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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Taxanes. [Updated 2018 Jan 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Taxanes

Updated: January 15, 2018.

OVERVIEW

The taxanes or taxoids are a closely related group of antineoplastic agents that have a unique mechanism of action as inhibitors of mitosis and which are widely used in the therapy of ovarian, breast, lung, esophageal, prostate, bladder and head and neck cancers. Three taxanes are in clinical use, paclitaxel (Taxol: 1992), docetaxel (Taxotere: 1996) and cabazitaxel (Jevtana: 2010). Paclitaxel was the first compound in this chemical group to be introducted into clinical use and was initially isolated from the bark of the Western yew tree. Docetaxel is a semisynthetic analogue of paclitaxel and a derivative of extracts from needles of the European Yew (Taxus baccata) that has somewhat better pharmacokinetics and different side effects than paclitaxel. Cabazitaxel is also a semisynthetic analogue of natural taxoids and was developed for its lack of affinity for P-glycoprotein, a common mediator of docetaxel reistance. The taxanes are similar to the vinca alkaloids in that they bind to tubulin and cause inhibition of mitosis. However, the taxanes bind at a different site than the vinca alkaloids and cause inhibition of mitosis by prevention of degradation of microtubules, rather than prevention of their assembly. Three three taxanes are all given intravenously, usually every 1 to 3 weeks. While taxanes have many side effects and can be associated with serum enzyme elevations during treatment, they have not been linked to idiosyncratic, clinically apparent liver injury with jaundice. The few case reports of acute liver injury associated with taxanes (largely docetaxel) have occurred in patients with acute hypersensitivity reactions, sepsis or multiorgan failure.

The taxanes are discussed separately, but general references to their hepatotoxicity and safety are given at the end of this Overview section.

Drug Class: Antineoplastic Agents

Drugs in the Subclass, Taxanes: Cabazitaxel, Docetaxel, Paclitaxel

ANNOTATED BIBLIOGRAPHY

References updated: 15 January 2018

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp.673-708.

(Textbook of hepatotoxicity published in 1999; paclitaxel and docetaxel are not mentioned).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 549-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; the taxanes are not specifically discussed).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Taxanes. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1707-9.

(Textbook of pharmacology and therapeutics).

Onetto N, Canetta R, Winograd B, Catane R, Dougan M, Grechko J, Burroughs J, Rozencweig M. Overview of Taxol safety. J Natl Cancer Inst Monogr 1993; (15): 131-9. PubMed PMID: 7912519.

(Among 655 patients treated with paclitaxel, dose limiting toxicities included bone marrow suppression [especially neutropenia], mucositis, neuropathy and rarely cardiomyopathy; hypersensitivity reactions can be controlled with premedication; liver test abnormalities were dose dependent with any AST elevations in 7-26% of patients and values >5 times ULN in only 2% of those receiving the highest dose).

Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 1993; 20 (4 Suppl 3): 1-15. PubMed PMID: 8102012.

(Extensive review of toxicities of paclitaxel; according to data on file with the sponsor, elevations of AST, Alk P and bilirubin >5 times the ULN occurred in <1% of 402 patients in phase II and III trials).

Von Hoff DD. The taxoids: same roots, different drugs. Semin Oncol 1997; 4 (4 Suppl 13): S13-3-S13-10. PubMed PMID: 9335511.

(Review of the development of paclitaxel and docetaxel, clinical use, efficacy and toxicity stressing the differences between the two taxoids, which are due largely to differences in pharmacokinetics).

Fumoleau P. Efficacy and safety of docetaxel in clinical trials. Am J Health Syst Pharm 1997; 54 (24 Suppl 2): S19-24. PubMed PMID: 9435929.

(Overall response rates to docetaxel and paclitaxel in advanced breast cancer ranged from 29-68% of patients; major dose related toxicities included neutropenia, mucositis, cardiomyopathy and fluid retention; hepatotoxicity was not mentioned).

Tomassini E, Muhizi J, al Raheb K, Steinbach G, Bemer M, Platini C. [Fulminant hepatocellular necrosis following administration of docetaxel]. Presse Med 2001; 30: 634. French. PubMed PMID: 11346902.

(52 year old woman with metastatic breast cancer developed jaundice and stupor 72 hours after an initial infusion of docetaxel [bilirubin 6.8 mg/dL, ALT 5540 U/L, GGT 116 U/L, protime 18 sec], with death from multiorgan failure and autopsy showing massive necrosis).

Ohlmann CH, Kohlmorgen S, Sahi D, Engelmann U, Heidenreich A. [Lethal course after chemotherapy with docetaxel. Acute liver failure with accompanying erythema multiforme major]. Urologe A 2007; 46: 1425-7. German. PubMed PMID: 17563866.

(67 year old man with prostate cancer developed Stevens-Johnson Syndrome, neutropenia and thrombocytopenia after 5 weekly infusions of docetaxel, with subsequent rise in liver tests and jaundice that progressed to hepatic failure and death; few details provided).

Minami H, Kawada K, Sasaki Y, Tahara M, Igarashi T, Itoh K, Fujii H, et al. Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. Cancer Sci 2009; 100: 144-9. PubMed PMID: 19018756.

(Analysis of pharmacokinetics of docetaxel in 200 patients found that liver test abnormalities were associated with delayed clearance and recommended 20-40% reduction in dose).

de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, et al.; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic c castration-resistant prostate cancer progressing

after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376 (9747): 1147-54. PubMed PMID: 20888992.

(Among 755 men with castration-resistant prostate cancer after failure of docetaxel who were treated with iv cabazitaxel or mitoxantrone every 3 weeks with daily oral prednisone, overall survival was greater with cabazitaxel [15.1 vs 12.7 months], but side effects required careful monitoring including neutropenia [94%], anemia [93%], thrombocytopenia [47%], diarrhea [47%], and adverse event related deaths [4.8% vs 1.1% with mitoxantrone] which were considered possibly related to therapy in 2.6% vs 0.3%).

Dorff TB, Quinn DI. Cabazitaxel in prostate cancer: stretching a string. Lancet 2010; 376 (9747): 1119-20. PubMed PMID: 20888974.

(Editorial on article by de Bono [2010] giving background to the study of cabazitaxel for patients with docetaxel resistance and concluding that the trial will reset the guidelines for therapy of this category of patients).

New treatments for metastic prostate cancer. Med Lett Drugs Ther 2010; 52 (1346): 69-70. PubMed PMID: 20814400.

(Concise review of the mechanism of action, clinical efficacy, adverse effects and costs of sipuleucel-T and cabazitaxel shortly after their approval as therapies of metastatic prostate cancer in the US; mentions deaths from febrile neutropenia due to cabazitaxel, but not liver related adverse events or ALT elevations).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed Citation

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5.5%] were attributed to antineoplastic agents of which only 1 was due to a taxane [docetaxel]).