Progress Of Paclitaxel as A Key Treatment for Cancer

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Keywords: Paclitaxel (Taxol); P53 target; Preclinical trials; cancer; Homotope Proteolysis-Targeting Chimeras (HPROTAC).

Abstract: Paclitaxel drug is vital breast cancer treatment, which have been extensively studied in clinical trials worldwide. Paclitaxel dose Optimization and evaluation in combination regimens are the main concerning problem. The efficacy of chemotherapy drugs may be mainly determined by the genotype of the tumor cells. The mutated p53 gene may lead to chemotherapy resistance. Although paclitaxel is widely effectively used in human tumor xenografts, p53-containing tumor cells were obviously more sensitive to treatment with this drug than p53-deficient tumor cells. Maximum tolerated dose (MTD) of first-line gemcitabine and albumin-bound paclitaxel in metastatic pancreatic cancer provided efficacy and safety data in preclinical trials. This paper reviews the therapeutic progress and clinical application of paclitaxel.

1. Introduction

The incidence rate of cancer in the world will increase by 50%. In recent years, the incidence rate of cancer in China has also continued to rise, with the incidence rate increasing by 20%. For every five people who die, one has cancer. Cancer is still a global problem. The incidence of cancer is not only related to the individual mood, but also has an inseparable relationship with their living environment, drinking water, and diet. The research has shown that the p53 gene is associated with cancer treatment and incidence. The inactivation of the p53 gene worked in tumor formation. P53 is an essential anti-cancer gene, and its wild type causes apoptosis of cancer cells, thus preventing canceration[1-2]. It also helps the genes of cells repair defects. Mutations in p53 promote cancer.

The activity of nab-paclitaxel is closely related to getting rid of the resistance of gemcitabine. Also, an enzyme called CDA could be down-regulated by paclitaxel (PTX). PTX showed his activity in gene expression by regulating miRNA. In the clinical I trials, maximum tolerated dose (MTD) in the treatment of metastatic breast cancer was determined, providing data on the efficacy and safety of gemcitabine and albumin-bound paclitaxel. Clinical II trials found that adding bevacizumab to albumin-bound paclitaxel could significantly increase the rate of PCR accompanied by the trend of improvement of EFS. Clinical III Trials evaluated whether weekly albumin-bound paclitaxel could increase the proportion of patients with complete pathological remission.

At present, there are no drugs on the market based on p53-MDM2 targets, and the main problems are: after MDM2 is inhibited, cells will be upregulated by negative feedback regulation, so higher concentrations of inhibitors are needed to reach the original inhibition level, while high concentrations of inhibitors will cause toxic side effects. Proteolysis-Targeting Chimeras (PROTAC) is a new antitumor drug research and development technology, which has the advantage of low-dose and efficient degradation of target proteins. However, PROTAC may inhibit or miss the second target protein when binding to E3 ubiquitin ligase, thus causing related side effects. Homotope Proteolysis-Targeting Chimeras (HPROTAC) is a new form of PROTAC technology, which is formed by the

direct connection of two identical ligand molecules, that is, E3 ligase ligand exists in the form of dimerization to mediate the degradation of its binding protein. Compared with traditional PROTAC molecules, the advantage of homologous PROTAC is that it does not introduce a second target, effectively avoiding potential side effects. Accordingly, paclitaxel could bind with PROTAC to have a better treatment.

In this paper, we first introduced the discovery process, mechanism of action and synthesis of PTX. Summarized part of the preclinical trials of PTX. Finally, the toxic effects of PTX are briefly explained.

2. Development of Paclitaxel

PTX is among the most critical new agents introduced for cancer therapy in several decades. It has shown activity against a broad range of human cancers. It is being evaluated in some studies as a component of initial chemotherapy regimens for diseases. PTX is not used in advanced solid tumors, although great enthusiasm exists among research group for the role of this compound in the future. Meanwhile, several formidable challenges have been overcome.

2.1 Isolation of Paclitaxel

Paclitaxel was screened as antitumor activity by the National Cancer Institute from the extracts of thousands of plants and natural products [3]. The crude extract from the bark of Taxus brevifolia was screened and found to have cytotoxic activity against KB cells. The researchers confirmed the in vivo activity of several preclinical models, including Walker 256 tumor, p1534, L1210 leukemia model and B16 melanoma model. Paclitaxel was extracted in 1969 and its structure was analyzed in 1971. It was finally selected by the cancer treatment department (DCT) for clinical trials. Although its structure is novel, people's enthusiasm for its development is very low. Initially, I didn't want it to be a high priority project. Preclinical activity is extensive, but not too impressive, and the compound is scarce and insoluble.

2.2 Mechanism of Paclitaxel working

PTX is a mitotic inhibitor whose function is similar to that of Catharanthus roseus alkaloids. Some studies have shown that it has a unique cytotoxic mechanism, which has significantly increased people's interest in the drug. Different from the decomposition of microtubules induced by vinca alkaloids, paclitaxel promotes the polymerization of tubulin [4]. Paclitaxel can easily meet the clinical requirements at the appropriate drug concentration. Paclitaxel promotes the formation of over stable and dysfunctional microtubules and prevents the occurrence of normal cellular processes dependent on these structures. The microtubules were arranged in thick "bundles" or multiple mitotic nuclei, and there was no obvious microtubule tissue center. After paclitaxel treatment, the cell cycle was limited and mainly stagnated in G2 phase and M phase. Guanosine triphosphate, Catharanthus roseus alkaloid, colchicine or podophyllotoxin have their own binding sites, while paclitaxel is different and exists in tubulin. The paclitaxel binding site was located in β the 31st amino acid at the N-terminal of subunit has research value for the therapeutic effect of subsequent compounds.

3. The P53 target and connection with Paclitaxel

Non-surgical treatments in general solid tumors are mostly adjuvant treatments in non-advanced cancer patients. Adjuvant therapy can be divided into adjuvant therapy before and after surgery. Among them, chemotherapy is one of the main methods of non-surgical treatment, and others include radiation therapy. Chemotherapeutic drugs are generally alkylating agents, cell metabolism and toxicity, etc., have a strong ability to kill tumor cells. Among them, PTX is a cytotoxic drug, which is widely used in the first-line treatment of solid tumors [4-6]. However, the resistance of tumor cells to PTX is one of the biggest obstacles to cancer treatment and postoperative recurrence. Unlike other anti-cancer drugs, PTX has its own unique features. The cells divide and eventually kill all kinds of

cancer cells [7]. A large number of studies have shown that the mechanism of tumor resistance to PTX is related to tumor suppressor genes (TSGs). TSGs are often inactivated in cancer cells, their main role is to regulate various biological processes, but they not work in the treatment response of PTX.

PTX has different clinical reactions to different individuals, and its drug resistance mechanism has not been fully clarified. It is reported that tumor suppressor genes (TSGs) are necessary mediators of drug sensitivity [8-9]. These TSGs prevent abnormal cells from surviving. However, when gene inactivation or expression decreases, abnormal cells cannot control growth, resulting in cancer formation [10].

Once a mutation occurs, it will cause normal cells to change in an uncontrolled direction, triggering the occurrence of tumors. Among them, the earliest discovered P53 gene has the highest mutation frequency. In most cancer cells, researchers found that more than half of TP53 mutations are loss-of-function. This is very easy to understand, because p53 plays an important function in normal cells. Under normal physiological conditions, P53 participates in the regulation of the cell cycle process. Not only that, it will also promote cell movement and accelerate cell senescence and apoptosis. A more important function is to participate in DNA repair, etc. This is the key point to maintain the normal function of the cell and prevent the occurrence of mutations. In addition, P53 also regulates angiogenesis, participates in cell metabolism, etc., and plays a key role in the entire process of cells. Therefore, once P53 is mutated, the corresponding function of the cell is lost and malignant transformation occurs [11]. A large number of studies have shown that the therapeutic and prognostic effects of PTX on tumors are closely related to the mutation status of the TP53 gene [12]. For example, if the concentration of p53 protein in non-small cell lung cancer (NSCLC) cells is high, they are more sensitive to PTX [13]. In addition, p53 up-regulates apoptosis regulator (PUMA) and participates in the resistance of tumor cells to PTX [14]. TP53 hot spot mutations (TP53-m273) increase the expression of multidrug resistance protein 1 (MDR1) and cause tumor resistance to PTX [16]. In addition, studies have found that the up-regulation of p53 inhibitor of apoptosis stimulating protein (iASPP) can cause PTX sensitivity in ovarian cancer [17]. Asstrin triggers the p53-dependent apoptosis pathway and induces Hela cells that are sensitive to PTX [18]. These studies indicate that tumor resistance to PTX may be regulated by some regulatory factors that depend on p53-related pathways.

4. The synthesis of taxol more side chains precursor

Semi-synthesis refers to the conversion of taxol analogs found in Taxus plants to taxol through specific chemical reactions. Because bacatine 111 and 10-deacylbacatine 1I are relatively high in plants, semisynthetic studies have focused on these two substances. J.N.Denis(1988) of Universite Joseph Fourier first reported the semi-synthesis of paclitaxel from 10-deacylbacatine 11 as raw material[19]. Subsequently, Professor Hohn in the United States and Professor Potier in France respectively applied for the patent of semisynthetic paclitaxel using Bacatine 111 as raw material. The paclitaxel semisynthetic precursor 10-deacylbacatine 11 was isolated from the needles, and its content was up to 0.1%. As needle regeneration is easy, paclitaxel semi-synthesis can have rich raw materials, BMS Plans to produce paclitaxel with Professor John patent immediately after the APPROVAL of the US FDA, and decided to stop the production of paclitaxel extracted from bark by the end of 1994[20]. Hohon and Potier both see semi-synthesis as a promising way to solve the paclitaxel supply problem. The semi-synthesis of paclitaxel and polypaclitaxel is mainly divided into three stages: synthesis of side chain precursors of paclitaxel (polypaclitaxel), selective protection of parent nucleus vacation11 or 10-deacylbacatine 11, esterification of side chain and parent nucleus, and removal of protection group to obtain paclitaxel (polypaclitaxel) [21].

The circular side-chain precursors are generally used in the synthesis of paclitaxel due to the defects of harsh reaction conditions, low conversion rate, formation of a large amount of C-2, and instability of carboxylic acid side chain protected by differential isomerism in the esterification reaction between the optically active linear side-chain precursors and the protected parent nucleus. It

mainly includes B- lactam type,furazolidone type, and umbos ketone type three.B-lactam is the structural unit of many antibiotics, which can take place all the reactions of chain amide.It is much more active than chain amide due to the action of ring tension. There are racemization and optically active types of b-lactam side-chain precursors.Still,the steroselectivity and yield of b-lactam side-chain precursors are high when esterified with protected vacation 11 and 10-deacylbacatine 111, so racemization mixture can be used in general production [22]. The Staudinger reaction is usually performed with alkoxyl chloride (e.g., acetoxy acetyl chloride) and imines in the presence of triethylamine to obtain CIS-B-lactam, which is then oxidized and deacylated to obtain the corresponding alcohol, and then the hydroxyl group in the four-membered ring is protected to form the desired side chain.Polyene side chain of taxol semisynthetic precursor is the use of well thiazole type alkyl side chain. Main method is to benzene different serine side-chains - hydroxyl 2 and 3, NH - tert-butyl membrane-based oxygen protection, use, and propyl groups or other protected, formation of thiazole alkyl carboxylic acid. The good azole alkane carboxylic acid in the presence of DCC/DMAP open-loop and Barca kiosks, and protection of 111 or 7, 10 pairs of protection of 10 - to take off the acyl Barca pavilion 11 to carry on the esterification reaction, the parent nucleus in C - the parent nucleus 13 hydroxy, and preparation of polyene PTX [23].

5. Preclinical trials

5.1 Distribution of the drug

Mass spectrometry was used to identify whether circulating paclitaxel was free ornot. The formulation of nab-paclitaxel allowed a much higher fraction of unbound paclitaxel for nab-paclitaxel vs. sb-paclitaxel. Sparreboom et al. [24] found that nab-paclitaxel achieves a higher plasma clearance and a larger volume of distribution vs. sb-paclitaxel in preclinical studies (table 1).

5.2 Effect on the drug resistance

The dissociation of circulating paclitaxel was detected by mass spectrometry [24]. Preclinical studies found that nab paclitaxel has higher plasma clearance and larger distribution volume than sb paclitaxel.

Table. 1 Pharmacokinetic linearity of sb-paclitaxel and nab-paclitaxel

Primary author	Year of publication	sb-Paclitaxel	*nab*-Paclitaxel
Gianni	1995	Not linear	NA
Van Tellingen	1999	Not linear	NA
Brouwer	2000	Not linear	NA
Gelderblom	2002	Linear 3-compartment	NA
Ibrahim	2002	NA	Linear
Nyman	2005	NA	Linear

5.3 Effect on the drug resistance

Use chemotherapy for cancer treatment. However, the drug-induced toxicity and drug resistance lead to the limited effect of chemotherapy. Preclinical studies evaluated the activity of albumin paclitaxel combined with gemcitabine. In the phase I / II advanced cancer trial, the research group [24] reported that albumin paclitaxel combined with gemcitabine had good curative effect. In contrast, nano albumin paclitaxel treatment depleted the stroma. In the tumor environment, the decrease of matrix content is accompanied by vasodilation, especially in the combined treatment group (Fig. 1). The experiment also showed that the concentration of gemcitabine in the combined treatment group was 2.8 times higher than that in the single treatment group. This shows that albumin paclitaxel clears the matrix barrier in the tumor microenvironment and enhances the tumor circulation, making gemcitabine easier to enter the tumor.

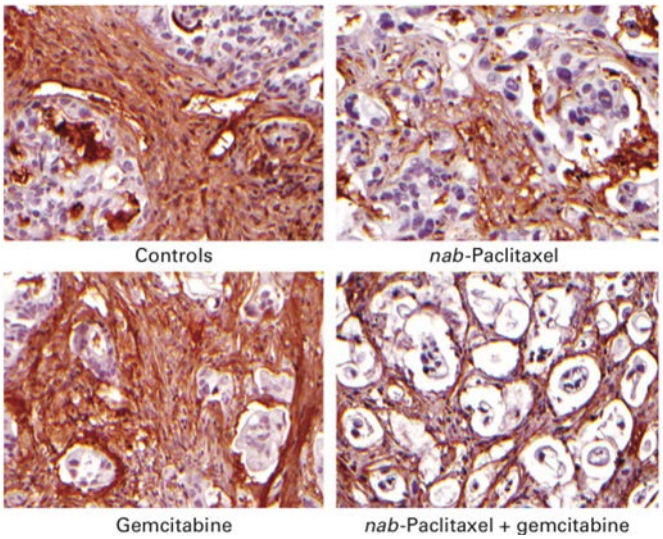

Fig. 1 Immunohisto- chemical assay for collagen type 1 fibers in a gemcitabine-resistant human pancreatic cancer xenograft treated with nab-paclitaxel, gemcitabine, or gemcit- abine plus nab-paclitaxel.

5.4 Effect on enzyme

Another separated test making use of a genetically engineered mouse model that replicated the clinical features of the disease, including the resistance to gemcitabine. The result showed that the combination treatment resulted in significantly smaller tumors and enhancement in levels of gemcitabine in tumors. Van Voff et al. ascribed a differed mechanism: a downregulation by nab-paclitaxel of the gemcitabine-metabolizing enzyme called CDA (cytidine deaminase) rather than a specific effect on tumor stroma directly by nab-paclitaxel. Also, exposure to ROS (also called reactive oxygen species) could destabilize CDA [25], preventing the breakdown of gemcitabine in cancer cells as a response. Consequently, the activity of gemcitabine could be enhanced to a large extent.

5.5 Effect on microRNA

Paclitaxel (PTX) can regulate its own mRNA expression and affect gene expression. MiRNA related studies show that there is a correlation between drug application and miRNA expression profile changes. After PTX intervention, the expression levels of let-7a and mir-205 in BC cell line BT-474 changed. Mir-205 has the potential to target K-ras and HER3. Preclinical trials have proved that PTX has the potential to regulate miRNA expression, but further research is needed to prove the role of PTX in BC treatment [26].

5.6 Safety (toxicity)

Cytotoxicity: This part evaluates the safety of paclitaxel biopolymer formulation (PBF) (paclitaxel-loaded poly (3-hydroxybutyrate) (PHB) microparticles). To study the cytotoxicity (to bone marrow stem cells), acute and chronic toxicity, sensitization and pyrogenicity, histological (mouse, rat and rabbit) characteristics of PBF. Studies have shown that when mice and rats are intraperitoneally injected with the same amount of PTX, the toxicity of PBF is smaller than that of traditional PTX. However, when administered intraperitoneally, PBF has obvious cumulative characteristics and toxic effects [27].

Peripheral neuropathy: Common side effects of paclitaxel include peripheral neuropathy. MTT assay and immunohistochemistry can detect the morphological differences, nuclear size differences and cell viability changes of neuronal F11 cells treated with nab or creel paclitaxel. Immunostaining showed the accumulation of paclitaxel in DRG neurons and SCN. Because different drug formulations have effects on paclitaxel induced neuropathy, different paclitaxel preparations also have effects on the severity and time course of paclitaxel induced peripheral neuropathy [28].

6. Conclusion

PTX alone or in combination can be used as a first-line treatment and salvage treatment for patients with advanced diseases. PTX has shown efficacy in patients who have previously received anthracycline therapy and anthracycline resistant diseases. In terms of adjuvant therapy, data from a randomized study showed that patients with positive lymph nodes continued to use paclitaxel after doxorubicin and cyclophosphamide treatment. The unique mechanism of paclitaxel and its relatively good tolerance toxicity make it a candidate drug for the treatment of breast cancer with other active drugs. Albumin paclitaxel combined with gemcitabine has good antitumor activity and can tolerate adverse reactions. In patients with metastatic pancreatic adenocarcinoma, albumin paclitaxel combined with gemcitabine significantly improved survival and mortality. In the future, the increase of peripheral neuropathy and bone marrow suppression rate need to be considered in the clinical treatment plan of PTX. How to improve the killing efficiency of tumor cells without damaging normal tissues needs further research.

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