventions for metastatic breast cancer – characteristics of included studies.

Trial	Interventions	Dosage	# patients	Type of trial & analysis	Treatment setting	ITT
Gradishar, 2005 (5)	<i>nab</i> -paclitaxel	260 mg/m ² q3w	229	Multicentre, phase III, noninferiority, final	≥ First-line	Yes
	Paclitaxel	175 mg/m ² q3w	225			
Gradishar, 2006 (7,8)	<i>nab</i> -paclitaxel	300 mg/m ² q3w	300	Phase II, interim	NR	NR
	<i>nab</i> -paclitaxel	100 mg/m ² qw 3/4				
	<i>nab</i> -paclitaxel	150 mg/m ² qw 3/4				
	Docetaxel	100 mg/m ² q3w				

ITT = intention-to-treat analysis; NR = not reported.

Outcomes

Randomized Phase III Trial

In this phase III trial (5), the overall response rate was greater for *nab*-paclitaxel than for paclitaxel in all patients and in patients in the following preplanned subgroups: first-line therapy, ≥ second-line therapy (Table 4), previous anthracycline therapy in the adjuvant (34% versus [vs] 18%, $p=0.002$) or metastatic setting (27% vs 14%, $p=0.010$), visceral dominant lesions (34% vs 19%, $p=0.002$), and < 65 years of age (34% vs 19%, $p<0.001$).

Median time to tumour progression was longer with *nab*-paclitaxel in all patients and reached statistical significance in those who received ≥ second-line therapy but not in those who received first-line therapy (Table 4).

A trend to greater median overall survival was seen but reached statistical significance only in a subgroup of patients who received it as ≥ second-line therapy (Table 4).

Adverse event-related discontinuations, dose reductions, and dose delays were infrequent in both *nab*-paclitaxel and paclitaxel groups (3% vs 7%), and groups did not differ for quality of life status scores. The most frequently reported adverse events (> 20%) were alopecia, sensory neuropathy, fatigue, neutropenia, arthralgia, myalgia, nausea, infection with unknown absolute neutrophil count, and diarrhea. *nab*-paclitaxel was associated with more sensory neuropathy, nausea, and diarrhea than paclitaxel ($p<0.05$), whereas paclitaxel was associated with more neutropenia ($p<0.05$). Despite the higher dose of paclitaxel received by patients in the *nab*-paclitaxel group, the rate of treatment-related grade 4 neutropenia was lower in the *nab*-paclitaxel group than the standard paclitaxel group (9% vs 22%, $p<0.001$). However, treatment-related grade 3 sensory neuropathy was more common in the *nab*-paclitaxel group than in the paclitaxel group (10% vs 2%, $p<0.001$). By day 28, the numbers of patients were similar in each group (1.7% vs 1.8%).

Table 4. Treatment outcomes for *nab*-paclitaxel vs standard paclitaxel (5).

Outcomes	Patient group	<i>nab</i> -paclitaxel	Paclitaxel	p Value	
Overall response rate	All patients	76/229 (33%)	42/225 (19%)	0.001	
	1 st -line therapy	41/97 (42%)	24/89 (27%)	0.029	
	≥ 2 nd -line therapy	35/132 (27%)	18/136 (13%)	0.006	
				Hazard ratio	p Value
Median time to tumour progression (wk)	All patients	23	16.9	0.75	0.006
	1 st -line therapy	24	19.7	Not significant	
	≥ 2 nd -line therapy	20.9	16.1	0.73	0.020
Median overall survival (wk)	All patients	65	55.7	NR	0.374
	1 st -line therapy	NR	NR	Not significant	
	≥ 2 nd -line therapy	56.4	46.7	0.73	0.024

NR = not reported

Randomized Phase II Trial

In the randomized phase II trial, data from the third planned interim analysis in November 2006 (8) showed increased response rates for *nab*-paclitaxel 100 and 150 mg/m² q 3 of 4 weekly (qw 3/4) over docetaxel (Table 5). Grade 4 neutropenia rates were significantly lower with *nab*-paclitaxel, and no significant increase was noted in peripheral neuropathy.

Table 5. Treatment outcomes for *nab*-paclitaxel 300 q3w, 100 and 150 mg/m² qw 3/4 vs solvent-based docetaxel 100 mg/d q3w November 2006 planned interim analysis (8).

Outcome	<i>nab</i> -paclitaxel 300	<i>nab</i> -paclitaxel 100	<i>nab</i> -paclitaxel 150	Docetaxel
Objective confirmed tumour response	33%	58%	62%	36%*
Grade 4 neutropenia	4%	3%	7%	74%†
Febrile neutropenia	1%	1%	1%	7%
Grade 3 peripheral neuropathy	14%	7%	12%	5%

*p=0.004 *nab*-paclitaxel 100 vs docetaxel; p=0.016 *nab*-paclitaxel 150 vs docetaxel†p<0.001 *nab*-paclitaxel 300, 100, and 150 vs docetaxel**DISCUSSION**

Evidence from one phase III randomized trial (5) and one phase II randomized (7,8) trial shows substantial benefit with *nab*-paclitaxel versus paclitaxel or docetaxel in women with metastatic breast cancer in terms of increased response rate and time to tumour progression. Overall survival is increased in women receiving *nab*-paclitaxel as second-line therapy (with a trend toward improvement with first-line therapy) compared with paclitaxel. *nab*-paclitaxel, (particularly 100 mg/m² given qw 3/4) is associated with decreased grade 4 neutropenia compared with paclitaxel or docetaxel. Compared with docetaxel, it does not increase peripheral neuropathy rates. Longer follow-up is required to determine if an overall survival benefit is seen in more than subgroups of patients, and given the current paucity of available evidence, more confirmatory trials of the effectiveness of *nab*-paclitaxel are desired. *nab*-paclitaxel may be

associated with cost savings in the oncology setting as this medication requires only a short infusion with no premedications, but a formal cost-effectiveness study is required to confirm this.

CONCLUSIONS

nab-paclitaxel as second-line therapy for metastatic breast cancer has been shown to offer improved overall survival compared with paclitaxel in this setting, and therefore could be included as a treatment option in this group of women. It is also reasonable to offer *nab*-paclitaxel as first-line therapy to women with metastatic breast cancer as it offers improved response rate over docetaxel in this setting, with a possible decrease in toxic side effects. *nab*-paclitaxel at a dose of 100 mg/m² qw 3/4 is the preferred dosing regimen because it offers the best combination of equivalent efficacy and minimal neuropathy.

Future Research

A search was made of the National Cancer Institute clinical trials database for ongoing RCTs comparing *nab*-paclitaxel alone or in combination with any other intervention in metastatic breast cancer. One phase II trial was identified: NCT00281528 (A Phase II Study of Weekly Versus Every 2-Week Versus Every 3-Week Administration of ABI-007 (Abraxane) in Combination With Bevacizumab in Women With Metastatic Breast Cancer) is a multicenter, open-label, RCT in previously untreated patients with metastatic breast cancer evaluating the antitumor activity and safety of weekly dose-dense *nab*-paclitaxel compared with a 2-weekly regimen vs the standard 3-weekly infusion.

Furthermore, Gradishar et al are planning a phase III trial of 1000 women with metastatic breast cancer randomized to *nab*-paclitaxel 100 mg/m² infused over 30 minutes every week with no premedication or to docetaxel 100 mg/m² infused over three hours every three weeks with standard premedication with dexamethasone and antihistamines (8).

CONFLICT OF INTEREST

The authors of this report declared that there were no potential conflicts of interest related to the topic of this CED advice report.

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