

TAXANES

DOCETAXEL (TAXOTERE®)

I. MECHANISM OF ACTION

- A) A dynamic equilibrium exists between cellular microtubules and their component parts, the tubulin dimers. Taxotere binds to the fully assembled microtubules. This reduces the number of dimers needed for polymerization, i.e., taxotere promotes microtubule assembly. Most importantly, taxotere inhibits microtubule disassembly. The binding site is different than for colchicine, vincristine, or vinblastine, but the same as paclitaxel. Cell cycle is arrested during mitosis. Docetaxel has 1.9 times more affinity for the tubulin binding site than paclitaxel.
- B) Docetaxel is now made via a semisynthetic process using needles from the European yew tree, *Taxus baccata*. The target compound to modify into docetaxel is 10-deacetylbaccatin III.
- C) Docetaxel is a radiosensitizer.
- D) Resistance is due to altered binding sites on the tubulin or p-glycoprotein.

II. PHARMACOKINETICS

- A) Distribution – Large volume of distribution because of binding to tubulin and plasma protein (97%).
- B) Metabolism – Docetaxel is metabolized by cytochrome P450 3A4 and 3A5 isoenzymes to one major and three minor metabolites. All four metabolites are oxidation products of the tert-butyl group attached to the C13-side chain. These metabolites have markedly less cytotoxic and myelotoxic effects.
- C) Elimination – Mostly biliary. 80% of a dose is recovered in the bile within 7 days. Less than 10% is recovered in the urine.

III. DOSAGE AND ADMINISTRATION

- A) Docetaxel has historically been given as a 1-hour infusion 75–100 mg/m² every 21 days. Recent work has used docetaxel weekly at 30–35 mg/m².
- B) This drug is not a vesicant and can be given peripherally or centrally.
- C) The administration of docetaxel should be in a non-PVC containing system because the vehicle used to dissolve docetaxel, polysorbate 80 would leach out potentially harmful substances from PVC. Very short contact with PVC is permitted.
- D) Patients with liver dysfunction (AST/ALT \geq 1.5 x ULN associated with alkaline phosphatase level \geq 2.5 x ULN) have a significantly reduced clearance of docetaxel as compared to those with normal liver function. This reduction is not observed in patients with increased serum transaminases or alkaline phosphatase alone. Docetaxel should not be given to patients with combined abnormalities of transaminase and alkaline phosphatase or to patients with serum bilirubin levels greater than the ULN.
- E) No dosage adjustment in renal dysfunction.

IV. TOXICITY

- A) Neutropenia – 50–80% of patients. Occurs by day 7 with recovery by day 15–21. G-CSF should be considered in patients requiring hospitalization after docetaxel but is not recommended as primary prophylaxis.
- B) Thrombocytopenia and anemia.

- C) Hypersensitivity Reaction (HSR) – Consists of flushing, rash, dyspnea, bronchospasm, hypotension, and angioedema. In Phase I trials was a significant cause of morbidity and mortality. Can occur with the first or subsequent infusion, but usually by the second dose. It usually presents within the first 10 minutes of the start of the infusion. The HSR is not related to infusion rate. Skin testing does not predict the potential for a HSR.
- Prevention**– Dexamethasone 8 mg PO BID for 3 days, starting the day prior to therapy. For weekly docetaxel regimens, dexamethasone 8 mg PO BID for 3 doses (24 mg/week), starting the evening prior to treatment is often used.
- **NOTE: THERE IS A 10% HYPERSENSITIVITY CROSS-REACTIVITY BETWEEN DOCETAXEL AND PACLITAXEL ****
- Infusion related adverse events: the hypersensitivity reaction if it occurs usually happens during the first 10 minutes. The vital signs should be monitored every 5 to 10 minutes for the 30 minutes in patients receiving the first dose of these drugs. If the patient continues to do well after the first hour, the rest of the drug will be complete according to infusion time.
- D) Fluid Retention – Cumulative with repeated dosing. Give dexamethasone as dexamethasone 8 mg PO q12hr beginning 1 day before chemotherapy, and continuing for 3 – 5 days total.
- E) Neurotoxicity – Peripheral sensory neuropathies in up to 40% of patients. Appears to be a cumulative dose effect. Appears as numbness and tingling in a stocking-and-glove pattern. Some patients have a perioral numbness. It can start within days of the first dose and last for 3–6 months after therapy complete. Motor impairment has been reported.
- F) Gastrointestinal – Emesis is not common and ondansetron or granisetron is rarely needed.
- G) Alopecia – Occurs in 80% patients. Occurs by day 14 and persists for 8 weeks after treatment. Involves all hairy areas of the body.

V. CLINICAL MONITORING: CBC + differential; LFT's (including bilirubin); neurological exam.

VI. DRUG INTERACTIONS

Docetaxel is metabolized by cytochrome P-450 3A. Potential exists for significant drug interactions between docetaxel and agents that inhibit or induce cytochrome P-450 enzymes (eg, rifampin, phenobarbital, erythromycin, ketoconazole).

Docetaxel is metabolized by cytochrome P450 3A (CYP3A4 and CYP3A5) enzymes. *In vitro* studies have shown drugs that inhibit, induce, or are also metabolized by CYP3A enzymes can significantly affect the metabolism of docetaxel. In a small PK study, 7 patients received 2 courses of docetaxel, one with concurrent ketoconazole (docetaxel 10 mg/m²) and one without ketoconazole (docetaxel 100mg/m²). The ketoconazole dosage was 200 mg once daily for 3 days. Concurrent administration of ketoconazole decreased the clearance of docetaxel by 49% as compared to giving docetaxel alone. However, there was large interpatient variability in the reduction in clearance. Potential CYP3A inhibition interactions may occur with docetaxel and anastrozole (high doses only), anti-retroviral protease inhibitors, aprepitant, clarithromycin, delavirdine, efavirenz (induces or inhibits), erythromycin, fluconazole, fluoxetine, fluvoxamine, imatinib, itraconazole, ketoconazole, mibefradil, nefazodone, voriconazole, and others. Potential hepatic CYP3A induction interactions can occur when agents such as barbiturates, bosentan, carbamazepine, nevirapine, phenytoin, fosphenytoin, rifabutin, rifampin, rifapentine, troglitazone, and others are given concurrently with docetaxel. Use docetaxel cautiously when administered concurrently with inducers or inhibitors of CYP3A enzymes. These lists may not include all agents that induce or inhibit CYP 3A isoenzymes.

PACLITAXEL (ONXOL[®]; TAXOL[®])

I. MECHANISM OF ACTION

- A) A dynamic equilibrium exists between cellular microtubules and their component parts, the tubulin dimers. Taxol binds to the fully assembled microtubules. This reduces the number of dimers needed for polymerization, i.e., taxol promotes microtubule assembly. Most importantly, Taxol inhibits microtubule disassembly. The binding site is different than for colchicine, vincristine, or vinblastine. Cell cycle is arrested during mitosis.
- B) Paclitaxel was initially derived from the Pacific yew tree, *Taxus brevifolia*. Paclitaxel is now made via a semisynthetic process using needles from another yew tree, *Taxus baccata*. The target compound to modify into paclitaxel is 10- deacetylbaccatin III.
- C) Paclitaxel is a radiosensitizer.
- D) Resistance is due to altered binding sites on the tubulin or p-glycoprotein.

II. PHARMACOKINETICS

- A) Distribution—Large volume of distribution because of binding to tubulin and plasma protein (97%).
- B) Metabolism—Metabolic pathway is not totally understood but hydroxylation does occur. The cytochrome P-450 system is involved. Nonlinear pharmacokinetics occurs at higher doses (over 175 mg/m²) with short infusion times. Distribution can be saturated at lower doses (<175 mg/m²) but it takes higher doses to saturate metabolism.
- C) Elimination – Mostly biliary. 40% of a dose is recovered in the bile within 24 hr. Less than 10% is recovered in the urine. No dosage adjustment in renal dysfunction.
Dosage adjustment in hepatic impairment:
 - Total bilirubin ≤ 1.5 mg/dL and AST > 2 x ULN: total dose < 135 mg/m²
 - Total bilirubin 1.6 – 3 mg/dL: total dose ≤ 75 mg/m²
 - Total bilirubin: ≥ 3.1 mg/dL: total dose ≤ 50 mg/m²
- D) Cisplatin appears to alter paclitaxel pharmacokinetics. When it is given prior to paclitaxel, there is a higher incidence of neutropenia than if paclitaxel precedes cisplatin. *****ENSURE THAT PACLITAXEL IS ADMINISTERED PRIOR TO PLATINUM ANALOGS****

III. DOSAGE AND ADMINISTRATION

- A) Paclitaxel is given as a 24 hour infusion 135 – 250 mg/m² mixed in 1000 mL of NS or D₅W or 500 mL over 3 hours. Current research involves longer infusions (72 and 96 hours). Three and 24-hour infusions are equally safe with appropriate pre-meds. The response rates in ovarian cancer are equal.
- B) This drug is not a vesicant and can be given peripherally or centrally. The high concentration of Cremophor El used as a diluent can be irritating to soft tissue.
- C) The administration of paclitaxel should be in a non-PVC containing system because the vehicle used to dissolve paclitaxel will leach out potentially harmful and carcinogenic substances from PVC. Very short contact with PVC is permitted.
- D) Infusion related adverse events: the hypersensitivity reaction if it occurs usually happens during the first 10 minutes. The vital signs should be monitored every 5 to 10 minutes for the 30 minutes in patients receiving the first dose of these drugs. If the pt continues to do well after the first hour, the rest of the drug will be complete according to infusion time.

IV. TOXICITY

- A) Neutropenia – 67% of patients. Related to dose and duration of infusion. Higher doses and longer duration of infusion cause worse neutropenia. Occurs by day 8–13 with recovery by day 15–21. G-CSF should be considered in patients requiring hospitalization after taxol but is not recommended as primary prophylaxis.
- B) Thrombocytopenia and anemia– 10% and 24% of patients, respectively.
- C) Hypersensitivity Reaction – Consists of flushing, rash, dyspnea, bronchospasm, hypotension and angioedema. In Phase I trials was a significant cause of morbidity and mortality. Can occur with the first or subsequent infusion, but usually by the second dose. It usually presents within the first 10 minutes of the start of the infusion. The HSR is not related to infusion rate. Skin testing does not predict the potential for a HSR. Incidence with appropriate premeds is 1–3%.

Prevention– See [Premedication section in handbook](#). Recent studies have shown that one dose of dexamethasone IV 20mg with parenteral cimetidine and diphenhydramine 30 minutes prior to the infusion is sufficient. Any H₂ blocker can be used. For weekly paclitaxel regimens, the starting dose of dexamethasone can be reduced to 10 mg and tapered as tolerated over time to 4 mg.

****NOTE: there is a 10% hypersensitivity cross-reactivity between paclitaxel and docetaxel****

- D) Cardiac – Bradycardia in 30–60% of patients but usually requires no intervention. Ventricular tachycardia, myocardial infarction, bigeminy, trigeminy, and PVC's have all been reported. Cardiac monitoring is **NOT** necessary unless there is a significant clinical history.
- E) Neurotoxicity – peripheral sensory neuropathies in up to 62% of patients. More common at doses over 200 mg/m² and with rapid infusions. Appears to be a cumulative dose effect. Appears as numbness and tingling in a stocking-and-glove pattern. Some patients have perioral numbness. It can start within days of the first dose and last for 3 – 6 months after therapy is completed. Motor impairment has been reported.
- F) Gastrointestinal – Mucositis at doses over 265 mg/m² or when given as an infusion over more than 24 hours. Concurrent doxorubicin administration worsens mucositis. Emesis is uncommon.
- G) Alopecia– Occurs by day 14 and persists for 8 weeks after treatment. Involves all hairy areas of the body.
- H) Musculoskeletal – Myalgias and arthralgias are sometimes seen after high dose regimens. Often responsive to NSAID's ± a short course of steroids.

PACLITAXEL (NANOPARTICLE ALBUMIN-BOUND) (ABRAXANE®)

I. MECHANISM OF ACTION

- A) Abraxane® is a new class of albumin-bound form of paclitaxel where albumin is integrated with paclitaxel to create an amorphous, nanoparticle form of the drug. The nanoparticles act as biological 'transporters' for paclitaxel. This formulation overcomes solubility issues with traditional formulations of paclitaxel and eliminates the need for solvents such as Cremophor EL®.
- B) Albumin formulation of paclitaxel utilizes a receptor-mediated (gp 60) pathway on microvessel endothelial cells to transport the albumin-paclitaxel complex out of the blood stream and into the tumor interstitium. It is suggested that once the albumin-paclitaxel complex is in the tumor interstitium, this complex would bind to the SPARC protein and would be rapidly internalized by the tumor cell. Traditional formulations of paclitaxel are not transported into tumor cells via these mechanisms.
- C) The cytotoxic effect of Abraxane® is similar to that of paclitaxel in which it promotes microtubule assembly from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

II. PHARMACOKINETICS

- A) Distribution- mean volume of distribution is 632 L/m²; extensive extravascular distribution and/or tissue binding of paclitaxel.
- B) Metabolism- Paclitaxel is metabolized by CYP 2C8 and CYP 3A4. Caution should be exercised when administering Abraxane® concomitantly with known substrates or inhibitors of CYP 2C8 and CYP 3A4.
- C) Elimination- terminal half-life 27 hours; < 1 % renally excreted as metabolites 6 - hydroxy- paclitaxel and 3'-p-hydroxypaclitaxel; fecal excretion was ~20% of the total dose administered.

III. DOSAGE AND ADMINISTRATION

- A) Approved dose is 260 mg/m² intravenously over 30 minutes q 3 weeks. No premedications with steroids or antihistamines are required.
- B) Each single-use vial of Abraxane® contains 100 mg of paclitaxel and approximately 900 mg of human albumin.
- C) Available as lyophilized powder for reconstitution with 20 mL of 0.9% sodium chloride injection. Each mL of reconstituted suspension contains 5 mg paclitaxel.

IV. TOXICITIES

- A) Hematologic: Grade 4 Neutropenia: 9%; Febrile neutropenia: 2%; thrombocytopenia uncommon; anemia (Hb < 11g/dL) 33%.
- B) Sensory neuropathy: 71% (10% severe). The frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent Abraxane[®].
- C) Ocular/visual disturbances: 13% (1% severe); reversible; severity is dose-dependent.
- D) Arthralgia/myalgia: 44% (8% severe); usually transient, occur 2 to 3 days after Abraxane[®] administration, and resolve within a few days.
- E) Hepatic: Elevation of bilirubin (7%), alkaline phosphate (36%), AST (39%).
- F) Gastrointestinal: Nausea/vomiting (33%); diarrhea (27%); mucositis (7%).
- G) Asthenia: 47% (8% severe).
- H) Hypersensitivity reaction (HSR): Grade 1 or 2 dyspnea (1%); flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of Abraxane[®] in patients previously exhibiting HSR to paclitaxel injection or human albumin has not been studied.

V. CLINICAL MONITORING

- A) Periodic CBC with diff, LFTs.
- B) Physical exam (vital signs, mouth sores, peripheral neuropathy).
- C) Dosing adjustment recommendation per manufacturer:
After the first cycle, if a patient's neutrophil count is < 500 cells/mm³ for more than a week or if severe sensory neuropathy develops, decrease subsequent doses to 220 mg/m² IV. Hold Abraxane[™] administration if grade 3 sensory neuropathy develops until resolution to grade 1 or 2 severity. If recurrence of either neutropenia or neuropathy occurs, further decrease subsequent doses to 180 mg/m².