WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 13, 142-148. Review Article ISSN 2277– 7105

TAXOL AS AN ANTICANCER AGENT

Rohan Kherud*[1], Sakshi Sarode[2], Vaishnavi Vavhal[1], Shital Shinde[1], Swapnil Kadam[1], Dhanashri Ohol[1] and Mayur Khemnar[1]

[1]Sanjivani College of Pharmaceutical Education and Research, Kopergan.

[2]Dr Sir. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik.

Article Received on
24 July 2022,

Revised on 14 August 2022,
Accepted on 04 Sept. 2022

DOI: 10.20959/wjpr202213-25491

***Corresponding Author**
Rohan Kherud
Sanjivani College of Pharmaceutical Education and Research, Kopergan.

ABSTRACT

The development of Taxol (paclitaxel) an anticancer drug is reviewed. Paclitaxel (formerly called Taxol), an important anticancer drug, inhibits cell replication by binding and stabilizing microtubule polymers. As drug-receptor interactions are governed by the three-dimensional stereo chemistries 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. Paclitaxel has long been recognized to induce mitotic arrest, which leads to cell death in a subset of the arrested population. However, recent evidence demonstrates that intratumorally concentrations of paclitaxel are too low to cause mitotic arrest and result in multipolar divisions instead. It is hoped that this insight can be used to develop a biomarker to identify the 50% of patients who will benefit from paclitaxel therapy. This review includes common and less common side effects for individuals taking Taxol. Very rare side effects occur 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, paclitaxel, vinca alkaloid, ovarian, breast, HPTLC, UV, TLC, colchicine, JNK pathway.

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 for a while ago and the

resulting action or the desired action are be observed positivelyTaxolol can use as an 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 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 microtubule 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 toxoids, 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 autumnal, 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 cantharidin thusroseus (Vincarosea) plantation at the University of Western Ontario in 1958. In 1962, samples of Pacific yew's barware were first collected by researchers from the Uthe S Department of Agriculture (USDA) to find natural products that might cure cancer. In 1964 and 1965, additional samples of bark were collected to isolate paclitaxel and its biological action. The first drug, along with the taxanes and paclitaxel, was discovered in extracts from the bark of the Yew tree, Taxusbrevifolia, in 1967 by Monroe Wall and Mansukh Wani but its tubulin (tumour) inhibition activity was not known until 1979. Yews are a poor source of active agents which limited the development of taxanes for over 20 years until the discovery of the way of synthesis (Jordan, 2012). In 1977, the trade name paclitaxel was also known as "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 brevi folia and structure was reported. In 2003 antitumor and antiangiogenic activity of paclitaxel was reported by Schmidt-Sody.[1]

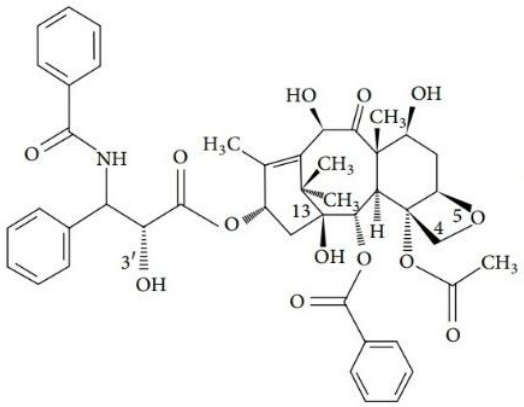
Extraction of Taxol

The extraction procedure was carried out by the method of,[2] the test fungus selected in this study was grown in 2-litre Erlenmeyer flasks containing 500 ml of MID medium

supplemented with 1 g soytone/l.[3] The test fungus was inoculated into the medium and incubated for 21 days at 26 ± 1°C. After completion of the incubation period, the culture was harvested and the culture filtrate was passed through four-layered cheesecloth. To avoid fatty acid contamination, 0.25 g of NaCO3 was added to the filtrate and extracted with two equal volumes of solvent Dichloromethane. The organic phase was collected and evaporated to dryness under reduced pressure at 35°C. The dry solid residue was re-dissolved in methanol and placed on a 1.5 × 30-cm column of silica gel (Baker 40 µ). Elution of the column was performed in a stepwise manner starting with 70 mL of 100% methylene chloride followed by mixtures of organic solvents at different proportions. The fractions thus obtained were collected, evaporated to dryness, and subjected to thin layer chromatography (TLC). The presence of TAXOL in the fungal sample was analysed by TLC, UV absorptions spectrophotometry, IR spectroscopic analysis, HPLC analysis, and MASS spectroscopic analysis.[4]

Chemical Structure of taxol

Paclitaxel consists of an eight-member taxane ring with a four-member oxetane ring and a bulky ester sidechain at C-13 that is necessary for the antitumor activity[5] but which can be modified (Fig. 1). The chemical formula of paclitaxel is C47H51O14 and its molecular weight is 853.9. It is highly lipophilic and insoluble in water, but soluble in Cremophor EL, polyethene glycols 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 consists of two molecules: a taxane ring with a four-membered oxetane side ring at positions C4 and C5 and a homochiral ester side chain at C13. The side chain at C13plays a crucial role, as this is the active portion that binds to microtubules, stabilises the tubulin

bundles, and stimulates the disassembly of microtubules in a guanosine triphosphate (GTP)-independent manner. As a result, cell proliferation is inhibited by halting the cell cycle at the metaphase/anaphase boundary and by the formation of an incomplete metaphase plate of chromosomes, induced by the stabilization of the microtubule dynamics. Extensive research has concluded that an intact taxane ring and an ester side-chain were essential forces to toxic 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 the 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 (eg, the vinca alkaloids), paclitaxel specifically stabilizes microtubules by binding to the polymeric tubulin, thereby preventing tubulin disassembly (Fig 1).[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.

Paclitaxel plays a vital role in anti-cancer treatment by the hyperphosphorylation of the anti-apoptotic agent Bcl-2(B-cell Lymphoma 2) attacking the serine residues at sites 70 and 87 when they act on the microtubules. Thus, being a tubule poison paclitaxel can kill the cancer cells that express Bcl-2. But to understand the phosphorylation techniques, it is essential to establish a relation between the mitogen-activated protein kinases that are capable of phosphorylating the Bcl-2 and the anti-cancer drug Paclitaxel. The various kinases whose activities were reviewed include JNK (c-Jun N-terminal Kinase), ERK (Extracellular Signal Related Kinase), Raf 1 & p38. To evaluate the role of JNK and its correlation with Paclitaxel, the effectiveness of the JNK inhibitors needs to be discussed. If JNK activation was blocked by transfect ions with either a stress-activated protein kinase dominant-negative (K→R) gene

(which prevents the activation of a kinase upstream of JNK) or MAPK phosphatase-1 gene (which dephosphorylates and inactivates JNK), Bcl-2 phosphorylation does not occur, and the cells are not killed by paclitaxel. It was seen that the cells treated with Paclitaxel produced a maximum kinase response at a much shorter time interval than in the absence of the drug. But similar treatment with ERK and p38 did not provide any supportive results for Paclitaxel.

To ensure the activity of Paclitaxel, the effect of JNK pathways on paclitaxel-induced Bcl-2 phosphorylation also needs to be considered. Experiments using a dominant-negative SEK1 (K→R) mutant suggested that the blocking of the JNK pathway inhibited the Paclitaxel-induced Bcl-2 phosphorylation and apoptosis. Recent studies also suggest that the activity of Paclitaxel includes activation of Raf 1 kinase which is also essential for Bcl-2 phosphorylation and apoptosis. But the action is not immediate and takes a minimum time of 4 hours, while maximum effects are required around 14-16 hrs, as the effectivity is dependent upon new RNA and protein synthesis. These overexposures might increase the chances of cytotoxicity, but the application of Actinomycin D or cycloheximide tends to reduce the cytotoxic effects. Although the action of Paclitaxel is independent of the p53 activity, indirect correlations can be cited as it might influence cell cycle progression following mitotic arrest. If a cell escapes mitotic arrest it can proceed to the S phase wan with an 8C DNA structure. So, the effectivity of the p53 gene is necessary in such cases to avoid excessive proliferation.[16]

Side Effects of Taxol

Chemotherapy is most effective for killing tumour cells that are rapidly dividing. Unfortunately, chemotherapy does not know the difference between cancerous cells and 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 & bowel and hair follicles. Paclitaxel interacts with a large number of medicines. A total of 353 drugs (1172 brand and generic names) are known to interact with paclitaxel. Of them 48 are major, 298 are moderate and 7 are minor drug interactions. Using paclitaxel and Daltopristin, Epirubicin, Fosphenytoin, Lapatinilo, phenytoin, and Quintuplicating may increase the risk of certain side effects. It has interactions with certain types of foods, tobacco and alcohol. The presence of medical problems like Bradycardia (slow heart rate), Heart Rhythm Problem, Hypertension (high

blood pressure), Hypotension (low blood pressure), and Pand 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.

REFERENCE

1. Phytochemical Studies of Taxus Species and Their Uses in Cancer Treatment Thaneshwar Subedi Tribhuvan University P.N. Campus, Pokhara, Nepal.
2. Strobel G, Yang X, Sears J, Kramer R, Sidhu RS, Hess WM. Taxol from Pestalotiopsis microspora, an endophytic fungus of Taxus Wallachian. Microbiology, 1996; 142: 435-40.
3. Pinkerton F, Strobel G. Serinol as an activator of toxin production in attenuated cultures of Helminth emporium saccharin. Proc Natl Acad Sci U S A., 1976; 73: 4007-11.
1. 4., JH. HPLC separation of taxol and cephalon manning. J Chrom., 1991; 14: 659.
4. Kingston DGI, Samaranayake G, Ivey CA. The chemistry of taxol, a clinically useful anticancer agent. J Nat Prod., 1990; 53: 1-12.
5. Correia JJ. Effects of antimitotic agents on tubulin-nucleotide interactions. Pharmac Ther., 1991; 52: 127-47.
6. D. Guenard, F. Gu´eritte-Voegelin, J. Dubois, and P. Potier, ´ "Structure-activity relationships of Taxol and Taxotere analogues," Journal of the National Cancer Institute. Monographs, 1993; 15: 79–82.
7. D. G. I. Kingston, "Taxol: the chemistry and structure-activity relationships of a novel anticancer agent," Trends in Biotechnology, 1994; 12(6): 222–227.
8. Bharadwaj R, Yu H. the spindle checkpoint, aneuploidy, and cancer. Oncogene, 2004; 23: 2016-2027.
9. Ganguly A, Yang H, Cabral F. Paclitaxel-dependent cell lines reveal a novel drug activity. Mol Cancer Ther., 2010; 9: 2914-2923.
10. Löwe J, Li H, Downing K H, Nogales E. Refined structure of alpha beta-tubulin at 3.5 A resolution. J MolBiol., 2001; 313: 1045-1057.
11. Manfredi JJ, Horwitz SB. Taxol: an antimitotic agent with a new mechanism of action. Pharmacol Ther., 1984; 25: 83–125. [PubMed] [Google Scholar]

12. Amos LA, Lowe J. How Taxol stabilises microtubule structure. ChemBiol., 1999; 6: R65–R69. [PubMed] [Google Scholar]
13. Foa R, Norton L, Seidman AD. Taxol (paclitaxel): a novel anti-microtubule agent with remarkable anti-neoplastic activity. Int J Clin Lab Res., 1994; 24: 6–14. [PubMed] [Google Scholar]
14. Hajek R, Vorlicek J, Slavik M. Paclitaxel (Taxol): a review of its antitumor activity in clinical studies Minireview. Neoplasma, 1996; 43: 141–154. [PubMed] [Google Scholar]
15. A Review on the role of Paclitaxel in Cancer –"Mechanism & Enhanced Bioavailability" Author Raj Mukherjee, Koyel Sen, Dr Ketousetuo Kuotsu Department of Pharmaceutical Technology, Jadavpur University. Assistant Professor, Department of Pharmaceutical Technology, Jadavpur University.