Dean&Francis
ISSN 2959-409X

Paclitaxel Anti-Tumor: Mechanism, Model Optimization and Drug Resistance Response

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Abstract:

Paclitaxel (PTX) is a first-line anti-cancer chemotherapy agent. Its core mechanism of action is to specifically bind to tubulin, inhibit microtubule depolymerization, stabilize microtubule structure, and ultimately induce apoptosis. It is widely used in the treatment of breast, ovarian, and gastric cancers. However, PTX suffers from poor water solubility, low oral bioavailability, and reliance on the toxic excipient Cremophor EL, which can cause allergic reactions. Long-term use can easily lead to drug resistance, severely limiting its clinical application. To overcome these bottlenecks, this paper analyzes research on PTX dosage forms and drug resistance, and find that dosage form optimization is crucial. Marketed nanoformulations, such as liposomes (Lipusu®), albumin nanoparticles (Abraxane®), and polymeric micelles (Genexol®-PM), significantly reduce toxic side effects and enhance efficacy by improving solubility, enhancing tumor targeting (via the EPR effect or active modification), and avoiding toxic excipients. To address drug resistance, research is underway to effectively reverse or delay the onset of drug resistance by inhibiting cancer stem cell (CSC) stemness and vascular mimicry (VM), as well as suppressing the expression of drug resistance genes. In the future, research on PTX can focus on its effectiveness and safety, continuously optimize the preparation process, and develop more efficient and safer PTX preparations.

Keywords: Paclitaxel; mechanism; dosage; drug resistance.

1. Introduction

The 2024 China Cancer Report pointed out that there were 4.8247 million new cases in China, with the number of males (2.5339 million) exceeding the number of females (2.2908). The top five cancers in terms of incidence were lung cancer, colorectal cancer, thyroid cancer, liver cancer, and gastric can-

cer [1]. It can be seen that the current burden of cancer is still heavy, and anti-cancer is still an important and difficult task. Tumors refer to uncontrolled cell proliferation caused by gene mutations, forming abnormal local agglomerations that damage tissues and organs. Depending on whether distant metastasis occurs, they can be divided into benign tumors and malignant tumors, malignant tumors are also cancers. The occurrence of tumors is related to many factors, such as physical factors (ultraviolet rays, X-rays), chemical factors (tobacco, aflatoxin), biological factors (viruses), and genetic background (individual susceptibility to environmental carcinogens). In the clinical treatment of cancer, the treatment system has gradually matured, including surgical treatment (one of the treatment methods for most solid tumors), radiotherapy, chemotherapy, etc.

Paclitaxel (PTX), derived from the bark of the yew tree, is a natural terpenoid drug and one of the drugs currently available for the treatment of cancer. It belongs to the category of chemotherapy. The mechanism of action of PTX is to inhibit the mitosis process of cancer cells, thereby inhibiting their growth and development, and ultimately playing an anti-tumor role. It is mainly used to treat breast cancer, ovarian cancer, and gastric cancer. However, PTX still has problems in clinical application, such as its poor solubility, resulting in low bioavailability; long-term use is prone to drug resistance and resource sustainability [2]. In recent years, with the continuous in-depth study of PTX, new breakthroughs have been made in its mechanism of action, dosage form optimization, and anti-drug resistance. This article aims to summarize the anti-tumor mechanism of action of PTX, summarize the latest dosage form optimization results, explore methods to combat drug resistance mechanisms, and provide a reference for clinical application.

2. The Antitumor Mechanism of PTX

PTX is a highly effective microtubule inhibitor that blocks cancer cells in the G2/M phase by binding to tubulin β-subunits and stabilizing microtubule structures, interfering with mitotic spindle formation and thereby activating pro-apoptotic signaling pathways.

The main mechanism of action of PTX involves multiple pathways that synergistically induce cell death, among which the main form of induced cell death is apoptosis. There are many forms of apoptosis induction, which can be divided into mitochondrial pathways, inhibition of signaling pathways, and activation of regulatory factors. Endoplasmic reticulum reactive oxygen species (ROS) are intermediates in cellular metabolism. PTX induces oxidative DNA damage by increasing ROS accumulation. Studies have shown that PTX can increase ROS accumulation, regulate hypoxia-inducible factor (HIF-1α) expression, and activate the JNK/caspase-3 pathway, ultimately leading to cell apoptosis [3]. In addition, PTX can also inhibit the PI3K/AKT/mTOR signaling pathway, which plays a key role in cell apoptosis. PTX can inhibit this pathway, thereby leading to cell apoptosis [4]. P53 is a cell death regulator. Studies have shown that PTX can activate P53-dependent apoptosis by upregulating long noncoding RNA maternally expressed gene 3 (lncRNA MEG3), thereby leading to apoptosis of human lung cancer A549 cells [5].

Secondly, pyroptosis is another type of programmed cell death. Programmed cell death and autophagic death mediated by the pore-forming protein family gasdermin (GSDM) have also been shown to be the mechanism of action of PTX. PTX induces pyroptosis through the caspase-1/GSDMD, caspase-3/GSDME, and NLRP3/caspase-1/GSDME pathways, which are significant in lung cancer, nasopharyngeal carcinoma, and gastric cancer cells. In addition, ROS activation can induce cell pyroptosis through GSDMD.

Finally, tumor metastasis remains a major challenge in tumor treatment. Studies have found that PTX can upregulate the expression of the neuronal splicing regulator RBFOX3. RBFOX3 binds to the precursor messenger RNA (pre-mRNA) of the insulin-like growth factor 1 receptor (IGF1R), thereby increasing the level of the circular RNA molecule circ-IGF1R. Circ-IGF1R can absorb RNA (miR-1270) like a sponge. MiR-1270 can inhibit the expression of VANGL2 protein. The function of VANGL2 protein is to inhibit tumor metastasis. In this way, PTX can ultimately increase the expression of VANGL2 protein, thereby achieving the effect of inhibiting tumors and synergistically inhibiting the invasion and migration of cancer cells through multiple pathways [6].

3. PTX Dosage form Optimization

Currently, traditional PTX formulations face three major problems: poor solubility (solubility in water is only 10-20 mg/L), poor absorption (oral bioavailability is only 10%), and high toxicity (requiring the use of the toxic solvent Cremophor EL, which can cause allergies and hyperlipidemia) [7]. Therefore, it is crucial to seek breakthroughs in new dosage forms, and nanoformulations are a major breakthrough.

Nanoformulation refers to a delivery system formed by loading drugs into 1-1000nm scale carriers through nanotechnology, which can play the role of solubilization and detoxification, targeted accumulation, and intelligent drug release. Nanoformulations increase the solubility of

ISSN 2959-409X

PTX through encapsulation of hydrophilic polymers or liposomes; improve tumor selectivity through passive targeting and active targeting; and reverse drug resistance by inhibiting drug efflux mediated by P-glycoprotein (P-PG) [8].

The carriers of nanoformulations that have been marketed can be mainly divided into three types: liposomes, albumin nanoparticles, and polymer micelles.

Liposomes combine cholesterol and phospholipids in a specific ratio to form a bilayer structure similar to that of skin cell membranes. This structure has a strong affinity for cell membranes, enabling the loading of PTX and increasing its solubility. The marketed Lipusu liposome has a particle size of 300 nm and an encapsulation efficiency of up to 99%. Compared with the PTX injection Taxol, its median lethal dose (LD50) is doubled and its half-life is doubled. At the same dose, the area under the plasma concentration-time curve (AUC) of Lipusu is lower than that of Taxol. However, Lipusu also has drawbacks, including long administration times, poor drug-carrier affinity, and low drug loading capacity. In addition, there are liposomes in the research stage, such as glycosylated liposomes, which use ginsenoside (Rg5) to replace the cholesterol in traditional liposomes. Studies have found that the sugar group of Rg5 forms a hydrogen bond network with phospholipids and PTX, significantly improving the stability of drug loading (drug loading concentration reaches 5 mg/mL); secondly, it can also achieve intelligent targeting, and the sugar group can specifically recognize the GLUT1 transporter protein that is highly expressed in tumors, achieving active targeting (not interfered with by blood glucose) [9]. In a breast cancer model, the tumor inhibition rate reached 90.3%, reversing drug resistance [10].

Albumin nanoparticles use human serum albumin (HSA) as a carrier and encapsulate PTX through the hydrophobic binding domain (Sudlow site). The half-life is as long as 19 days, which can achieve long-term circulation and delivery of drugs in the body. It has high biocompatibility and can reduce toxic side effects [11]. Abraxane, which has been launched on the market, can avoid the use of irritating excipients and has a shorter infusion time, which improves the safety of the drug. At the same time, in an experiment against breast cancer, Abraxane® has a stronger anti-tumor effect at a higher tolerance dose and can significantly prolong the survival of mice [9]. A study found that redox-responsive HPTX nanoparticles were developed for breast cancer. They are made of human serum albumin nanoparticles encapsulating PTX-pentadecanoic acid conjugates, with a particle size of 120 nm, a drug loading of 29.78%, and an encapsulation efficiency of 94.16%. In a 20 mmol glutathione environment, the PTX release rate reached 92.3% in 30 hours. Biodistribution analysis of breast cancer-bearing mice showed that PTX concentrations in organs and tumors were lower than Abraxane concentrations 1 hour after injection, and were significantly higher after 12 hours, reflecting a sustained-release property [12].

Polymer micelles are a typical supramolecular core-shell structure with a particle size usually between 20 and 100 nanometers. A variety of drugs can be encapsulated in the core region by chemical or chemical means to improve the stability of the drug [8]. Genexol®-PM is the world's first PTX micelle to be marketed. Its advantages are mainly reflected in three aspects: First, the carrier uses a new amphiphilic polymer polyethylene glycol-polylactide, which has a strong binding affinity with PTX, can reach a drug loading capacity of 16.7%, and has good degradability and safety. Second, in terms of formulation technology, unlike Abraxane®, which uses albumin derived from human blood (which may have contamination risks, is easy to adhere to infusion bags and catheters, and takes a long time to re-dissolve), Genexol®-PM uses polymer micelles to avoid these problems. Third, in terms of safety, its preparation process does not use polyoxyethylene castor oil, the clinical dosage is consistent with Taxol® (260 $mg \cdot m^{-2}$), and the probability of bone marrow suppression is lower than Taxol [9]. Researchers developed a mixed micelle F127/TPGS that can co-deliver PTX and regorafenib (REG) for the targeted treatment of triple-negative breast cancer. The micelle particle size is approximately 29.96±2.31 nm, and the encapsulation efficiency of PTX and REG is 42.93%±1.33 and 89.88%±3.99, respectively. In vitro experiments showed that its drug release is controllable and its cell uptake ability is enhanced. It can induce apoptosis of MDA-MB-231 triple-negative breast cancer cells (IC_{50} is 0.61±4.41 μM) and inhibit the proliferation and migration of these cells. This shows that micelles are high-quality carriers for PTX delivery with low toxicity and side effects [13].

In addition, some novel delivery vehicles are being developed. For example, natural amphiphilic peptides (AmP) extracted from soy protein are combined with D-α-tocopheryl polyethylene glycol succinate (TPGS) to form mixed micelles (PTX@TPGS-AmP), which serve as novel delivery vehicles for PTX. Using a pyrene fluorescence probe assay, the critical micelle concentrations (CMCs) of TPGS, AmP, and TPGS-AmP were 0.029 μg/mL, 0.804 μg/mL, and 0.412 μg/mL, respectively, indicating that mixed micelles are easier to form and more stable than single AmP micelles. In terms of preparation, the optimal process was obtained through $L_{16}(4^4)$ orthogonal test optimization. The mixed micelles had a drug loading of 7.32%, an encapsulation rate of 69.78%, a particle size of about 116 nm and good stability. The performance was

stable after incubation in PBS containing 10% fetal bovine serum for 96 hours, and the cumulative drug release rate was 46.6% in 36 hours, showing a sustained release characteristic. In terms of safety, the hemolysis rate was ≤5%, the osmotic pressure was consistent with that of normal saline, there was no immunogenicity and the acute toxicity was extremely low. In vitro and in vivo efficacy evaluations showed that its IC_{50} for 4T1 cells was only 48.9 ng/mL, the tumor inhibition rate was 73.0%, the pharmacokinetic parameters were better than Taxol and PTX@TPGS, the drug accumulation in the tumor site was higher, and there was no significant pathological damage to various organs [14].

Another example is a hyaluronic acid (HA)-modified hollow manganese dioxide (H-MnO_2) nanocarrier (PTX@H-MnO_2@HA) for targeted delivery of PTX. H-MnO_2 has a large cavity structure, which allows for strong adsorption and high drug loading for lipid-soluble small molecule anticancer drugs such as PTX. H-MnO_2 also responds to the high levels of H^+ and glutathione (GSH) in the tumor microenvironment (TME), degrading to produce paramagnetic Mn^{2+}, which enhances T1 magnetic resonance imaging (MRI) contrast. The structure was characterized by TEM, FTIR, XPS, etc., and combined with cell experiments (4T1, HEK293T cells) and 4T1 tumor-bearing mouse model experiments, it was confirmed that the system had a drug loading of 47.5% and an encapsulation rate of 74.3%. It could release 87.4% of PTX in the acidic microenvironment of the tumor (pH = 5.0). Targeted delivery was achieved by binding HA to the CD44 receptor. The cellular uptake was twice that of normal cells. The tumor inhibition effect in vivo was significant and there was no obvious organ toxicity [15].

4. Anti-resistance Strategies

Although PTX is a first-line drug for cancer treatment, it still faces many challenges, such as the development of drug resistance, which can reduce the drug's therapeutic effectiveness. Therefore, exploring the mechanisms of drug resistance and their solutions is crucial to improving efficacy and prolonging patient survival. The following describes several drug resistance mechanisms and their solutions.

4.1 Cancer Stem Cell (CSC) Stemness and Vascular Mimicry (VM)

PTX is a core chemotherapy drug for triple-negative breast cancer (TNBC). However, long-term use can lead to drug resistance due to the formation of cancer stem cells (CSCs), vascular mimicry (VM), and the tumor immunosuppressive microenvironment (TIME), significantly reducing efficacy. Studies have found that pyruvate kinase M2 (PKM2) is highly expressed in TNBC and functions in two ways: as a tetramer in the cytoplasm regulating glycolysis and as a dimer in the nucleus binding to β-catenin to activate signaling pathways, thereby maintaining the stemness of CSCs, promoting VM formation, and exacerbating immunosuppression. Therefore, inhibiting PKM2 could reverse CSC stemness, block VM formation, and thus overcome drug resistance. Researchers used the natural PKM2 inhibitor shikonin (SHK) to co-load PTX into an albumin nanoparticle biomimetic system.

Studies have shown that the stemness of tumor stem cells (CSCs) in TNBC cells can be significantly reversed in vitro. Western blot was used to detect CSCs stemness markers (OCT4, SOX2, NANOG), and it was found that the markers could be downregulated; flow cytometry was used to detect the ratio of $CD44^+/CD24^-$ stem cells, and it was found that the ratio was reduced; vascular mimicry (VM) formation was inhibited, CDH5, VEGFA expression and lactate production were reduced, and immunogenic cell death (ICD) was induced to reshape the tumor immune microenvironment (TIME). In vivo, the tumor inhibition rate in the 4T1 mouse orthotopic TNBC model was 80%, and the metastatic nodule inhibition rate in the lung metastasis model was 86%, without obvious liver and kidney toxicity and weight loss, providing a new strategy for improving the efficacy of TNBC and overcoming PTX resistance [16].

4.2 Nucleocytoplasmic Shuttling-Mediated Export of Drug Resistance Genes

To further explore the mechanism of drug resistance, the researchers collected specimens from 183 TNBC patients who received taxane chemotherapy at the Sun Yat-sen University Cancer Center and analyzed the prognostic value of genes using immunohistochemistry (IHC) combined with a Cox regression model. They also constructed sensitive and resistant strains of TNBC cell lines and established an orthotopic xenograft model in nude mice and patient-derived organoids to evaluate drug synergy. The results showed that ALYREF was retained in the cytoplasm in PTX-sensitive TNBC, while ALYREF was efficiently translocated into the nucleus in resistant TNBC, and high nuclear ALYREF expression was associated with poor prognosis in patients. Immunoprecipitation-mass spectrometry (IP/MS) screening found that RNF31 could modify ALYREF through linear ubiquitination. Knockdown of RNF31 and inhibition of RNF31 with the Thiolutin inhibitor significantly reduced the ubiquitination level of ALYREF. Under PTX treatment, IPO13 promoted ALYREF nuclear translocation, and nuclear ALYREF bound

ISSN 2959-409X

to and exported mRNAs of resistance-related factors such as TUBB3, STMN1, and TAU. Knockdown of RNF31/IPO13 or use of the RNF31 inhibitor Thiolutin reduced ALYREF nuclear localization and reduced the expression of resistance factors, and reversed TNBC PTX resistance both in vitro and in vivo. This study provides a new basis for targeted therapy of TNBC PTX resistance [17].

5. Conclusion

At present, although the incidence and mortality of cancer have decreased, the treatment of cancer still needs further exploration. As a classic anti-tumor drug, the role and status of PTX are self-evident. This article discusses its mechanism of action, dosage form optimization, and anti-resistance strategy; its mechanism of action has been extended to inducing apoptosis, pyroptosis, inhibiting tumor metastasis, etc. In terms of dosage form, traditional dosage forms face problems such as difficult to dissolve, difficult to absorb, and high toxicity, and nanoformulations can solve these problems to a certain extent. According to the type of nanoformulation carriers that have been on the market, they can be divided into liposomes, albumin nanoparticles, polymer micelles, etc. At the same time, the emergence of some new preparations has provided new solutions to the drug resistance problem of PTX; and in solving the drug resistance problem, researchers have provided new ideas and methods for reversing the drug resistance of PTX by inhibiting CSC stemness and VM and reducing the output of drug-resistant genes. Although significant progress has been made in the dosage form optimization and anti-drug resistance strategies of PTX, there are still some problems, such as how to apply the results to clinical practice, ensure the effectiveness and safety of the drug, and the process methods for preparing new dosage forms to improve production efficiency. In the future, the development of PTX needs to focus on the research and development of more efficient and less toxic new preparations, combined with cutting-edge technologies such as gene editing, immunotherapy, etc., to further enhance its therapeutic effect, and continue to optimize the preparation process and reduce costs.

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