Review Article

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TAXOL AS AN ANTICANCER AGENT: A REVIEW

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ABSTRACT

The development of Taxol (paclitaxel) as an anticancer drug is reviewed. Paclitaxel (formerly called taxol), an important anticancer drug, inhibits cell replication by binding to and stabilizing microtubule polymers. As drug-receptor interactions are governed by the three-dimensional stereochemistry of both participants. Paclitaxel (Taxol) is a chemotherapy drug widely used to treat different types of solid tumours (e.g. ovarian, breast, and pancreatic). Taxol acts by hyper-stabilizing microtubules, inhibiting mitosis and eventually causing cell apoptosis. Taxol belongs to a class of chemotherapy drugs called plant alkaloids. Plant alkaloids are made from plants. From long time paclitaxel is used to induce mitotic arrest, which is responsible for cell death in a subset of the arrested population. Now it is demonstrated that intra-tumoral concentration of paclitaxel are low to produce mitotic arrest and which result in multi polar division instead. It may possible that this insight can be used to develop a biomarker to identify the 50% patients may set benefit from paclitaxel therapy. This review includes common and less common side effects for individuals taking Taxol. Side effects that is very rare, occurring in less than 10% of patients. Here I discuss the history of paclitaxel and our recently evolved understanding of its mechanism of action.

Keywords: Taxol, Anticancer agent, chemotherapy.

INTRODUCTION

In the following article we study the total taxol crude drug and their classification and types regarding the site of action. The Taxol crude drug is being used since while ago and the resulting action or the desired action are be observed positively. The taxol can use as the anticancer drug in the treatment. Taxol (paclitaxel) is a cancer chemotherapy medication that interferes with the growth of cancer cells and slows their growth and spread in the body and is used to treat breast cancer, lung cancer and ovarian cancer. Taxol is also used to treat AIDS-related Kaposi's sarcoma. The genus *Taxus* L. has interested many researchers since the discovery of the anticancer agent paclitaxel (Taxol TM), a diterpenoid alkaloid originally isolated from the bark of the pacific yew, *T. brevifolia* (Wani *et al.*, 1971). The drug is the first natural product described that stabilized microtubules and has been approved by the FDA for the treatment of ovarian, breast and non-small cell lung carcinomas (Rowinsky, 1997). So far, several hundred different taxoid, lignans, flavonoids, steroids and sugar derivatives have been isolated from different parts of various *Taxus* species.

History

The first known compound which binds to tubulin was colchicine, Colchicum atumnale, but it has not been used in cancer treatment. The first anticancer drugs approved for clinical use were Vinca alkaloids, Vinblastine and Vincristine, in the 1960s. They were isolated from leaves of the *Cantharanthus roseus* (Vinca rosea) plants in the University of Western Ontario in 1958. In 1962, sample of Pacific yew's bark were first collected by the researchers from US department of Agriculture (USDA) to find natural product that might cure cancer. In 1964 and 1965, additional samples of bark were collected to isolate paclitaxol and its biological action. First drug, along the taxanes and paclitaxel, was discovered in extracts from the bark of the Yew tree, *Taxus brevifolia*, in 1967 by Monrie Wall and Mansukh Wani but its tubulin (tumour) inhibition activity was not known until 1979. Yews are poor source of active agents which limited the development of taxanes for over 20 years until discover of the way of synthesis (Jordan, 2012). In 1977, the trade name of paclitaxel was also known by "Taxol". In December 1992, paclitaxel was approved to be used in chemotherapy (Gordoliza, 2008). In 1984, and 1994 the FDA (Food and Drug Administrated) approved taxol for use against ovarian cancer and breast cancer respectively. In 1992 USDA isolated paclitaxel from *Taxus brevifolia* and structure was reported. In 2003 antitumor and anti angiogenic activity of paclitaxel was reported by Schmidt-Sody.[1]

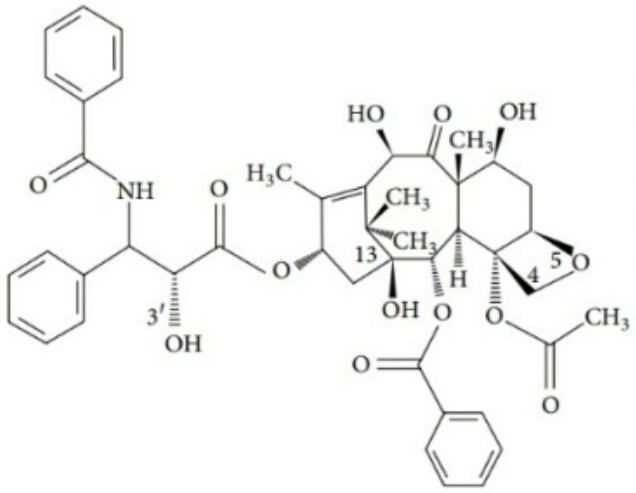
Extraction of Taxol

The 2-liter Erlenmeyer flasks was taken containing 500 ml of MID medium supplemented with 1 g soy tone/l.[3] At 26 ± 1°C for 21 days the test fungus was inoculated into the medium. The culture was harvested and the culture filtrate was passed through four-layered cheese cloth, after completion of the incubation period. 0.25 g of $NaCO_3$ was added to the filtrate and extracted with two equal volumes of solvent Dichloromethane, in order to avoid fatty acid contamination. Under reduced pressure at 35°C, the organic phase was collected and evaporated to dryness. The dry solid residue was re-dissolved in methanol and placed on a 1.5 × 30-cm column of silica gel (Baker 40 µ). Starting with 70 mL of 100% methylene chloride followed by mixtures of organic solvents at different proportions, elution of the column was performed. The fractions thus obtained were collected, evaporated to dryness, and subjected to thin layer chromatography (TLC). By TLC, UV absorptions spectrophotometry, IR spectroscopic analysis, HPLC analysis, and MASS spectroscopic analysis, the presence of Taxol in the fungal sample was an analysed.[4]

Chemical Structure of taxol

Paclitaxel consists of an eight-member taxane ring with a four-member oxetane ring and a bulky ester side chain at C-13 that is

necessary for antitumor activity[5] but which can be modified (Figure 1). The chemical formula of paclitaxel is $C_{47}H_{51}O_{14}$ and its molecular weight is 853.9. It is highly lipophilic and insoluble in water, but soluble in Cremophor EL, polyethyleneglycols 300 and 400, chloroform, acetone, ethanol and methanol. For clinical use paclitaxel is formulated in50% Cremophor EL and 50% dehydrated alcohol.[6]



Empirical formula: $C_{47}H_{51}NO_{14}$

Molecular weight: 853.9 g/mol

Average mass: 853.9 Da

Systemic name: (2α, 5β, 7β, 10β, 13α)-4,10-Diacetoxy-13-{[(2R, 3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate

Paclitaxel is a taxane ring with a four-membered oxetane side ring at positions C_4 and C_5 and ahomochiral ester side chain at C13. Ahomochiral ester side chain is an active portion that plays important role binds to microtubules, stabilizes the tubulin bundles, and stimulates disassembly of microtubules in a guanosine triphosphate (GTP). As a result of, cell proliferation is inhibited by halting the cell cycle at the metaphase/anaphase boundary and by formation of an incomplete metaphase plate of chromosomes, induced by the stabilization of the microtubule dynamics. According to above it is concluded that taxane ring and ester side chain is essential for activity.[7, 8]

Mechanism

Paclitaxel drug targets tubulin. Researchers have observed that Paclitaxel treated cells have difficulty with the spindle assembly, cell division and also chromosome segregation which is in opposing nature to Colchicine, a drug that targets tubulin. The major difference between Colchicine and Paclitaxel is that Colchicine inhibits the microtubule assembly whereas Paclitaxel stabilizes and protects microtubule against disassembly. At a higher dose, Paclitaxel is known to suppress microtubule minus ends detachment from centrosomes.[9, 10] The beta-tubulin subunit is known to have the binding site for Paclitaxel.[11]

The primary mechanism of action of paclitaxel is the suppression of microtubule spindle dynamics.[12] This results in the blockage of metaphase-anaphase transitions, and ultimately the inhibition of mitosis and induction of apoptosis. Unlike other microtubule disrupting drugs (e.g. the vinca alkaloids) paclitaxel specifically stabilizes microtubules by binding to the polymeric tubulin, thereby preventing tubulin disassembly.[13] The broad-spectrum activity of paclitaxel was predicted by this mechanism of action (i.e., control of cell proliferation and DNA repair),[14, 15] which targets the very basic elements of the cancer phenotype.

Recent studies also suggest that the activity of Paclitaxel includes activation of Raf 1 kinase which is also an essential for Bcl-2 phosphorylation and apoptosis. The action takes a minimum time of 4 hours, while maximum time required for the action is 14-16 hours, as the RNA and Protein synthesis play an important role. The action of Paclitaxel although is independent of the p53 activity, yet correlations can be cited as it might influence cell cycle progression following mitotic arrest. Experiments following dominants-negative SEKI mutant suggested the blocking of JNK pathway inhibited the paclitaxel induced Bcl-2 phosphorylation and apoptosis. In order to make sure the action of paclitaxel the effect of JNK pathways on paclitaxel induced Bcl-2 phosphorylation also needs to be considered.

Side Effects of Taxol

Chemotherapy is most effective for killing tumour cells that are rapidly dividing. Unfortunately, chemotherapy does not know the difference between the cancerous cells and the normal cells. The normal cells will grow back and become healthy but in the meantime, side effect occurs. The normal cells most commonly affected by chemotherapy are blood cells, cells in the mouth, stomach and bowel and hair follicles. Paclitaxel has interaction with a large number of medicines. A total of 353 drugs (1172 brand and genetic names) are known to interact with paclitaxel. Of them 48 are major, 298 are moderate and 7 are minor drug interactions. Using paclitaxel and Dalta pristin, Epirubicin, Fosphenytoin, Lapatinib, phenytoin, Quinupristin may increase risk of certain side effects. It has interactions with certain type of foods, tobacco and alcohols. The presence of medical problems like Bardycardia (slow hearth rate), Heart Rhythm Problem, Hypertension (high blood pressure), Hypotension (low blood pressure), and Peripheral Neuropathy may affect the use of this medicine. Paclitaxel may cause unwanted side effects that require medical attention.[1]

CONCLUSION

The preceding review has summarized one small part of the enormous amount of work that has been done on taxol. PX is one of most effective anticancer drugs ever developed. It is active against a broad range of cancer. Some of them have demonstrated certain advantages in term of toxicity, such as lower incidence of hypersensitive reaction myelo suppression, etc. However, whether these novel formulations may improve survival is largely unknown.

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