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Drug Review

# Taxanes – The Backbone of Medical Oncology

**Abstract**

Drug development in oncology has witnessed a revolutionary growth from its humble beginning with nitrogen mustard in 1940 to immunotherapy in 1986 (Interferon alpha). The arsenal of cytotoxics is ever increasing, contributing to better survival outcomes and improved quality of life. Over the years, many cytotoxics have fallen out of favor too, due to its side effects and availability of drugs with better efficacy and toxicity profile. Taxane, a microtubule stabilizing agent extracted from the poisonous Yew tree, was discovered in 1964 and came into clinical use in 1992 with its approval for ovarian cancer. This group has grown into a cornerstone of many treatment protocols, spanning multiple tumor types. This review discusses in brief the salient features of cytotoxic agents in this drug group, its history, physico-chemical properties, mechanism of action, pharmacodynamics, and pharmacokinetics. Though the benefits of taxanes are well understood, there are unique problems associated with the use of taxanes and there is an expanding literature on taxane resistance. We briefly look at the resistance mechanisms. There have been significant efforts to circumvent the problems related to conventional taxanes, with an attempt at creating newer carrier molecules and adjunct drugs with taxanes, which is slowly gaining traction in clinical practice.

**Keywords:** *Cabazitaxel, cremophor, diethylhexyl phthalate, docetaxel, paclitaxel, toxicity*

**Wesley M Jose**

*Department of Medical Oncology and Hematology, Amrita Institute of Medical Sciences, Amrita Vishwavidyapeetham, Health Science Campus, Kochi, Kerala, India*

## Introduction

Phytochemicals have been extensively researched for natural substances that could hold promise to mitigate human diseases. Plant alkaloids are one of the effective derivatives found to be useful due to its cytotoxic effects.[1] Taxanes, a class of diterpenes with antineoplastic effects, are primarily plant alkaloids.[2] The discovery of taxanes is in itself a huge success story of modern oncology. Among all the classes of antineoplastic agents, taxanes undoubtedly are the most versatile. This is evidenced by their effective use in multiple cancer type. Taxanes have become a cornerstone in many standard treatment protocols. The taxane drugs in common clinical use are paclitaxel, docetaxel, and cabazitaxel.

## The Tree of Life

The Yew is an ancient tree which is a gymnosperm from the family Taxaceae. This genus in Taxaceae family are coniferous and resinous, however, peculiarly the yew does not produce either cones or resin. Currently, there are as many as 24 species of yew trees with a wide geographical distribution. Yew is an evergreen poisonous tree which grows slowly and has a very long life. This tree has a smooth trunk, a height of about 30 m, and diameter of 5 m. Yew toxicity has been recorded as early as the 1st century BCE. Julius Caesar (102–44 BCE) wrote of Catuvolcus, the king of Eburones, who poisoned himself with yew "juice." Note also has been made of using yew extract as agent for ritual suicides and spiking arrowheads by ancient "Celts." Some primitive cultures are reported to have used yew extracts as hunting and fishing aids. In Europe and India during the 18th–19th centuries, concoctions brewed from yew leaves were used as an abortifacient or an emmenagogue (a substance that stimulates or increases menstrual flow) by women.[3] These plants are highly toxic and have been implicated in human and animal poisonings. The poisonous character of this tree is due to taxine alkaloid present in the foliage, bark, and seeds.[4]

Yew tree grows at high altitudes, steep slope ranging from rocky, and semi-humid to wet and cold conditions. This species is native to Europe, the Caucasus, North Africa, and Iran. Pacific or western yew (Taxus brevifolia) is a scarce tree and is found in the old-growth forests of the

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***Address for correspondence:***
*Prof. Wesley M Jose, Department of Medical Oncology and Hematology, Amrita Institute of Medical Sciences, Amrita Vishwavidyapeetham, Health Science Campus, Kochi - 682 041, Kerala, India. E-mail: wesleymjose@aims.amrita.edu*

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Pacific Northwest. The bark of this tree was the initial source of paclitaxel drug discovery.[5] Due to scarcity of this natural resource, it was difficult to procure and extract the drug in enough quantities for large-scale use. Therefore, the attention was turned to other sources. English or European Yew called Taxus baccata is a more abundant yew plant which was later used to obtain the alkaloid.[6] Canadian yew (Taxus canadensis) and Chinese yew (Taxus chinensis) have also been studied for procuring taxanes.[7,8] The species endemic in India is Himalayan yew (Taxus wallichiana). To date, more than 400 taxane diterpenoids have been isolated from the bark, seeds, leaves, etc., of the genus Taxus.[8]

## The Indian Connect

Mansukh C. Wani, born at Nandurbar, Maharashtra, who studied chemistry at the University of Bombay in 1950 and migrated thereafter to the United States of America, is the co-discoverer (with Monroe E. Wall) of the cytotoxic compound (NSC 125973) which we now call Paclitaxel.[9] In 1962, researchers at the National Cancer Institute, USA, in an effort to find natural products to cure cancer collected the bark of the Pacific yew tree (Taxus brevifolia). This plant's bark was provided to Monroe Wall and Mansukh C Wani at Research Triangle Institute's Natural Product Laboratory in Research Triangle Park, NC, who in 1964 discovered that extracts from this bark contained cytotoxic properties.[10] It took them several years to isolate the extract's most active component in a pure form.

Dr. Wani is also credited with leads to discovery of Camptothecins class of cytotoxics (irinotecan and topotecan).

## Structure and Chemical Properties of Taxane Drugs

### Paclitaxel (NSC 125973)

Paclitaxel was discovered from the bark of Taxus brevifolia. The chemical structure of paclitaxel was established in 1971 by Wani *et al*.[10] Later, researchers were able to extract a precursor of paclitaxel called 10-deacetyl-baccatin III from the more common European Yew plant. In 1977, National Cancer Institute, USA, confirmed the antitumor activity in mouse melanoma B16 model and against MX-1 mammary, LX-1 lung, and CX-1 colon tumors in animal models. Phase 1 trials of paclitaxel began in 1984. In 1989, William McGuire and his team at Johns Hopkins reported 30% partial or complete responses in a non-randomized phase 2 prospective trial among patients with advanced ovarian cancer.[11] Paclitaxel was approved by the Food and Drug Administration (FDA) for use in ovarian cancer in 1992 and subsequently for breast cancer in 1994. Thus, began the success story of taxanes.

The molecular formula of paclitaxel is $C_{47}H_{51}NO_{14}$ and its chemical name is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Currently, the drug is mass manufactured by cell culture method developed by phyton catalytic. Paclitaxel is highly lipophilic and insoluble in water. It is soluble in polyoxyethylated castor oil (Kolliphor® EL, formerly known as Cremophor® EL; BASF, Ludwigshafen, Germany), polyethylene glycol, chloroform, acetone, ethanol and methanol. For clinical use, paclitaxel is formulated in 50% cremophor EL and 50% dehydrated alcohol.[5]

### Docetaxel (NSC 628503)

It is a semi-synthetic esterified analog of paclitaxel, and its antineoplastic activity was reported in 1991 in preclinical models. Docetaxel is manufactured from N-DebocDocetaxel, which is obtained from 10-deacetyl baccatin III from the needles of Taxus baccata. Docetaxel differs from paclitaxel in the presence of a functional hydroxyl group on carbon 10 (where paclitaxel has an acetate ester) and a tert-butyl carbamate ester on the phenylpropionate side chain (instead of the benzamide in paclitaxel). The molecular formula is $C_{43}H_{53}NO_{14}$. The chemical name of docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. It is highly lipophilic and insoluble in water, but soluble in 0.1 N hydrochloric acid, chloroform, dimethylformamide, 95%–96% v/v ethanol, 0.1 N sodium hydroxide, and methanol. The current formulation consists of 100% polysorbate 80. Docetaxel is two to three times as effective as paclitaxel in promoting the assembly of mammalian brain tubulin *in vitro* and has a binding constant that is greater than that of paclitaxel by the same factor.[12]

### Cabazitaxel (NSC 761432)

It is another semi-synthetic derivative of the natural taxoid 10-deacetyl-baccatin III. The chemical formula is $C_{45}H_{57}NO_{14}$. The chemical name of cabazitaxel is (2α,5β,7β,10β,13α)-4-acetoxy-13-({(2R,3S)-3[(tertbutoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl} oxy)-1-hydroxy-7,10-dimethoxy-9oxo-5,20-epoxytax-11-en-2-yl benzoate – propan-2-one (1:1). Structurally, cabazitaxel and docetaxel are very similar except for 2 methoxy side chains in cabazitaxel that substitute for hydroxyl groups in docetaxel.[13] It is highly lipophilic and insoluble in water, but soluble in ethanol. Like docetaxel, the current formulation of cabazitaxel also consists of polysorbate 80.

## Mechanism of Action of Taxanes in General

Peter Schiff and his mentor Susan B Horwitz, an American biochemist and professor at the Albert Einstein College of Medicine, New York City, is credited with deciphering the mechanism of action of Paclitaxel in 1979.[14] She described the paclitaxel action of binding to microtubules, resulting in arrest of the cell cycle in metaphase.

Microtubules are important structural and functional components of the eukaryotic cytoskeleton. They are involved in cell division, migration, signaling, and intracellular trafficking and are important in cancer cell proliferation and metastasis.[15] Microtubules depict a phenomenon called "dynamic instability" which is critical for its functioning. Dynamic instability is a highly dynamic transition between alternating periods of slow growth/elongation by adding tubulin dimers to existing microtubule polymer ends (called rescue) and rapid shortening by removal or loss of tubulin dimers (called catastrophe).[16] This dynamic instability is crucial during mitosis where chromosome alignment during metaphase and separation during anaphase needs to happen leading to successful cell division.[17] Suppression of dynamic instability or microtubule-stabilizing due to polymerization, simultaneously inhibiting their disassembly, leads to mitotic arrest, inhibition of cell proliferation, and ultimately cell death.[18] The taxanes are microtubule-stabilizing drugs that enhance microtubule polymerization at high concentrations.[19] All taxanes bind to the same or to an overlapping taxoid-binding site on β-tubulin, located on the inner surface of the microtubule.[20]

The physical, pharmacokinetic, and pharmacodynamic properties of the different taxane molecules are quite varied and are tabulated in Table 1.[21-24]

Paclitaxel was first approved for use in ovarian cancer, but over the years, taxanes have been incorporated into various chemotherapy protocols for different malignancies both in adjuvant and metastatic settings. Table 2 lists the approved indications, reported off-label uses, drug interactions, and dosing schedules.

Taxanes have been variably combined with other chemotherapeutic agents for its additive effect. It is, however, important to understand the sequencing of these drugs to accrue the best benefits from these schedules and reduce toxicities to the minimum. Table 3 compiles the sequencing of a few common drugs used in combination with taxanes.[33,34] Cabazitaxel is approved for use as a single agent, hence there is limited data on sequencing. In a single phase 1/2 study of cabazitaxel with carboplatin, there is no specific mention of the sequencing of the two drugs.

## Unique Precautions with Taxanes

### Non-inert vehicle

Paclitaxel posed a major challenge in the way of formulating an appropriate delivery system acceptable for human use. For clinical purpose paclitaxel is dissolved in 50% Cremophor® EL (CrEL) and 50% dehydrated alcohol. CrEL is polyoxyethylated castor oil, a formulation vehicle used for poorly water-soluble drugs. The most significant concern with CrEL is that it is not an inert vehicle, but exerts a range of dose-independent biological effects of clinical importance ranging from severe anaphylactoid hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria (2%–4% in clinical trials), hyperlipidaemia, abnormal lipoprotein patterns, aggregation of erythrocytes and peripheral neuropathy.[35] The systemic clearance of CrELis highly influenced by duration of the infusion.[36] Therefore, all patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Fatal reactions have occurred in patients despite premedication. Patients who experience severe hypersensitivity reactions should not be re-challenged.

### Leaching enigma

Di-(2-ethylhexyl) phthalate (DEHP) is the most common member of the class of phthalates and is used as plasticizers in polymer products to make the plastic flexible. DEHP is noncovalently bound to plastics and can easily leach out of these products by physical or chemical interactions. Contact of the undiluted paclitaxel concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion leaches the plasticizer DEHP, from PVC infusion bags or sets and can cause endocrine, testicular, ovarian, neural, hepatotoxic, and cardiotoxic effects.[37] Therefore, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. The presence of the extractable plasticizer DEHP levels increases with time and concentration when dilutions are prepared and stored in PVC containers. Paclitaxel should be administered through an in-line filter with a microporous membrane not >0.22 μ.

### Radiation recall

It is an acute inflammatory reaction confined to previously irradiated areas that can be triggered when chemotherapy agents are administered after radiotherapy. Radiation recall is drug specific for any individual patient. Increased awareness aids early diagnosis and appropriate management. Both paclitaxel and docetaxel have been reported to produce radiation recall.[38]

### Cross-reactivity between taxanes

Early on, it was understood that paclitaxel and docetaxel are not simply two of a kind.[39] Patients are usually cross-sensitive to the two taxane drugs (paclitaxel and docetaxel). Literature reports the incidence of cross-reactions between paclitaxel and docetaxel ranging from 49% to 90%.[40] In a retrospective analysis of paclitaxel and docetaxel usage, cross-sensitivity of docetaxel after paclitaxel was 50%. Given the different vehicles used in both the taxanes, it is probably attributable to the taxane moiety. Although docetaxel may be used, caution should be exercised in those patients who have had prior severe hypersensitivity reaction with paclitaxel, more so if treated within 4 weeks.[41]

**Table 1: Comparative features of taxanes**

| | Paclitaxel | Docetaxel | Cabazitaxel |
|---|---|---|---|
| Approved for clinical use in[25] | 1992 (ovary)<br>1994 (breast)<br>1997 (Kaposi's sarcoma)<br>1998 (lung) | 1996 (breast)<br>1999 (lung)<br>2004 (prostate)<br>2006 (head and neck) | 2010 - Standard dose<br>2017 - Lower dose (approval only for prostate cancer) |
| **Physical properties, pharmacodynamics and pharmacokinetics** | | | |
| Appearance | Clear colourless to slightly yellow viscous solution | White to almost-white powder | Yellow to brownish-yellow viscous solution |
| Terminal half life | 20.2 h (175 mg/m$^2$/3 h IV)<br>13.1 h (135 mg/m$^2$/3 h IV)<br>15.7 h (175 mg/m$^2$/24 h IV)<br>52.7 h (135 mg/m$^2$/24 h IV)<br>11.6 h (80 mg/m$^2$/1 h IV) | 11.1 h | 95 h |
| Protein binding (%) | 89-98 | 94-97 | 80-92 |
| Distribution | Extensive extravascular distribution and tissue binding | Extensive extravascular distribution and tissue binding | Extensive extravascular distribution and tissue binding |
| Metabolism | Primarily in liver<br>Metabolism catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 | Primarily in liver<br>Metabolism catalysed by cytochrome P450 isoenzymes CYP3A4 | Primarily in liver<br>Metabolism catalysed by cytochrome P450, isoenzyme CYP3A4/5 (80%-90%), to a lesser extent CYP2C8 |
| Primary metabolite | 6α-hydroxypaclitaxel (CYP2C8) | Hydroxydocetaxel | Docetaxel<br>RPR123142 (10-O-demethyl-cabazitaxel) |
| Secondary metabolites | 3'-p-hydroxypaclitaxel and<br>6",3'-p dihydroxypaclitaxel, by (CYP3A4) | Hydoxyoxazolidinones<br>Oxyzolidinediones | RPR112698<br>RPR123142 |
| Excretion | 71% faeces<br>14% urine | 75% faeces<br>6% urine | 76% faeces as numerous metabolites<br>3.7% renal (2.3% as unchanged drug) |
| **Clinical utilization** | | | |
| Supplied as (including generic formulations) | 30 mg/5 ml<br>100 mg/16.7 ml<br>260 mg/43.4 ml<br>300 mg/50 ml | 20 mg/0.5-2 ml<br>80 mg/2-8 ml<br>120 mg/3-12 ml<br>160 mg/8-16 ml (polysorbate 80) | 60 mg/1.5 mL (polysorbate 80) |
| Diluent | 6 mg paclitaxel, 527 mg of purified Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP | 13% (w/w) ethanol in water for injection | 5.7 mL of 13% (w/w) ethanol in water for injection |
| Approved IV doses | 80 mg/m$^2$ (1 h infusion) weekly[26]<br>100 mg/m$^2$ (3 h infusion) q2 weekly for AIDS related Kaposis sarcoma<br>135 mg/m$^2$ (3 h infusion or CIV 24 h) q3 weekly<br>175 mg/m$^2$ (3 h infusion) q3 weekly<br>200-250 mg/m$^2$ CIV 24 h q3 weekly (in metastatic germ cell tumor)[27] | 75-100 mg/m$^2$ q3 weekly<br>35 mg/m$^2$ weekly[26] | 20-25 mg/m$^2$ q3 weekly |
| Other routes of administration | 60 mg/m$^2$ intraperitoneal in ovary cancer[28] | 45 mg/m$^2$ intraperitoneal in gastric cancer with peritoneal carcinomatosis[29] | None |
| IV infusion time | 1 h[26]<br>3 h<br>24 h | 1 h | 1 h |

*Contd...*

**Table 1: Contd...**

| | Paclitaxel | Docetaxel | Cabazitaxel |
|---|---|---|---|
| Dilution fluid | 0.9% sodium chloride<br>5% dextrose<br>5% dextrose + 0.9%<br>Sodium chloride | 0.9% sodium chloride<br>5% dextrose | 0.9% sodium chloride solution<br>5% dextrose solution |
| Storage time post mixing | 27 h | 4 h | 8 h under ambient conditions<br>24 h under refrigeration |
| Mandatory premedication | Antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine)<br>Corticosteroid (dexamethasone 20 mg or equivalent steroid administered 12 and 6 h before paclitaxel)<br>Reduced doses have been studied, including withholding of steroids if there has been no infusion hypersensitivity reactions in the first 2 cycles[30,31]<br>H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist)<br>Antiemetic | 3 days corticosteroids 16 mg/day (8 mg twice daily) starting 1 day prior to injection | Antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine)<br>Corticosteroid (dexamethasone 8 mg or equivalent steroid)<br>H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist)<br>Antiemetic |

IV – Intravenous; CIV – Continuous intravenous; USP – Unites States Pharmacoepia

There are a few case reports suggesting absence of cross reactivity between albumin bound paclitaxel and standard paclitaxel and docetaxel.[42,43]

In terms of efficacy, in case of patients developing early sensory neuropathy during paclitaxel schedule, there are anecdotal reports that docetaxel may be used as a replacement due to relatively lower risk of neuropathy.[44,45] Some small Phase II studies have reported benefit of docetaxel use in patients who have previously failed paclitaxel therapy.[46,47]

## Clinical Use of Taxanes

Paclitaxel and docetaxel have been approved for a large number of cancer types. Cabazitaxel, however, is only approved in castration resistant prostate cancer. Table 4 records a few landmark trials of each of these taxanes with its outcomes. This list is not exhaustive but mentions only those trials which lead to drug approval and laid a foundation for today's standard of care.

## Taxane Resistance

The resistance to cytotoxic effect of taxane can be primary or acquired. Colon and renal malignancy are inherently resistant to taxanes and therefore not recommended in these cancer types. However, even in malignancies which initially are sensitive to taxane effect subsequently fail to respond to repeated course of taxane treatment and this is acquired resistance. Both are major limiting factors for taxane therapy.

The mechanism of resistance to taxanes is quite complex and is not in purview for a detailed discussion in this article. These mechanisms include the following:[63]

### Alterations in tubulin

a. Mutations in tubulins (e.g., β-tubulin – human (*h*) $26^{Asp \rightarrow Glu}$; kα-1 tubulin (*h* $379^{Ser \rightarrow Arg}$)
b. Change in expression of five of α and six of β tubulins isotypes
c. Post-translational modifications (glutamylation, glycylation, acetylation, tyrosination, and phosphorylation).

### Altered microtubule-associated proteins expression

a. Microtubule-associated proteins 4 (increased phosphorylation causing silence and more destabilized microtubules)
b. Stathmin (dephosphorylation causes destabilized microtubules)
c. Survivin.

### Increased expression of drug efflux systems

a. P-glycoprotein (encoded by multidrug resistance [MDR1] [ABCB1])
b. Bile salt export protein (encoded by ABCB11)
c. MDR protein MRP7 (encoded byABCC10)
d. MDR3 (sometimes called MDR2 and encoded by ABCB4).

### Activation of anti-apoptotic pathways

a. Bcl2 and Bcl-XL upregulation
b. Increased inhibitors of apoptosis proteins (IAP) expression.

### Constitutive activation of transcription factors and gene induction

a. Nuclear factor of kappa B
b. Interferon regulatory factor-9
c. Signal transducer and activator of transcription-3.

**Table 2: Clinical indications, toxicity, drug interactions, and dosing of taxanes**

| | Paclitaxel | Docetaxel | Cabazitaxel |
|---|---|---|---|
| Approved indications | Ovary<br>Breast<br>Lung<br>Esophageal carcinoma<br>Kaposis sarcoma | Breast<br>Head and neck<br>Prostate<br>Lung<br>Gastric | Hormone refractory metastatic prostate cancer |
| Off-label indications[32] | Head/neck cancer, Small-cell lung cancer, upper gastrointestinal adenocarcinoma, hormone-refractory prostate cancer, Non-Hodgkin's lymphoma, urothelium transitional cell carcinoma, Stage IIB-IV melanoma | Limited information | Limited information |
| **Comparative toxicities** | | | |
| Grade 3-4 adverse drug reaction (CTCAE) | Anaphylaxis and severe hypersensitivity (2%-4%)<br>Sensory neuropathy (8%-28%)<br>Arthralgia myalgia (3%-11%)<br>Conduction abnormalities (<1%) | Anaphylaxis and severe Hypersensitivity (2.2%-2.8%)<br>Grade 4 neutropenia (75%-85%)<br>Severe asthenia (18%)<br>Febrile neutropenia (0%-12%)<br>Fluid retention<br>Sensory neuropathy (1.7%) | Anaphylaxis and severe Hypersensitivity<br>Neutropenia (82%)<br>Febrile neutropenia (7%)<br>Diarrhea (6%)<br>Fatigue and asthenia (5%) |
| **Drug interactions** | | | |
| CYP3A4 inhibitors | Atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin | Atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin | Atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin - 20% decrease in cabazitaxel clearance |
| CYP3A4 inducers | Rifampicin | Rifampicin | Rifampicin - 21% increase in cabazitaxel clearance |
| CYP2C8 inhibitors | Gemfibrozil | - | - |
| **Dose reductions** | | | |
| Hepatic impairment | For standard 3 h infusion (transaminase and bilirubin levels)<br><10 × ULN and ≤1.25 × ULN (175 mg/m$^2$)<br><10 × ULN and 1.26-2.0 × ULN (135 mg/m$^2$)<br><10 × ULN and 2.01-5.0 × ULN (90 mg/m$^2$)<br>≥10 × ULN or >5.0 × ULN not recommended | Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with docetaxel (transaminase and ALP)<br>>2.5 to ≤5 × ULN and ≤2.5 × ULN, >1.5 to ≤5 × ULN and >2.5 to ≤5 × ULN, reduce by 20%<br>>5 × ULN and/or >5 × ULN Docetaxel should be stopped | Contraindicated in patients with severe hepatic impairment (total bilirubin and AST)<br>>1 to ≤1.5 × ULN or >1.5 × ULN: 20 mg/m$^2$>1.5 to ≤3 × ULN and AST=Any: 15 mg/m$^2$<br>Total bilirubin >3 × ULN: contraindicated |
| Neuropathy | Grade 2 neuropathy - 20% dose reduction for all subsequent cycles<br>≥ Grade 3 - Discontinue | Grade 2 neuropathy - 20% dose reduction for all subsequent cycles<br>≥ Grade 3 - Discontinue | Grade 2 - Delay treatment until improvement or resolution, then dose reduce by one dose level<br>≥ Grade 3 - Discontinue |
| Neutropenia | ANC <500 cells/mm$^3$ for 7 days or more - Reduce dose by 20% and use GCSF as secondary prophylaxis | ANC <500 cells/mm$^3$ for 7 days or more in spite of primary prophylaxis - Reduce dose by 25%. (100 mg → 75 mg)<br>For ANC <500 cells/mm$^3$ for 7 days or more on 75% dose - Reduce dose by another 15% (75 mg → 60 mg)<br>For patients who still have ANC <500 cells/mm$^3$ for 7 days or more - Discontinue docetaxel | ANC <1000 cells/mm$^3$ for 7 days or more despite appropriate GCSF - Delay treatment until improvement or resolution, then dose reduce by one dose level and use GCSF as secondary prophylaxis |

*Contd...*

**Table 2: Contd...**

| | Paclitaxel | Docetaxel | Cabazitaxel |
|---|---|---|---|
| Hypersensitivity reactions in spite of appropriate premedications | If severe (generalized rash/ erythema, hypotension and bronchospasm) - Do not rechallenge | If severe (generalized rash/erythema, hypotension and bronchospasm) - Do not rechallenge | If severe (generalized rash/erythema, hypotension and bronchospasm) - Do not rechallenge |

CTCAE – Common Terminology Criteria for Adverse Events; ULN – Upper limit of normal; ALP – Alkaline phosphatase; AST – Aspartate transaminase; GCSF – Granulocyte colony-stimulating factor; ANC – Absolute neutrophil count; → means "change the dose to"

**Table 3: Chemotherapy drug sequencing with taxanes**

| | Paclitaxel | Docetaxel |
|---|---|---|
| Cisplatin | Paclitaxel should be administered first followed by cisplatin<br>Paclitaxel clearance is reduced by approximately 33% when paclitaxel is administered following cisplatin leading to higher toxicity especially myelo-suppression | Docetaxel should be administered first followed by cisplatin for the same reason as paclitaxel |
| Carboplatin | Sequencing does not have any impact | Sequencing does not have any impact |
| Pamidronate | Paclitaxel should be administered first followed by pamidronate<br>Pamidronate can cause nephrotoxicity, which manifests as nephritic syndrome, kidney function deterioration and renal failure, which could alter paclitaxel excretion | Docetaxel should be administered first followed by pamidronate for the same reason as paclitaxel |
| Trastuzumab/pertuzumab | Administering trastuzumab/pertuzumab first results in better sensitization of breast cancer cells which when followed by paclitaxel causes increased activation and induction of programmed cell death or cell apoptosis | Trastuzumab/pertuzumab first followed by docetaxel for the same reason as paclitaxel |
| Cyclophosphamide/ifosfamide (no strong data for order of sequencing with taxanes) | Cyclophosphamide/ifosfamide should be administered first followed by paclitaxel. This lessens cytopenias | Docetaxel should be administered before cyclophosphamide<br>Docetaxel is a cell cycle specific drug, while cyclophosphamide is a cell cycle nonspecific drug, which justifies this infusion sequence. But there are debatable data suggesting reverse sequence purporting less Grade 4 neutropenia |
| Vinorelbine | Vinorelbine first followed by paclitaxel to achieve synergistic effect since paclitaxel has a significantly shorter half life than vinorelbine | Docetaxel followed by vinorelbine in order to decrease incidence of neutropenia which is attributed to polysorbate-80 in docetaxel which probably blocks P-glycoprotein-mediated clearance of vinorelbine |
| Topotecan | Topotecan followed by paclitaxel results in lesser toxicity and better tolerance (Phase 1 studies) | Docetaxel followed by topotecan<br>Given first Topotecan would reduce docetaxel clearance by 50% causing increased neutropenia |
| Doxorubicin/epirubicin/liposomal doxorubicin | Doxorubicin/epirubicin followed by paclitaxel. Paclitaxel reduces the clearance of doxorubicin leading to increased myelosuppression and mucositis | Doxorubicin followed by docetaxel reduces Grade 4 neutropenia |
| Gemcitabine | Paclitaxel followed by gemcitabine causes less risk of hepatotoxicity | Sequencing does not have any impact |

### Kinase activation

a. Erb/EGFR family members (Her2/neu; EGFRvIII)
b. Aurora A (serine threonine kinase)
c. Inhibitory (I)κBα kinase.

### Increased cytokine/chemokine expression and secretion

a. Cytokine interleukin (IL-6)
b. Chemokine IL-8
c. Monocyte chemoattractant protein-1.

In contrast to the first-generation taxanes (paclitaxel and docetaxel), cabazitaxel is a poor substrate for P-glycoprotein, which is an advantageous property.

## Newer Taxanes

The difficulties with taxane administration and toxicities related to the carrier have fuelled the effort to look for better formulations. Several novel formulations such as taxane analogues and prodrugs, docetaxel-encapsulated

**Table 4: Landmark trials with taxanes**

| Organ | Trial | Chemotherapy arms | Eligibility | Outcomes |
|---|---|---|---|---|
| | | **Paclitaxel** | | |
| Ovary | ICON 3 (2002)[48] | Paclitaxel 175 mg/m²/3 h + carboplatin AUC 6 (P + C) or control arm of either CAP (cyclophosphamide + doxorubicin + cisplatin) or single agent carboplatin | Stage I-IV (*n*=2074) | Median PFS<br>17.3 (P + C) versus 16.1 months (control)<br>Median OS<br>36.1 (P + C) versus 35.4 months (control) |
| | GOG study (2003)[49] | Cisplatin 75 mg/m² + 24 h infusion of paclitaxel 135 mg/m² (arm I) or carboplatin AUC 7.5 + paclitaxel 175 mg/m² over 3 h (arm II) | Small-volume, resected, stage III disease (*n*=792) | Median PFS<br>19.4 (arm I) versus 20.7 months (arm II)<br>Median OS<br>48.7 (arm I) versus 57.4 months (arm II) |
| Breast | NSABP-B-28 (2005)[50] | Doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² (AC) every 21 days for four cycles or four cycles of AC followed by four cycles of paclitaxel 225 mg/m² 3 h (AC-P) every 21 days | Resected operable breast cancer and histologically positive axillary nodes (*n*=3060) | Five-year DFS 76% ±2% (AC-P) versus 72%±2% (AC)<br>OS was the same at 85% ± 2% in both arms |
| | CALGB 9344 (2003)[51] | Cyclophosphamide (C), 600 mg/m², with one of three doses of doxorubicin (A), 60, 75, or 90 mg/m², (AC) for four cycles followed by either no further therapy or four cycles of paclitaxel at 175 mg/m² (AC-P) | Post-surgery for operable node positive breast cancer (*n*=3121) | No evidence of a doxorubicin dose effect<br>At 5 years, DFS was 65% (AC) versus 70% (AC-P)<br>OS was 77% (AC) versus 80% (AC-P) |
| Lung | ECOG trial (1997)[52] | Cisplatin, 75 mg/m² IV (day 1) + etoposide 100 mg/m² IV (day 1-3) or Paclitaxel, 250 mg/m² IV over 24 h (day 1) + cisplatin, 75 mg/m² (day 2) + GCSF 5 µg/kg starting on day three and continuing until the granulocyte count was >10,000/cells/mm³ or paclitaxel, 135 mg/m² IV over 24 h + cisplatin, 75 mg/m² IV on day two | Stage IIIB/IV disease without brain metastasis (*n*=600) | Response rates were 12% in cisplatin + etoposide group<br>31% in paclitaxel + cisplatin + GCSF group<br>26% in paclitaxel + cisplatin group |
| | Co-operative multinational trial (2002)[53] | Paclitaxel 200 mg/m² as 3 h infusion + carboplatin AUC 6 or paclitaxel 200 mg/m² as 3 h infusion + cisplatin 80 mg/m² every 3 weeks | Stage IIIB/IV disease (*n*=600) | Median survival 8.2 months in paclitaxel/carboplatin and 9.8 months in the paclitaxel/cisplatin<br>2 years survival rates 9% (paclitaxel/carboplatin) and 15% (paclitaxel/cisplatin) |
| GIT | CROSS (2015)[54] | Neoadjuvant chemoradiotherapy (CTRT) with five cycles of weekly carboplatin (AUC 2 mg/mL/min) and paclitaxel (50 mg/m²) with concurrent radiotherapy (41·4 Gy, given in 23 fractions of 1·8 Gy on 5 days/week) followed by surgery or surgery alone | Clinically resectable, locally advanced cancer of the esophagus or esophagogastric junction.<br>(*n*=368) | Median OS<br>Squamous cell carcinomas - 81.6 (CTRT) versus 21.1 months (surgery alone)<br>Adenocarcinomas 43.2 (CTRT) versus 27.1 months (surgery alone) |
| | | **Docetaxel** | | |
| Breast | BCIRG 001 (2013)[55] | Docetaxel 75 mg/m² + doxorubicin 50 mg/m² + cyclophosphamide 500 mg/m² (TAC) or 5FU 500 mg/m² + doxorubicin 50 mg/m² + cyclophosphamide 500 mg/m² (FAC)<br>Every 3 weeks for 6-cycles | Node-positive, early breast cancer (*n*=1491) | DFS was 62% (TAC) versus 55% (FAC)<br>10 years OS 76% (TAC) versus 69% (FAC) |

*Contd...*

**Table 4: Contd...**

| Organ | Trial | Chemotherapy arms | Eligibility | Outcomes |
|---|---|---|---|---|
| Lung | TAX 326 (2003)[56] | Docetaxel 75 mg/m$^2$ + cisplatin 75 mg/m$^2$ every 3 weeks (DC); or docetaxel 75 mg/m$^2$ + carboplatin AUC 6 mg/mL every 3 weeks (DCb); or vinorelbine 25 mg/m$^2$/week + cisplatin 100 mg/m$^2$ every 4 weeks (VC) | Stage IIIB-IV NSCLC (*n*=1218) | ORR 31.6% versus 24.5% (DC vs. VC)<br>Median OS 11.3 versus 10.1 months (DC vs. VC)<br>2 years survival rate 21% versus 14% (DC vs. VC)<br>Results of DCb were similar to those of VC |
| Prostate | TAX 327 (2004)[57] | Mitoxantrone 12 mg/m$^2$ + prednisone 5 mg twice daily every 3 weeks or docetaxel 75 mg/m$^2$ + prednisone 5 mg twice daily every 3 weeks or docetaxel 30 mg/m$^2$ weekly prednisone 5 mg twice daily for five of every 6 weeks | Metastatic hormone-refractory prostate cancer (*n*=1006) | Median survival 16.5 months (mitoxantrone) versus 18.9 months (docetaxel 3 weekly) versus 17.4 months (docetaxel weekly) |
| Head and Neck | TAX 324 (2011)[58] | Three cycles of (TPF) docetaxel 75 mg/m$^2$ + cisplatin 100 mg/m$^2$ + 5FU 1000 mg/m$^2$/day CIV for 4 days or (PF) Cisplatin 100 mg/m$^2$ + 5FU 1000 mg/m$^2$/day CIV for 5 days<br>Both regimens were followed by 7 weeks of chemoradiotherapy with concomitant weekly carboplatin (AUC 1.5) | Stage III or IV disease with no distant metastases and tumors considered being unresectable or were candidates for organ preservation (*n*=501) | Median PFS 38.1 (TPF) versus 13.2 months (PF)<br>Median survival time 70.6 (TPF) versus 34.8 months (PF) |
| Gastric | V325 (2006)[59] | Docetaxel 75 mg/m$^2$ (day 1) + cisplatin 75 mg/m$^2$ (day 1) + 5FU 750 mg/m$^2$/day (DCF) for 5 days every 3 weeks or Cisplatin 100 mg/m$^2$ (day 1) + 5FU 1000 mg/m$^2$/day (CF) for 5 days every 4 weeks | Untreated advanced gastric cancer patients (*n*=445) | TTP was longer with DCF versus CF (32% risk reduction)<br>OS was longer with DCF versus CF (23% risk reduction)<br>Two-years survival rate was 18% with DCF and 9% with CF |
| | | **Cabazitaxel** | | |
| Prostate | TROPIC (2010)[60] | Mitoxantrone 12 mg/m$^2$ + prednisone 10 mg daily (MP) or cabazitaxel 25 mg/m$^2$ + prednisone 10 mg daily (CP) every 3 weeks | Metastatic castration-resistant prostate cancer who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen (*n*=755) | Median survival 15·1 (CP) versus 12.7 months (MP)<br>Median PFS 2·8 (CP) versus 1.4 months (MP) |
| | PROSELICA (non-inferiority study) (2017)[61] | Cabazitaxel 20 mg/m$^2$ (C20) or cabazitaxel 25 mg/m$^2$ (C25) | Post-Docetaxel patients with mCRPC (*n*=1200) | C20 maintained ≥50% of the OS benefit of C25. Secondary end points (PFS, PSA, tumor and pain responses and progression, HR-QOL and safety) favored C25<br>C20 arm had fewer adverse events |
| | Phase 1-2 Trial Combination Therapy (2019)[62] | Cabazitaxel 25 mg/m$^2$ with or without carboplatin AUC 4 mg/mL per min + prednisone 10 mg daily | Progressive metastatic castration-resistant prostate cancer (*n*=160) | Median PFS improved from 4.5 months to 7.3 months in combination arm |

PFS – Progression-free survival; OS – Overall survival; DFS – Disease-free survival; AUC – Area under curve, Gy – Gray; 5FU – 5-fluorouracil; NSCLC – Non-small cell lung cancer; IV – Intravenous; CIV – Continuous IV; PSA – Prostate-specific antigen; HR-QOL – Health-related quality of life; GIT – Gastrointestinal tract; CTRT: Chemoradiation; mCRPC – Metastatic castrate resistant prostate cancer nanoparticle-aptamer bioconjugates albumin nanoparticles, polyglutamates, emulsions, liposomes, docetaxel fibrinogen-coated olive oil droplets, and submicronic dispersion have been developed. The major concern of hypersensitivity due to CrEL has been overcome to a large extent with the availability of these newer formulations. We look at three important formulations available for clinical use.

## Nanoparticle Albumin-Bound (NAB)-Paclitaxel (Abraxane)

Abraxane is an albumin-bound paclitaxel.[64] Paclitaxel exists in the particles in a noncrystalline, amorphous state. The mean particle size is 130 nm. This nano-formulation has helped enhance permeability and retention effect, which allows passive tumor-targeting. Unlike conventional paclitaxel, it does not have a solvent. The standard dose is 260 mg/m$^2$ administered intravenously over 30 min every 3 weeks or 100–125 mg/m$^2$ administered on day 1, 8, and 15 of a 4-weekly cycle. No premedication to prevent hypersensitivity reactions is required prior to abraxane infusion. Abraxane does not cause DEHP leaching and does not require an in-line filter. The reconstituted abraxane may be stored up to a maximum of 8 h. Nab-paclitaxel has a linear pharmacokinetics compared to standard paclitaxel that has nonlinear pharmacokinetics. This provides a better tissue and tumor distribution and a predictable dose–effect response.[65] A USA community-based analysis of standard paclitaxel versus nab-Paclitaxel found that nab-paclitaxel had significantly lower rates of any-grade anemia, diarrhea, pain, and neuropathy. Fewer doses of pre-medication doses of antiemetics, antihistamines, and steroids were required.[66] Risk of hypersensitivity reaction is <1%. The disease response has been variable, with some studies showing better response with nab-paclitaxel and others no difference between them. Paclitaxel had been ineffective in pancreatic adenocarcinoma, however the nano formulation of paclitaxel was found to be effective and due to its expanded activity FDA in 2013 approved its use for pancreatic cancer treatment in combination with gemcitabine.[67] The other indications for nab-paclitaxel use are metastatic breast cancer and non-small cell lung cancer (NSCLC).

## Pacliaqualip/Doceaqualip

Nanoaqualip™ technology is a proprietary lipid-based nanotechnology, in which the therapeutic drugs are formulated in an aqueous medium without the use of any toxic solvents during the manufacturing process, yielding a homogenous nanoparticle size products (~100 nm) that allows the drug to penetrate the tumor tissue through leaky vasculature.[68] Pacliaqualip/Doceaqualip is an albumin-free nanosomal paclitaxel/docetaxel lipid suspension (NPLS/NDLS) formulation, which is made from lipids generally regarded as safe by the US FDA. As NPLS/NDLS is devoid of CrEL and ethanol, the toxicities associated with it are avoided, thus negating the need for corticosteroid premedication.

The NPLS/NDLS formulation is prepared using paclitaxel/docetaxel, soyphosphatidylcholine, and sodium cholesteryl sulfate in an aqueous medium under high-pressure homogenization to make <100 nm mean particle size of paclitaxel/docetaxel-lipid suspension. The resulting drug–lipid suspension is lyophilized and made available for use. The reconstitution and dilution are done in 5% dextrose. The storage time post-mixing is up to 8 h. NPLS/NDLS can be administered without premedication with corticosteroids. The concern of DEHP leaching is also negated. In a small Phase 2 industry-sponsored, open-label, randomized multidose parallel study, NPLS/NDLS is reported to be safer and more efficacious.[69] Nanotechnology has jettisoned the progress of drug delivery system research in nano-formulations related to docetaxel delivery.[70]

An expert panel of Indian oncologists opine that using a novel formulation of paclitaxel would add value to the current management of metastatic breast cancer and found greatest value in avoiding steroid premedication due to the absence of CrEL/Polysorbate 80 in these taxanes.[71]

## Oral Paclitaxel (Oraxol [Athenex, USA])

The greatest shortcoming of taxanes was that the drugs were only available in intravenous (IV) forms. One of the common reasons for inability to synthesize oral formulations of first-generation taxanes is their higher molecular weight (800 dalton) which does not satisfy Lipinski's rule of oral administration which prescribes the molecular weight to be <500 daltons.[72] The other important reason for the poor availability of oral taxane is the presence of P glycoprotein (P-gp), encoded by the MDR-1 gene, which is a member of the ATP-binding cassette (ABC) superfamily of transmembrane transporters. P-gp prevents the intestinal uptake and intracellular accumulation of various cytotoxic agents.[63]

Oraxol (paclitaxel/HM30181A; paclitaxel-HM30181 methanesulfonate monohydrate) is a formulation composed of paclitaxel and a MDR efflux pump P-glycoprotein (P-gp) inhibitor HM30181A (encequidar). Upon oral administration of oraxol, the HM30181A moiety binds to and inhibits P-gp, which prevents P-gp-mediated efflux of paclitaxel, therefore enhancing its oral bioavailability.[73]

A recent Phase III trial presented at the San Antonio Breast Cancer Symposium in San Antonio, Texas, oral paclitaxel with encequidar, the first orally administered paclitaxel, was shown to exhibit superior confirmed response and survival with less neuropathy for patients with metastatic breast cancer compared with IV paclitaxel.[74] A Phase Ib study of oraxol in combination with ramucirumab is ongoing in patients with gastric or esophageal cancers who have failed previous chemotherapy.[75] The US FDA has granted orphan drug designation to Oraxol (Athenex) for the treatment of angiosarcoma in April 2018.[76]

## Other Taxanes (Not Approved for Clinical Use)

It is difficult to judge if any of the following taxanes would go through Phase III trials and reach the stage of routine clinical use.

1. Larotaxel (RPR 109881A) is a taxane analog with a broad spectrum of activity and different toxicity profile and with the possible advantages of surpassing some mechanisms of resistance and penetrating into the CNS.[77] It was reported to be effective in previously taxane treated metastatic breast cancer.[78] Larotaxel advanced to Phase III trials in combination with cisplatin for advanced/metastatic urothelial tract or bladder cancer, but could not exceed the benefits produced by cisplatin/gemcitabine combination[79]
2. Milataxel (MAC-321, TL-139) at a dose of 35 mg/m$^2$ as a 4 h IV infusion every 3 weeks showed efficacy with durable response in a Phase II trial in platinum refractory and heavily pretreated patients of NSCLC including those who had previously received taxanes.[80] Milataxel, however, failed to show benefit in previously treated colorectal cancer[81]
3. Ortataxel (DB11669) is not a substrate for the Pgp efflux pump and therefore is orally active. It is active in tumor models resistant to paclitaxel and docetaxel and elicits responses in taxane-resistant NSCLC . It is administered at 75 mg/m$^2$ IV every 3 weeks. Ortataxel is found to cross the blood–brain barrier. Ortataxel has been studied in breast cancer and glioblastoma multiforme with some success.[82,83] Ortataxel is in Phase II trials for taxane-refractory NSCLC, metastatic breast cancer, and also recurred glioblastoma
4. BMS-184476 is an analog of paclitaxel and has shown efficacy in previously treated NSCLC. At a dose of 60 mg/m$^2$ administered intravenously over 1 h, every 21 days, BMS-184476 was well tolerated. Partial responses were observed in 14.3% of patients and stable disease in 58.9%. The median progression-free survival was 3.7 months and the median overall survival was 10 months[84]
5. Tesetaxel is another oral semisynthetic taxane derivative but failed to demonstrate improved efficacy in Phase II trials for metastatic colorectal cancer, as compared to the standard treatment, but recently completed Phase I/II trials for solid tumors.[85]

## Conclusion

Taxanes have changed the landscape of cancer chemotherapy over the past three decades. It stands out as the backbone of cancer care. The ongoing effort to build on its efficacy is likely to keep this class of drug in the limelight for foreseeable future.

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### Conflicts of interest

There are no conflicts of interest.

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