



Oncology: Taxanes

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Executive Summary

- Taxanes are antimicrotubule agents that prevent cancer cells from growing and dividing in an efficient manner.^[1]
- Taxanes are recognized in NCCN Guidelines as either recommended or acceptable first-line treatments for early breast cancer, metastatic breast cancer, advanced or metastatic non-small cell lung cancer, or ovarian cancer because they appear to impact health outcomes (such as progression free survival and overall survival).
- While paclitaxel and docetaxel have been widely studied in many cancers, albumin-bound paclitaxel has only been established in metastatic breast cancer.
- The efficacy data for taxane chemotherapy is largely unreliable making it very difficult to measure the extent of clinical benefit for a given medication or to compare across medications.
- There is no reliable evidence that one taxane is more effective than another, yet there may be differences in efficacy for a given cancer type or stage of cancer.

Evidence

Paclitaxel versus docetaxel:

- Six well-conducted systematic reviews evaluated studies using taxane containing regimens versus non-taxane regimens in the treatment of early breast cancer, metastatic breast cancer, ovarian cancer and non-small cell lung cancer.^[5-10] None of the reviews found adequate evidence to reliably distinguish between the effectiveness of the taxanes in these cancer types.
- Ten additional Phase II and Phase III randomized controlled trials that were not included in the systematic reviews were also evaluated. These studies offered a direct comparison between paclitaxel and docetaxel containing regimens in the treatment of early breast cancer, metastatic breast cancer, ovarian cancer, non-small cell lung cancer and gastric cancer.^[11-20] Because of significant methodological flaws, these were also appraised as unreliable for making health care decisions.

Paclitaxel versus albumin-bound paclitaxel:

One randomized, controlled trial compared paclitaxel to albumin-bound paclitaxel in patients with metastatic breast cancer.^[21] This trial was appraised as unreliable because of flaws including an open-label design and primary endpoint that had a subjective component.

Other considerations

Without reliable evidence to guide decision making, issues considered in the formulary recommendation include:

Formulary Considerations for Taxanes	
Consideration	Impact
Safety	<ul style="list-style-type: none"> • There are differences in rates and severity of adverse effects. <ul style="list-style-type: none"> - Docetaxel may be associated with a higher incidence of severe neutropenia compared to the other taxanes. - Albumin-bound paclitaxel and paclitaxel may be associated with a higher incidence of peripheral neuropathy than docetaxel. - Albumin-bound paclitaxel is associated with a lower incidence of hypersensitivity reactions but a higher risk of neuropathy. • Approximately 2-4 percent of patients will have a severe hypersensitivity reaction to paclitaxel or docetaxel requiring discontinuation of the drug. Hypersensitivity reactions can occur with the first infusion or develop over time.
Differences in administration	<p>Paclitaxel and docetaxel contain solvents that may be associated with side effects requiring premedication with corticosteroids, diphenhydramine and H₂-antagonists.^[3] Albumin-bound paclitaxel formulation does not contain solvents, is more easily prepared for administration, and is infused over a shorter time period.^[3]</p>
Potential place in therapy	<ul style="list-style-type: none"> • Where a patient is responding to paclitaxel and develops a hypersensitivity reaction to the taxane, albumin-bound paclitaxel may be a preferred option versus changing to a different chemotherapy agent. • In metastatic breast cancer where other treatment regimens have failed, Abraxane is an option for women who choose to continue therapy but the clinical benefit in terms of time to progression and overall survival is unclear. • Albumin-bound paclitaxel is currently being studied in other cancers.
Clinical Practice Guidelines	<p>There are other NCCN recommended treatment options available as first, second, third line and beyond chemotherapy regimens for metastatic breast cancer. Some examples of these other treatments include anthracyclines, antimetabolites, other microtubule inhibitors or combination regimens.</p> <p>Taxane containing regimens are recommended as first line treatments for ovarian cancer and non-small cell lung cancer.</p>
Cost	<ul style="list-style-type: none"> • Paclitaxel is available as a generic medication. • Docetaxel (Taxotere) and albumin-bound paclitaxel (Abraxane) are available as brand name medications that cost at least ten times the cost of generic paclitaxel.

Decision

- Add paclitaxel and docetaxel (Taxotere) as preferred/formulary because both agents offer value in the treatment of various cancer types including breast, ovarian and non-small cell lung cancer.
- Maintain non-preferred/non-formulary status for albumin-bound paclitaxel (Abraxane) because:
 - There is no evidence that it is superior to other agents for the treatment of metastatic breast cancer.
 - Although albumin-bound paclitaxel (Abraxane) may offer an option for the small number of paclitaxel patients who have responded to therapy but have developed severe hypersensitivity reactions, there is no evidence that its overall safety profile offers an advantage over the other products.

Products

Table 1: Approval dates, indications, dosing, and cost of taxanes:

Drug Products	FDA approval ^a	Patent expiration ^b	FDA approved indications	Usual Dose
paclitaxel (Taxol [®])	December 1992	expired	<ul style="list-style-type: none"> AIDS-related Kaposi's sarcoma, Second line treatment. Breast cancer, Adjuvant therapy for node-positive disease, administered sequentially to the standard doxorubicin-containing regimen. Breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Non-small cell lung cancer, first-line therapy, in combination with cisplatin in patients who are not candidates for surgery and/or radiation. Ovarian cancer, advanced, first-line therapy in combination with cisplatin. Ovarian cancer, advanced, in patients previously treated with chemotherapy. 	80mg/m ² IV over 1 hour q week 135mg/m ² IV over 3 hours q 3 weeks 175mg/m ² IV over 3 hours 3 3 weeks 135mg/m ² IV over 24 hours followed by cisplatin 75mg/m ² q 3 weeks
docetaxel (Taxotere [®])	May 1996	May 2010	<ul style="list-style-type: none"> Breast cancer, adjuvant treatment in combination with doxorubicin and cyclophosphamide for patients with operable node-positive disease. Breast cancer, locally advanced/metastatic disease, after failure of prior chemotherapy. Gastric cancer. Head and neck cancer, locally advanced squamous cell disease, induction treatment in combination with cisplatin and fluorouracil. Hormone refractory prostate cancer, metastatic, in combination with prednisone. Non-small cell lung cancer, locally advanced/metastatic disease, as monotherapy after failure of prior platinum-based chemotherapy. Non-small cell lung cancer, unresectable, locally advanced/metastatic disease, first-line therapy in combination with cisplatin. 	60 to 100 mg/m ² IV over 1 hour q 3 weeks 75 mg/m ² IV over 1 hour q 3 weeks
paclitaxel protein bound (Abraxane [®])	January 2005	February 2013	<ul style="list-style-type: none"> Breast cancer, following failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant therapy. 	260 mg/m ² IV over 30 minutes every 3 weeks

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in the Orange Book as of 12/12/2008.

Table 2: Comparison of selected characteristics of taxanes:

	paclitaxel	docetaxel	albumin-bound paclitaxel
Administration			
Dosing interval	q week or q 3 weeks	q 3 weeks	q 3 weeks
Infusion period	1-3 hours (for NSLC over 24 hours)	1 hour	30 minutes
Additional dosage forms/routes	n/a	n/a	n/a
Pregnancy Category	D	D	D
Clinically relevant drug-drug interactions?	cisplatin, CYP2C8 and CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) or inhibitors (erythromycin, fluoxetine, gemfibrozil), doxorubicin	cisplatin, CYP3A4 inducers or inhibitors (cyclosporine, ketoconazole and erythromycin), doxorubicin	CYP2C8 and CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) or inhibitors (erythromycin, fluoxetine, gemfibrozil)
Dosing: Pediatric age range	safety and efficacy not established in pediatric patients	safety and efficacy not established in pediatric patients	safety and efficacy not established in pediatric patients
Dosing: Adjustment in geriatrics?	Not specified. Reduced dosage recommended in patients with impaired hepatic function	Not specified. Patients with hepatic impairment should generally not receive docetaxel.	Not specified. The appropriate dose of albumin-bound paclitaxel for patients with bilirubin > 1.5 mg/dL is not known.

Table 3: Pipeline medications

Medication	Manufacturer	Trials in progress	Anticipated approval date
paclitaxel poliglumex (OPAXIO [®] formally Xyotax [®])	Cell Therapeutics, Inc.	Pivotal trials for non-small cell lung cancer (NSCLC), ovarian, and other cancers.	unknown
tesetaxel (oral semi synthetic taxane)	Genta, Inc.	Phase I and Phase II trials completed in metastatic colorectal cancer, NSCLC and advanced gastric cancer. FDA recently lifted a clinical hold on the medication permitting clinical trials to resume.	unknown

References

1. Taxol® (paclitaxel) Injection prescribing information. Bristol-Myers Squibb Company: Princeton, NJ; July 2007.
2. Taxotere® (docetaxel) Injection Concentrate, Intravenous Infusion prescribing information. Sanofi-Aventis U.S. LLC.: Bridgewater, NJ; November 2007.
3. Abraxane for Injectable Suspension (paclitaxel albumin-bound particles for injectable suspension) (albumin bound) prescribing information. Abraxis Oncology: Los Angeles, CA; August 2007.
4. Abraxane® for Injectable Suspension website. Available at: www.abraxane.com. (Last accessed on 1/15/2009.)
5. Ghersi D, Wilcken N, Simes J, Donoghue. Taxane containing regimens for metastatic breast cancer. *The Cochrane Database of Systematic Reviews*: Reviews 2005 Issue 2. John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003366.pub2. YR: 2005. NO: 2
6. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *The Cochrane Database of Systematic Reviews*: Reviews 2007 Issue 4. John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004421. YR: 2007. NO: 4.
7. Kehoe S, Morrison J. Ovarian cancer (advanced). *BMJ Clin Evid* 2007;12:816. Available at: <http://clinicalevidence.bmj.com/ceweb/conditions/woh/0816/0816.jsp>. Accessed: 1/15/09.
8. Centre for Reviews and Dissemination. Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: a systematic review. Database of Abstracts of Reviews of Effects (DARE) ©2008. Available at: <http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12005001065>. Accessed on 11/12/2008.
9. Centre for Reviews and Dissemination. A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. Database of Abstracts of Reviews of Effects (DARE) ©2008. Available at: <http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12000008609>. Accessed on 11/12/2008.
10. Centre for Reviews and Dissemination. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer. Database of Abstracts of Reviews of Effects (DARE) ©2008. Available at: <http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12002008444>. Accessed on 11/12/2008.
11. Sparano JA. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*. 2008 Apr 17;358(16):1663-71. Erratum in: *N Engl J Med*. 2008 Jul 3;359(1):106.
12. Lin YC. A phase II randomized study of two taxanes and cisplatin for metastatic breast cancer after anthracycline: a final analysis. *Jpn J Clin Oncol*. 2007 Jan;37(1):23-9. Epub 2006 Dec 15.
13. Jones SE. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol*. 2005 Aug 20;23(24):5542-51.
14. Cassier PA. A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. *Breast Cancer Res Treat*. 2008 May;109(2):343-50. Epub 2007 Jul 5.
15. Mori T. A pilot study of docetaxel-carboplatin versus paclitaxel-carboplatin in Japanese patients with epithelial ovarian cancer. *Int J Clin Oncol*. 2007 Jun;12(3):205-11. Epub 2007 Jun 27.
16. Esteban E. Prospective randomised phase II study of docetaxel versus paclitaxel administered weekly in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Ann Oncol*. 2003 Nov;14(11):1640-7.
17. Schiller JH. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002 Jan 10;346(2):92-8.
18. Krug LM. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced non-small cell lung carcinoma. *Cancer*. 2005 Nov 15;104(10):2149-55.
19. Sweeney CJ. Outcome of Patients with a Performance Status of 2 in Eastern Cooperative Oncology Group Study E1594. A Phase III Trial in Patients with Metastatic Nonsmall Cell Lung Carcinoma. *Cancer*. November 15, 2001 / Volume 92 / Number 10.
20. Park SH. Paclitaxel versus docetaxel for advanced gastric cancer: a randomized phase II trial in combination with infusional 5-fluorouracil. *Anticancer Drugs*. 2006 Feb;17(2):225-9.
21. Gradisher WJ. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil-Based Paclitaxel in Women With Breast Cancer *Journal of Clinical Oncology*, Vol 23, No 31 (November 1), 2005: pp. 7794-7803
22. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™: Breast Cancer v.1.2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed on 1/15/2009
23. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™: Ovarian Cancer v.1.2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf. Accessed on 1/15/2009.
24. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™: Non-small cell lung cancer v.2.2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Accessed on 11/12/08.
25. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™: Gastric Cancer 2.2009. Available at: http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf. Accessed on 1/15/2009.

26. Pfister D, Johnson D, Azzoli C, Sause W, Smith T, et al. American Society of Clinical Oncology Treatment of Unresectable Non-Small-Cell Lung Cancer Guideline: Update 2003. *J Clin Oncol*. 2004;22(2):330-53. Available at: <http://jco.ascopubs.org/cgi/reprint/22/2/330>. Accessed on 11/13/08.