The pharmacology of paclitaxel in cancer therapy

Xinmei Jiang*

Shenzhen College of International Education, Shenzhen, Guangdong Province, 518043, China

Abstract. Paclitaxel (PTX) had been identified as an anticancer ingredient from the bark of *T. brevifolia* by 1967. In 1971, it had officially entered the National Cancer Institute drug development program. PTX is a microtubule-stabilizing drug that has been approved for treating various kinds of cancers as a first-line or a second-line drug. As a natural anticancer drug, PTX targets in microtubules to block cell divisions, thereby leading to tumor cells death. It has a wide use of clinical applications in treating various cancer, including ovarian cancer, bladder cancer and breast cancer etc. In this review, we discuss the discovery history of PTX and summarize its pharmacology, including the effects on cancer cells and the tumor immune microenvironment. We also aims to offer a comprehensive understanding in PTX for expanding its clinic application in future.

1. Introduction

Cancer is a disease threatened millions of people every year worldwide. With an estimated 9.6 million deaths worldwide, cancer ranks as the second most common cause of death, according to the World Health Organization. Men are more likely to have lung, prostate, colorectal, stomach, and liver cancers than women are to develop breast, colorectal, lung, cervical, and thyroid cancers[1]. As a result, finding effective treatments for cancer become concerning and challenging tasks for scientists. Chemotherapy as a type of standard cancer therapy for majority of human cancers has been application in clinic since 1960s. Chemotherapy significantly improve the lifespan of patients with cancer.

Paclitaxel (also called taxane, PTX), is a classical chemotherapy drug in clinical over the past two decades. As a natural anticancer drug with high efficiency, low toxicity and broad spectrum, paclitaxel has been approval by Food and Drug Administration (FDA) for the treatment of ovarian, breast, lung cancer, and Kaposi's sarcoma. In addition, it is also used in the clinical treatments of gastroesophageal, prostate, cervical, endometrial, and head and neck cancers. However, inevitably side effects appear in cancer patients with paclitaxel therapy, such as gastrointestinal reaction, alopecias, and allergy. In this article, we review the pharmacology of PTX, with an emphasis on its discovery history, mechanisms of killing tumor cell and applicant in clinic.

2. The discovery of paclitaxel

In 1955, the National Cancer Institute (NCI) established the Cancer Chemotherapy National Service Center (CCNSC) to conduct research on cancer treatments. This partnership focused on a plant screening program aimed at identifying potential compounds with antitumor effects. More than 30,000 compounds were studied, culminating in the identification of paclitaxel, a compound derived from Taxus brevifolia (T. brevifolia), which proved effective in killing tumor cells.

T. brevifolia, a species of Pacific yew tree, was obtained by Arthur Barclay, a botanist from USDA, in 1962. Extracts from the bark, twigs, needles, and fruit were examined, revealing that the bark extract was cytotoxic to tumors. Subsequently, in 1964, Monroe E. Wall, Ph.D., and Mansukh Wani, Ph.D., who were affiliated with NCI at the Research Triangle Institute in North Carolina, received a sample of T. brevifolia and isolated the most cytotoxic compound from the bark, which they named paclitaxel in 1967. Paclitaxel is characterized by a tetracyclic 17-atom skeleton with a total of 11 stereocenters(figure 1).

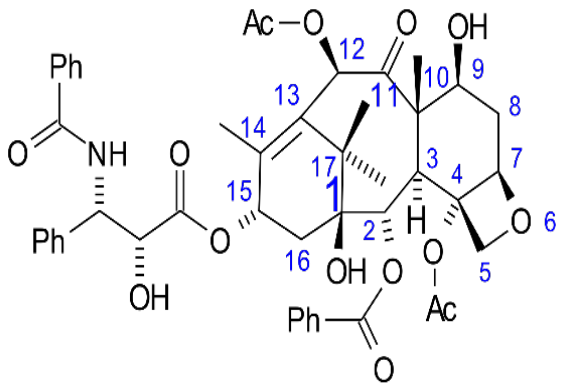

Figure 1. The structure of paclitaxel. $C_{47}H_{51}NO_{14}$

Paclitaxel's anticancer effectiveness was confirmed by the National Cancer Institute in 1977 after it shown efficacy in mice tumor models, and the medicine was regarded as one of the most promising plant products for

*Corresponding author's e-mail: 3382315992@qq.com

human trials. In 1979, Dr. Susan Band Horwitz of Yeshiva University's Albert Einstein College of Medicine identified the mechanism of action of paclitaxel, with the support from NCI. The compound was discovered to be an antimitotic agent that impede cancer cell growth by blocking cell division, resulting in cell death. Paclitaxel worked differently than other antimitotic medicines available at the time. The discovery was a great progress as it brought hope to patients who failed responding to current treatment options or patients with drug resistance. In 1989, Dr. McGuire and his colleges worked on a clinical study about ovarian cancer. They discovered an impressive 30% of patients responded positively to paclitaxel treatment. Paclitaxel appeared to be a very promising discovery for cancer treatment. However, the increasing demand for paclitaxel and the slow growth of the pacific yew blocked researchers. In 1988, it was predicted that manufacturing paclitaxel from the existing T. brevifolia would cost 10 times the budget available for the project. What's more, concerns for environment were growing. Extraction of paclitaxel caused severe depletion, as the removal of bark kills trees. In 1990, the Department of the Interior added T. brevifolia on its list of endangered species. Considering the limited accessibility of paclitaxel, scientists strived to develop a synthetic form of the compound. Eventually, several methods for complete synthesis were developed.

3. The mechanism of PTX in killing tumor cell

3.1. PTX directly affect tumor cell

PTX is a broad-spectrum anti-tumor drug. Schiff et al. confirmed that PTX has a unique anti-cancer mechanism. It acts on microtubules in cells, inducing and stabilizing microtubule polymerization by binding to the 31st and 217-231st amino acids at the N-terminus of microtubule proteins, inhibiting their depolymerization, preventing vascular bundles from interconnecting with microtubule tissue centers, blocking the cell cycle at the G2PM phase, causing abnormal or stopped mitosis, and preventing cancer cells from continuing to divide and dying (usually a large number of tubular structures are formed during cell division, and after chromosomes are correctly distributed to the two daughter cells, the microtubule system decomposes and completes division). But it does not affect the synthesis of DNA, RNA, and proteins. PTX has good therapeutic effects on ovarian cancer and also has certain therapeutic effects on cancer cells such as other solid tumors and leukemia. PTX is a mitotic inhibitor or spindle toxin, and its mechanism of action is different from commonly used chemotherapy drugs. It induces and promotes microtubule assembly. PTX has the ability to polymerize and stabilize microtubules, causing rapidly dividing tumor cells to be firmly fixed during the mitotic stage, blocking cancer cell replication and leading to death. Tumor cells divide repeatedly and uncontrollably, leading to the rapid growth of tumor. PTX directly disrupts the abnormal process of cell division to suppress tumor growth. Studies showed that PTX involves in binding to tubulin (α-tubulin and β-tubulin), the component of microtubules, resulting in stabilizing microtubules. Microtubule assembly is a key process in cell division. They are long, rigid, hollow tubes in the cytoplasm. They form mitosis spindles, which organize and separate chromosomes during cell division. As a result, PTX stabilizing microtubules affects the normal action of spindles. This disruption of cell division leads to the accumulation of detained cells, and eventually the non-progression of the cell cycle leads to tumor cell death. Moreover, PTX can induce cell apoptosis, which is a cellular suicide program that plays a critical role in inhibiting tumor cell division. Studies reported that PTX induces cellular apoptosis via activates or inhibits either the pro-apoptotic (BAX/BAK) or anti-apoptotic (Bcl-2/MCL-1) proteins. This successfully prevents the evasion of tumor cells and controls their excessive proliferation. Recently, researchers discovered that PTX boosted ROS generation and disturbed endoplasmic reticulum homeostasis in osteosarcoma cells. However, it is unclear whether the disruption of the endoplasmic reticulum is caused by protein activation.

3.2. PTX affects tumor immune microenvironment to enhance tumor killing

The tumor immune microenvironment (TME) plays an important role in killing tumor cells as well. The TME includes many immune cells with different functions, such as dendritic cells (DCs), natural killer (NK) cells, cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAM), etc[2]. PTX could inhibit tumor growth by influencing TME. PTX can induce the upregulation of TLR4 in DCs, which lead to DCs polarization and maturation by TLR4 pathway. Mature DCs presented antigens to CD8+ T lymphocytes to induce the activation of CD8+ T to kill tumor cells. In addition, PTX could also activate NK cells, leading to lysis and apoptosis of tumor cells. PTX is also shown to be effective in CAF reduction by modulating TGF-β/Smad signaling in tumor desmoplasia and liver desmoplasia. This suppress α-SMA and collagen I synthesis, which regulates CAFs in tumor stroma. Moreover, paclitaxel stimulates an immunological response in the tumor microenvironment via TLR4 signaling and directly shifts mature TAMs to a less immunotolerant profile, which contributes to paclitaxel's anticancer properties.

3.3. Toxic side effects of PTX

The main hematological adverse reactions of PTX are leukopenia and low toxicity to platelets and red blood cells. If preventive colony-stimulating factors can be combined, the safety and tolerance of patients to this product can be further improved. Neurotoxicity is mainly manifested as numbness in the limbs, and the severity of symptoms increases with the increase of dosage. Allergic reactions to PTX include dyspnea, hypotension, angioedema, urticaria, etc. Therefore, the use of diphenhydramine and antihistamines can reduce the rate of allergic reactions. A small number of patients treated with PTX experienced

myocardial infarction, atrial fibrillation, mild congestive heart failure, ventricular and supraventricular tachycardia, and ventricular arrhythmia. Other adverse reactions of PTX include hair loss in almost all patients; Joint pain and muscle pain often occur 2-3 days after medication; Mild nausea, vomiting, and local phlebitis reactions are relatively mild.

4. The application of Paclitaxel in clinic

Paclitaxel is commonly used in chemotherapy for the treatment of various cancers, especially as the first line drug used in breast cancer, ovarian cancer, lung cancer, and cervical cancer (Table 1). General recommended dosage of Taxonomy is 150-175mg/m^2, and it is given intravenously for 3 hours, once every 3-4 weeks, with 2-3 cycles as a course of treatment. The MD. Anderson Cancer Center in the United States took the lead in using this drug in the clinical treatment advanced breast cancer. the dosage is 200-250mg/m2, and the recommended dosage of paclitaxel in combination therapy is 135mg/m^2.

One specific clinical application is the combination therapy of carboplatin and paclitaxel in treating endometrial cancer. A study published in 2020 examined whether the chemotherapy regimen of carboplatin and paclitaxel (TC) could serve as a replacement for the paclitaxel-doxorubicin-cisplatin (TAP) protocol as the front-line therapy for advanced or recurrent endometrial cancer. In this study, patients were randomly assigned to one of two treatment regimens, in total, 1,381 women were enrolled, and the study concluded noninferiority of TC to TAP regarding overall survival, suggesting that TC can be considered as the first-line standard for advanced endometrial cancer.

Table 1. The application of PTX as the first line drug in cancer treatment.

Type of cancer	Application	Details	Ref
Breast cancer	Node-positive or high-risk node-negative breast cancer	PTX + doxorubicin	[3]
	MBC or relapse within 6 months of neoadjuvant therapy	Failure of neoadjuvant therapy; monotherapy of PTX	[3]
	Untreated MBC	PTX or PTX + Bevacizumab	[4]
Ovarian cancer	Ovarian cancer	Monotherapy of PTX	[5]
	Recurrent advanced ovarian cancer	PTX + carboplatin	[5]
Bladder cancer	Transitional cell bladder cancer without treatment history	Monotherapy of PTX	[6]
	Advanced bladder cancer	PTX + Gemcitabine or Cisplatin	[7]
Gastric cancer	Advanced gastric cancer	PTX+cisplatin+5-fluorouracil+ aldehydrofolate	[8]
lung cancer	Non-small cell lung cancer	PTX + carboplatin	[9]
Endometrial cancer	Endometrial cancer		[10]

Treatment of breast cancer. In the treatment of breast cancer, paclitaxel is often used as a first-line or second-line chemotherapy drug, especially in adjuvant treatment and treatment of patients with late recurrence and metastasis. Studies have shown that paclitaxel alone or in combination with drugs such as doxorubicin and cyclophosphamide can significantly improve progression free survival (PFS) and overall survival (OS) of patients, and reduce the risk of recurrence. It effectively inhibits tumor growth by interfering with the mitotic process of tumor cells, bringing hope for survival to patients.

Ovarian cancer treatment. For ovarian cancer patients, paclitaxel also plays an important role. As a key drug in the standard treatment plan for ovarian cancer, paclitaxel is often used in combination with carboplatin to form a "TC" regimen, becoming the first choice for patients with initial and recurrent ovarian cancer. This plan not only improved the remission rate of patients, but also significantly prolonged their survival period and improved their quality of life.

Lung cancer treatment. In the field of lung cancer, paclitaxel is also widely used in the treatment of non-small cell lung cancer (NSCLC). Whether used as a first-line treatment in combination with drugs such as cisplatin, or as a second-line treatment for patients resistant to platinum based drugs, paclitaxel has shown good therapeutic effects. It effectively inhibits the progression of lung cancer through various pathways such as inducing tumor cell apoptosis and inhibiting angiogenesis.

Multiple clinical trials and long-term follow-up data have shown that paclitaxel and its combination chemotherapy regimen have achieved significant efficacy in the treatment of various cancers. The patient's tumor response rate, PFS, and OS were significantly improved. Especially in some refractory tumors, the introduction of paclitaxel provides patients with new treatment options and survival opportunities.

5. Conclusion

As the cornerstone of tumor treatment, chemotherapy is used to treat both primary and metastatic tumors for many years. There are multiple types of chemotherapy drugs in clinic, such as alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic inhibitors (plant alkaloids) and antitumor antibiotics. In this review, we focused on the mechanism of PTX, a mitotic inhibitor, summarizing its mechanism in killing tumor and its application in clinic. PTX kills cancer cells not only by blocking cell division, but also by affecting tumor immune microenvironment. For clinical applications, PTX has been employed as a first-line treatment of both primary and metastatic cancers including breast cancer, ovarian cancer and lung cancer. Moreover, PTX also used as a second-line treatment in some advanced cancers such as gastric cancer and esophageal cancer. Because of its unique mechanism of action, PTX has become another important anti-tumor drug after cyclophosphamide, adriamycin and cisplatin. At present, paclitaxel is widely used as a broad-spectrum anti-tumor drug in all countries, and many gratifying achievements have been made, but there are also some problems: for example, although there are many reports on PTX and the curative effect is good, most of them are small samples which lack large sample and more random research. Therefore, by understanding the mechanism of PTX and its clinical application, scientists will be able to resolve these problems and improve the efficiency of PTX. With the continuous advancement of science and technology and the deepening of clinical research, the potential of paclitaxel will be more fully explored and utilized, bringing brighter prospects for cancer patients. In summary, this review advances our understanding of the pharmacological mechanisms of PTX, highlighting its vital role in clinical application.

Reference

1. World Health Organization. (2022). Cancer. *World Health Organization*. https://www.who.int/news-room/fact-sheets/detail/cancer
2. Yu, D. L., Lou, Z. P., Ma, F. Y., & Najafi, M. (2022). The interactions of paclitaxel with the tumor microenvironment. *International Immunopharmacology, 105*. https://doi.org/10.1016/j.intimp.2022.108558
3. Emens, L. A. (2021). Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer. *Journal for Immunotherapy of Cancer, 9*(8), e002597. https://doi.org/10.1136/jitc-2021-002597
4. Fasching, P. A. (2023). Inferred immune-cell activity is an independent predictor of HER2-negative breast cancer prognosis and response to paclitaxel-based therapy in the GeparSepto trial. *Clinical Cancer Research, 29*(13), 2456–2465. https://doi.org/10.1158/1078-0432.CCR-22-4005
5. Kalachand, R., Busschots, S., Doherty, B., Kapros, E., Lawlor, D., Hall, N., & Stordal, B. K. (2022). Taxane monotherapy regimens for the treatment of recurrent epithelial ovarian cancer. *Cochrane Database of Systematic Reviews, 2022*(7), CD008766. https://doi.org/10.1002/14651858.CD008766.pub4
6. Peiqi, M. (2003). Research progress of clinical application of paclitaxel. *China Medical Guide, 6*(3), 210–211.
7. Tran, L., Xiao, J.-F., Agarwal, N., Duex, J. E., & Theodorescu, D. (2021). Advances in bladder cancer biology and therapy. *Nature Reviews Cancer, 21*(2), 104–121. https://doi.org/10.1038/s41568-020-00313-1
8. Qichuan, W., Lixin, W., & Xiao, S. (2007). Observation on the efficacy of paclitaxel in the treatment of advanced gastric cancer. *Chinese Journal of Practical Medicine, 34*(8), 76–77.
9. Ikeda, N., Arai, R., Soda, S., Inoue, T., Uchida, N., Nakamura, Y., Masawa, M., Kushima, Y., Okutomi, H., Takemasa, A., Shimizu, Y., & Niho, S. (2022). Carboplatin plus nab-paclitaxel for recurrent small cell lung cancer: A phase II study. *Thoracic Cancer, 13*(9), 1342–1348. https://doi.org/10.1111/1759-7714.14359
10. Iowa Health Care. (2016). Types of chemotherapy. University of Iowa Hospitals &Clinics. https://uihc.org/health-topics/types-chemotherapy