Taxanes in the Metastatic Setting

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Single-agent paclitaxel and docetaxel are the most common first-line chemotherapeutic approaches in previously untreated patients in the first-line metastatic setting. Data presented at last year's San Antonio Breast Cancer Symposium demonstrated improved efficacy with docetaxel compared to paclitaxel on an every three-week schedule. Docetaxel is associated with a significant rate of febrile neutropenia when used at 100 mg/m², and a recent placebo-controlled randomized trial demonstrated that pegfilgrastim dramatically reduces the incidence of this complication. Nanoparticle paclitaxel appears to be as efficacious as docetaxel, but this agent does not require premedication and thus avoids secondary side effects and toxicity.

TAX 311: A PHASE III RANDOMIZED TRIAL OF DOCETAXEL VERSUS PACLITAXEL IN METASTATIC BREAST CANCER

Response rate and duration data

Parameter	Intent-to-treat population		Evaluable population	
	Docetaxel (n=225)	Paclitaxel (n=224)	Docetaxel (n=189)	Paclitaxel (n=205)
Response rate (CR + PR)	32.0%	25.0%	37.0%	25.9%
	$p = 0.10$		$p < 0.05$	
Stable disease	38.2%	39.7%	42.9%	42.9%
Duration of response	7.5 mo	4.6 mo	7.5 mo	4.6 mo
	$p < 0.05$		$p < 0.05$	

Time to progression (TTP) and survival data

Parameter	Docetaxel	Paclitaxel	*p*-value
Median TTP	5.7 months (95% CI 4.6-6.9)	3.6 months (95% CI 3.1-4.2)	<0.0001
Overall survival	15.4 months (95% CI 13.3-18.6)	12.7 months (95% CI 10.6-14.8)	0.03

Toxicity data

Parameter	Docetaxel (n=222)		Paclitaxel (n=222)	
	Overall	Grade 3/4	Overall	Grade 3/4
Neutropenia*	96%	93%	83%	55%
Febrile neutropenia*	15%		2%	
Anemia	77%	10%	61%	7%
Infection*	33%	10%	10%	2%
Stomatitis*	51%	11%	16%	0%
Asthenia*	74%	21%	55%	5%

Secondary G/GM-CSF administered to 23.4% of patients receiving docetaxel and 4.1% of patients receiving paclitaxel

* For the difference in Grade 3/4 toxicities, $p < 0.05$

SOURCE: Jones S et al. **Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 10.

ANTHRACYCLINES WITH OR WITHOUT TAXANES AS FIRST-LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER: COMPREHENSIVE REVIEW OF 2,805 PATIENTS IN SEVEN PHASE III TRIALS

Parameter	Risk ratio	95% CI	*p*-value
Time to progression	1.10	1.00-1.21	0.05
Overall response rate	1.21	1.10-1.32	<0.001
Complete response rate	2.04	1.41-2.94	<0.001
Overall survival	1.05	0.90-1.23	0.58
Neutropenia	1.19	1.11-1.29	<0.001
Febrile neutropenia	2.82	1.39-5.69	<0.001
Cardiotoxicity	3.34	0.90-12.41	Not reported
Neurotoxicity	13.20	1.51-115	Not reported

Conclusions:
- The combination of taxanes and anthracyclines is significantly more active in terms of overall response and complete response rates and slightly but significantly more beneficial in terms of time to progression when compared to standard anthracycline therapy.
- Toxicity (mainly neutropenia and febrile neutropenia) is significantly greater for the combination of taxanes and anthracyclines than standard anthracycline therapy.

SOURCE: Bria E et al. **Impact of taxanes in association with anthracyclines in 1st line chemotherapy for metastatic breast cancer (MBC): Comprehensive review of 2805 patients in 7 Phase III trials.** Presentation. ASCO, 2004;Abstract 659.

PHASE III TRIAL OF NANOPARTICLE PACLITAXEL (ABI-007) VERSUS PACLITAXEL IN METASTATIC BREAST CANCER

Efficacy data

Investigator response assessments	All treated patients		First-line patients	
	ABI-007 (n=229)	Paclitaxel (n=225)	ABI-007 (n=97)	Paclitaxel (n=89)
Overall response rate (CR + PR)	33% (95% CI 27-39%)	19% (95% CI 14-24%)	42% (95% CI 32-52%)	27% (95% CI 18-36%)
	$p < 0.001$		$p = 0.029$	
Independent radiology review	**All treated patients**		**First-line patients**	
	ABI-007 (n=215)	Paclitaxel (n=214)	ABI-007 (n=97)	Paclitaxel (n=89)
Overall response rate (CR + PR)	21% (95% CI 16-27%)	10% (95% CI 6-14%)	29% (95% CI 20-38%)	14% (95% CI 6-21%)
	$p = 0.002$		$p = 0.011$	
Time to tumor progression	ABI-007 21.9 weeks	Paclitaxel 16.1 weeks	*p*-value 0.029	

Toxicity data*

Parameter	ABI-007 (n=229)		Paclitaxel (n=225)		*p*-value
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia	25%	9%	31%	22%	< 0.001
Sensory neuropathy	10%	0%	2%	0%	< 0.001

SOURCE: O'Shaughnessy J et al. **ABI-007 (Abraxane™), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in metastatic breast cancer: A Phase III trial.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 44.

PHASE III STUDY OF PEGFILGRASTIM VERSUS PLACEBO IN PATIENTS RECEIVING DOCETAXEL

Accrual: 928 (Closed)

Eligibility	Stage 1-4 breast cancer, ECOG performance of 0-2, ≥18 years of age
ARM 1	Docetaxel + pegfilgrastim*
ARM 2	Docetaxel + placebo*

* Patients on either arm experiencing febrile neutropenia entered an open-label phase in which they received docetaxel + pegfilgrastim

EFFICACY DATA

Parameter	Placebo** (n=465)	Pegfilgrastim** (n=463)	*p*-value
Febrile neutropenia (FN)	17%	1%	<0.0001
FN-related hospitalizations	14%	1%	<0.0001
FN-related IV anti-infective use	10%	2%	<0.0001
Chemotherapy planned dose on time (cycles 2-4)***	78%	80%	Not reported

** 62% of patients had metastatic disease
*** Placebo arm included patients receiving open-label pegfilgrastim

Summary:
- Pegfilgrastim was well tolerated and resulted in a relative reduction of 94% in FN, 93% in FN-related hospitalizations and 80% in IV anti-infective use.
- 65% of FN occurred during the first cycle in the placebo group.

SOURCE: Vogel CL. Presentation. *Breast Cancer Update* Think Tank on Adjuvant Chemotherapy, August 2004.

SELECT PUBLICATIONS

Fortner BV et al. **Medical visits for chemotherapy and chemotherapy-induced neutropenia: A survey of the impact on patient time and activities.** *BMC Cancer* 2004;4(1):22.

Ghersi D et al. **Taxane containing regimens for metastatic breast cancer.** *Cochrane Database Syst Rev* 2003(3):CD003366.

Holmes FA et al. **Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer.** *J Clin Oncol* 2002;20(3):727-31.

Jones S et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2003;Abstract 10.

O'Shaughnessy J et al. **ABI-007 (Abraxane™), a nanoparticle albumin-bound (nab) paclitaxel demonstrates superior efficacy vs taxol in metastatic breast cancer: A Phase III trial.** San Antonio Breast Cancer Symposium, 2003;Abstract 44.

Schwartzberg LS. **First and subsequent cycle pegfilgrastim significantly reduces febrile neutropenia (FN) in patients with breast cancer receiving moderately myelosuppressive chemotherapy: A double-blind, placebo-controlled Phase 3 study.** Multinational Association of Supportive Care in Cancer Annual Meeting, 2004;Abstract A-52.

Zielinski CC. **Gemcitabine, anthracycline, and taxane combinations for advanced breast cancer.** *Oncology (Huntingt)* 2003;17(12 Suppl 14):36-40.

TAX-311: DOCETAXEL VERSUS PACLITAXEL

The TAX-311 trial was completed in 2003 and basically confirmed that docetaxel was probably a more potent taxane, at least the every three-week schedule. I didn't expect the results to be so dramatic. The evaluable patients demonstrated a significant difference in the response rate, time to tumor progression and survival in favor of docetaxel. The survival advantage was surprising — few regimens have a documented survival advantage in patients with metastatic breast cancer. More toxicity was associated with docetaxel, but it was the usual manageable toxicity.

— Stephen E Jones, MD

NANOPARTICLE PACLITAXEL IN THE METASTATIC SETTING

The pivotal trial of nanoparticle paclitaxel in anthracycline-pretreated patients showed it to be as efficacious as docetaxel in terms of response rates. The Phase III trial demonstrated superior efficacy of nanoparticle paclitaxel 260 mg/m² over paclitaxel 175 mg/m² in terms of response rate and time to progression. I believe in the next few years physicians will use nanoparticle paclitaxel for palliation in the metastatic setting in patients whom they want to experience as few side effects as possible. I expect it will be used weekly at 100 mg/m² for three weeks, followed by one week off, as in Joanne Blum's study.

I have treated several patients with this agent and found it to be extremely well tolerated, particularly at the 100 mg/m² dose. I don't premedicate patients receiving nanoparticle paclitaxel, because most patients on weekly taxanes do not have problems with hypersensitivity reactions. In addition, I find weekly dexamethasone is not well tolerated by patients — it tires them and has a crash effect. Avoiding premedication may be one of the reasons we don't see significant side effects with the nanoparticle paclitaxel.

— Joyce O'Shaughnessy, MD

TRIAL COMPARING PEGFILGRASTIM TO PLACEBO IN PATIENTS RECEIVING DOCETAXEL

The objective of this study was to determine if pegfilgrastim significantly reduces febrile neutropenia in patients receiving a chemotherapy regimen associated with an expected rate of approximately 20 percent. Patients were eligible for the trial whether they were receiving docetaxel in the adjuvant or the metastatic setting. In this double-blind, randomized trial, patients received docetaxel plus pegfilgrastim versus a placebo. If a patient developed febrile neutropenia, they were able to subsequently receive pegfilgrastim.

Febrile neutropenia, related hospitalizations and intravenous anti-infective use were all significantly reduced by pegfilgrastim. While the difference in the rates of patients receiving their planned chemotherapy dose on time doesn't look impressive, all the placebo patients who developed febrile neutropenia received pegfilgrastim. Consequently, both groups experienced delivery of planned dose on time.

— Charles L Vogel, MD

This study provides compelling evidence that administering pegfilgrastim in the first and subsequent cycles of moderately myelosuppressive chemotherapy can significantly reduce the risk of potentially life-threatening infections that can result in hospitalizations and require IV antibiotics. Approximately 600,000 chemotherapy patients are at risk of developing neutropenia, which has traditionally been treated reactively. Doctors usually reserve proactive use of pegfilgrastim for only those patients considered at very high risk of developing chemotherapy-induced neutropenia. This study may give physicians the evidence they need to help protect cancer patients from chemotherapy-induced neutropenic complications beginning in the first cycle of chemotherapy treatment.

— Lee Schwartzberg, MD