Abstract: Breast cancer has been brought to the forefront of scientific research because of its increasing incidence as well as the growing demands to prolong the life span of patients and improve their quality of life. Paclitaxel (PTX), a small-molecule cytotoxic agent, is one of the most effective anti-cancer drugs against a variety of solid tumors, including breast cancer. Taxol®, a commercial preparation of PTX, has been widely used for the treatment of breast cancer since its approval for use by the US Food and Drug Administration in 1994. However, further development is limited by its poor aqueous solubility and by P-gp substrate and complex synthesis caused by excipient (Cremophor EL) used. Thus, there exist an urgent need to design and develop new-generation formulations of PTX, especially nano-formulations, to maximize the therapeutic effects and minimize the side effects. This paper provides a comprehensive review of the treatment of breast cancer with different formulations of PTX.

Keywords: antitumor efficacy; breast cancer; nano-formulation; paclitaxel.

1 Introduction

The estimated number of new cases of breast cancer in 2016 is 249,260, accounting for 29% of all new cancer diagnoses in women. The expected number of breast cancer deaths in 2016 is 40,890 [1]. Surgical resection of the lesion remains the cornerstone for patients diagnosed with early stage breast cancer. Chemotherapy, including adjuvant and neoadjuvant chemotherapy, can reduce the risk of relapse in patients with early stage cancer [2]. Breast cancer encompasses a group of very heterogeneous diseases at the molecular, histopathologic, and clinical levels. Hormonal therapy and targeted therapy also play important roles in the treatment of breast cancer because of the overexpressed receptors on the cell surface, such as progesterone receptor (PR), estrogen receptor (ER), and HER2 (Human Epidermal growth factor receptor-2) [3].

Paclitaxel (PTX), a taxane plant product discovered in 1962, and isolated from the bark of the Pacific yew, is one of the most effective anti-cancer agents to treat diverse solid tumors, including breast cancer. Its molecular formula is $C_{47}H_{51}NO_{14}$ and its molecular weight is 853.9 Da. The chemical formula of PTX is shown in Figure 1. The anticancer mechanism of the small-molecule drug involves interference with the normal breakdown of microtubules by preventing depolymerisation during cell division [4, 5]. Taxol® (Bristol-Myers Squibb, Sermoneta, Latina, Italy), a commercial preparation of PTX dissolved in Cremophor EL (a polyoxyethylated castor oil) with dehydrated alcohol at a 50:50 (v/v) ratio, was approved in 1992 by the US Food and Drug Administration (FDA) to treat ovarian, breast, lung, bladder, prostate, melanoma, esophageal, and other types of solid tumors as well as Kaposi’s sarcoma. Taxol® has been confirmed to be effective for patients suffering from metastatic breast cancer with remission rates of 56%–62% [6]. However, premedication, special infusion sets, and a substantial “chair time” for drug administration are required. Many side effects, such as allergy, hypersensitivity, and myelosuppression, are also associated with the excipient used [7]. Further development is limited by the poor aqueous solubility, P-gp substrate, and complex synthesis caused by CrEL. In this condition, new formulations of PTX that possess lower toxicity and equal or even better antitumor efficacy are urgently needed [8].

Meanwhile, the continuous development of nanocarriers has experienced three stages: “first generation nanocarriers” rely solely on the physical characteristics of the passive and targeted delivery of anticancer drugs. With the deliberate modification of targeting molecules to achieve active targeting of nanoparticles, “second
generation nanocarriers” have been formed. Hence, pushed by the improvement of tumor diagnosis and treatment, “third generation nanocarriers”, which are smarter and more theranostic, have been introduced. Following this development, different formulations, such as nanoparticles, liposomes, micelles, emulsions, prodrugs, co-delivery, cyclodextrins, dendrimers, and oral formulations, were employed to improve PTX solubility and minimize side effects. Another exciting development is that a plethora of products based on different formulations, such as Abraxane® (Celgene Fresenius Kabi, USA), Genexol-PM® (Samyang Biopharmaceuticals Corporation, Seoul, Korea), Lipusu®, Xyotax® and other new PTX products, are either available in the market or on clinical trials. In addition, newer formulations are being continuously developed and optimized; therefore, reviewing the progress in this area and finding a new breakthrough towards tumor-targeted drug delivery systems are necessary and meaningful.

PTX is a first-generation taxane anticancer agent. Docetaxel (Taxotere®), a semi-synthetic analog of PTX, was also approved for the treatment of advanced breast cancer in 1996 by the FDA. Cabazitaxel (Jevtana®), a most recent taxane anti-cancer agent approved by the FDA, is superior to both PTX and docetaxel because of the presence of methoxy groups at C7 and C10 (as shown in Figure 2), which causes a poor affinity to P-glycoprotein. Accordingly, new formulations of docetaxel and cabazitaxel have also been developed. For example, the “One-vial-Taxotere” formulation was approved in 2010 by the FDA, and a one-pot cabazitaxel formulation was also developed. However, in this review, we only focus on different formulations of PTX for the treatment of breast cancer.

2 Drug delivery systems

Drug delivery is a process of administering a pharmaceutical compound to achieve therapeutic effects in a specific disease, and it has become increasingly important in clinical drug development. Drug delivery systems (DDS) are engineered technologies for the targeted delivery and/or controlled release of therapeutic agents (Figure 3). In the context of cancer therapy, DDS play roles in transferring small-molecule hydrophobic cytotoxic agents or targeted delivery of therapeutic agents. Several formulations include nanoparticles, liposomes, micelles, emulsions, prodrugs, co-delivery, cyclodextrins, dendrimers, oral formulations, etc. (Figure 4).

3 Novel delivery options for PTX in breast cancer

3.1 Nanoparticle

The interdisciplinary developments of nanomaterial and clinical medicine have vigorously promoted the theranostics of breast cancer. Nanoparticle-based drug delivery platforms have shown significant improvements in tolerability and overall survival of patient with breast cancer, indicating that this is an emerging trend in the further development of breast cancer therapeutic modalities [9]. Nanoparticles function with chemotherapeutics that can either passively or actively target tumor tissues and cells. Passive targeting is based on the leaky blood

Figure 1: Chemical structure of paclitaxel.

Figure 2: Chemical structure of docetaxel and cabazitaxel.
vessels and poor lymphatic drainage of tumor microenvironment, which allow nanoparticles to accumulate in the tumor through the enhanced permeability and retention (EPR) [10].

Abraxane®, a representative albumin-bound formulation based on nano-technology for PTX [11], demonstrated better pharmacokinetic profiles and higher therapeutic efficacy compared with Taxol®, which has been approved by the FDA in 2005 for the treatment of metastatic breast cancer after failure of combination chemotherapy trials [12]. Abraxane® is a popular drug in drug combination basic science studies and clinical trials for breast cancer, and has been confirmed to possess enhanced transport across endothelial cell monolayers, greater tumor-targeted delivery, and slower elimination of PTX in preclinical models. In addition, Abraxane®, in combination with capcitabine, trastuzumab plus carboplatin, gemcitabine, and gemcitabine plus bevacizumab, has also been used in Phase II studies on the treatment of breast cancer. Inspired by the success of Abraxane®, a large amount of nanoparticle-based formulations consisting of PEG, PLGA, PVA, DPPC as well as carbon-nanotubes, and metal-nanoparticles for PTX delivery are under investigation (Table 1), and have already exhibited...
higher anti-cancer efficacy on either breast cancer cell or tissue compared with Taxol®. Furthermore, such nanoparticles can be actively targeted by conjugation with specific ligands for tumor tissue [21].

3.2 Liposome

Liposomes are self-assembling systems that consist of a bilayer membrane surrounding an aqueous interior compartment (Figure 5). Liposomes protect the drug against degradation and prevent side effects on patients [22]. In general, liposomes have the following features: (a) characteristic of targeting and lymphatic orientation for passive targeting to the endothelial reticular system of liver and spleen, (b) sustained release to ensure prolonged duration of action, and (c) reduced toxicity with improved stability of the drug. Liposomal PTX formulations are in various stages of clinical trials with exciting outcomes. Lipusu® has already been commercialized. LEP-ETU (NeoPharm) and EndoTAG®-I (Medigene) [23] have reached Phase II of their respective clinical trials. Some liposomal formulations are under investigation, such as immunoliposomes [24], NGR-modified liposomes [25], folate-modified lipid polymers [13], liposomal lipid systems [26], liposome-encapsulated albumin-PTX nanoparticles [27], and co-loaded liposomes [28]. They all achieved satisfactory therapeutic effects on clinical and preclinical levels for breast cancer.

3.3 Micelles

Micellization is defined as the spontaneous passage of poorly aqueous-soluble solute molecules into an aqueous solution of a detergent, in which a thermodynamically stable solution is formed (Figure 6). Polymeric micelles are convenient passive targeting carrier systems for the delivery of chemotherapeutic agents, because they are structurally strong and are not captured by the reticular endothelial system (RES) due to their small particle size (20–100 nm) compared with liposomes. In the last decade, many micelle formulations of PTX were introduced. Genexol-PM® is a polymeric micelle formulation of PTX that has been approved in South Korea for the treatment of breast cancer and NSCLC [29], which is exactly a perfect combination of this novel nanomaterial and traditional anti-cancer agent. Genexol-PM® is composed of low-molecular-weight amphiphilic diblock copolymer, monomethoxy poly (ethylene glycol)-block-poly (D, L-lactide) (mPEG-PDLLA) and PTX. Lu et al. established PEG(5K)-EB(2) micelles that exhibited more potent cytotoxicity than Taxol® in several cultured tumor cell lines and in vivo xenografted tumor mice model including breast cancer [30]. Dehghan Kelishady et al. invented Pluronic F127 polymeric micelles for the co-delivery of PTX and lapatinib against metastatic breast cancer with increased therapeutic efficacy in drug-resistant metastatic breast cancer [31]. Wu et al. invented MPEG2K-C28 PTX micelles that demonstrated significant antitumor activity and were safer in a murine 4T1 breast cancer model [32]. All these successful cases indicate the promising development of liposomal PTX for breast cancer treatment.

3.4 Emulsions

An emulsion is a heterogeneous mixture of two or more immiscible liquids, in which one phase is dispersed in a second immiscible or partially miscible phase. Micro-emulsion is a type of emulsion with several advantages, including thermodynamic stability, small globule size, good solubilizing capacity, and the use of food grade. Emulsions typically
consist of food grade, surfactant(s), co-surfactant, oil, and water having an internal phase of less than 100 nm in diameter. Self-emulsifying drug delivery systems (SEDDS) are another class of emulsion, which are isotropic mixtures of oils and surfactants that can disperse in the gastrointestinal (GI) lumen to form micro-emulsion. Pawar et al. developed Vitamin E based nano-emulsion which could be loaded efficiently with PTX and demonstrated improved cytotoxicity, cell cycle arrest, and apoptosis against breast cancer cells with the contribution of a mitochondria-dependent pathway furnished by both PTX and vitamin E. Furthermore, nano-emulsion can also retard the chronic tumor growth by modulating the tumor cell immunology [33].

3.5 Prodrug

The term “prodrug” was first introduced in 1958, and was used to describe bioreversible derivatives of drug molecules that must undergo a chemical or enzymatic biotransformation to the active forms within the body, prior to exerting a pharmacological action (as shown in Figure 7). Prodrug was designed to overcome the low drug loading and other problems associated with the high rate of drug release from other formulations. For PTX, some prodrugs have already been synthetized by covalent conjugation of various molecules to the hydroxyl group in position C7 or C2’. A typical model of PTX prodrug, DHA-PTX (omega-3 fatty acid [docosahexanoic acid (DHA)] – poly (amido) amine (PAMAM) – PTX conjugates), also called Taxoprex®, reached Phase III clinical trials for the treatment of metastatic malignant melanoma. However, DHA-PTX still contains 10% of Cremophor, which might not be able to decrease the associated side effects. Zhong et al. developed novel endosomal pH-activatable PTX prodrug micelles based on hyaluronic acid-b- dendritic oligoglycerol (HA-dOG-PTX-PM) with excellent target ability and antitumor efficacy to CD44-passive breast cancer cells and tumor, thus indicating that it would have great potential for the targeted chemotherapy of CD44-positive cancers [34]. In other words, the synthesis of prodrug is a cumbersome and complex process with expensive cost and unpredictable pharmacodynamics and pharmacokinetics. However, it is still a promising and worthy topic of further research.

3.6 Co-delivery

Co-delivery strategies have been proposed to minimize the amount of each drug and to achieve the synergistic effect for cancer therapies. In fact, co-delivery is a concept based on various formulations. Attempts have been made to deliver chemotherapeutic drugs simultaneously using drug carriers, such as micelles, liposomes, and inorganic nanoparticles (NPs) [35]. The use of co-delivery nanoparticles with controlled release patterns is also an effective strategy for enhanced cytotoxicity and less side effects. For example, PTX-loaded sirolimus-conjugated albumin nanoparticles with 0.01 µg/ml and 0.1 µg/ml PTX have been found to be cytotoxic on MDA-MB-468 and MCF-7 cell lines, respectively, which are much smaller than the common formulation of PTX [36]. Zhu et al. prepared biodegradable cationic micelles from PDMAEMA-PCL-PDMAEMA triblock copolymers to deliver VEGF siRNA and PTX into breast cancer cells with an efficient knock-down of VEGF expression and an enhanced drug efficacy as compared with free PTX. This is a successful attempt in combination therapy in therapeutic siRNA and chemotherapeutics [37]. Additional attempts towards co-delivery of DNA [38], anti-cancer drugs [35], and antibodies [39] for breast cancer have also been made.

3.7 Cyclodextrins

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces contain numerous glucose monomers ranging from six to eight units in a ring, creating a cone shape (Figure 8). CDs are often used to increase the solubility and bioavailability of poorly soluble drugs. When lipophilic drugs are implanted to the hydrophobic core of the cyclodextrin, non-covalent

Figure 7: Schematic illustration of prodrug.
inclusion complexes are formed, such that the outer layer of hydrophilic substance can be dissolved in water. CDs are capable of interacting with a large variety of guest molecules, and are expected to solve many problems associated with drug delivery. The application can be further expanded by conjugating a specific carrier to the outside layer. The biggest drawback, however, is the precipitation reaction at the drug dilution site. Although CDs have been used as solubilizers for decades, more advanced CD-based DDS are still urgently needed. Jing et al. designed a new kind of Lbl. (layer-by-layer) capsules containing PTX in the shell, which rely on the very high affinity of PTX to HA (hyaluronic acid) grafted with β-CD through inclusion complexation [40]. With the combination of the inclusion capacity of β-CD and the unique biological properties of HA, the capsule exhibited controlled release properties and cytotoxicity to breast cancer cells. In conclusion, HA-CD-based capsules have the potential for clinical use for breast cancer treatment.

3.8 Dendrimers

Dendrimers, with a core, dendrons (repeated iterations surrounding the core), and the periphery groups, are a category of synthetic, monodisperse, and multivalent nanoparticles (Figure 9). The number of branches emanating from the core can be counted as subsequent “generations.”

Dendrimers have a wide variety of applications, including drug delivery vesicles and therapeutic agents. Dendrimers vary greatly in terms of solubility, degradability, and biological activity. However, polyamidoamines (PAMAM), polyamines, polyamides, carbohydrates, DNA, etc. are commonly used. Dendrimers possess abilities of high drug-loading and specific, targeted release of the drug. PTX delivery through dendrimers has been established, after which more precise vehicles with active targeting properties have been invented. Tekade et al. established dendrimer-stabilized smart-nanoparticle (DSSN; pD-ANP-f) for the targeted delivery of PTX, with stronger suppression of breast cancer cell growth and higher cellular uptake, which indicate a promising platform for its applications [41].

3.9 Oral formulations

The oral administration of PTX with a chronic treatment schedule eliminates systemic exposure to the vehicle Cremonophor EL, which is responsible for various side effects. On the other hand, oral formulations are limited by the possible interaction with unpredictable GI disorders [42]. A Phase II study revealed that oral PTX (Paxoral®) combined with CsA (ciclosporin, P-gp inhibitor) in anthracycline-pretreated metastatic breast cancer patients made an ORR of 51.7% and facilitates overall survival of 16 months [43]. Yao et al. developed functional PTX nanomicelles, which can increase the solubility of PTX as well as overcome the resistant breast cancer in vitro. Moreover, significant anti-tumor efficacy in the xenografted resistant breast cancers in mice by oral administration has also been observed, thus providing a strategy for overcoming multi-drug resistance in cancer therapy [44]. Oral PTX in combination with other oral cytotoxic agents, such as capecitabine and vinorelbine, have been proven to have a clinical potential, although this requires further research.
4 Other formulations

4.1 Paclitaxel(TAXUS)-eluting stent

The development of PTCA (Percutaneous Transluminal Coronary Angioplasty) has certainly brought good news to patients with coronary artery obstructive disease, but the major limitation of this technique is restenosis. Numerous factors contribute to luminal narrowing in stented blood vessels [45]. To overcome such limitations, the TAXUS-eluting stent has been invented; it contains PTX 1 μg/mm², which is slowly released into the intimal tissue of the coronary artery to prevent cell proliferation and neointimal hyperplasia [46]. Stent is often used for blocked bile duct and esophageal stricture, which rarely occurs in breast cancer.

4.2 Paclitaxel poliglumex (CT-2103; XYOTAX®)

A form of PTX has been combined with a protein called poliglumex, and may have fewer side effects and work better than PTX by taking advantages of EPR effect. This is currently being studied in the treatment of breast, ovarian, lung, and other types of cancer, and belongs to the family of drugs called mitotic inhibitors [47].

4.3 Mimics

Taxane-type cytotoxic drugs, including PTX, DTX, and cabazitaxel, are known to be effective in various cancer types. However, they are generally limited by scarce natural resources, various side effects, and multi-drug resistance. Therefore, developing PTX-mimics with simplified structure, fewer side effects, and improved pharmaceutical properties is significant. There exist several kinds of mimics, including core-simplification, core-replacement, macro-ring, and microtubule-bound mechanism mimics [48]. The development of PTX mimics remains a challenge because of the lack of unique microtubule-stabilizing activity or even the lack of in vitro cytotoxicity of PTX. However, they still deserve research attention because of their simplified structures that show diverse antitumor activities. Meanwhile, appropriate modifications on the flexible side chain can significantly improve efficacy, indicating that further modifications on some current mimics are required.

4.4 Antibody-drug conjugates

Antibody-drug conjugates (ADCs) employ monoclonal antibodies (mAbs) to specifically bind tumor-associated target antigens and deliver a highly potent cytotoxic agent. T-DM1, the first ADC developed specifically for the treatment of HER2-positive breast cancer, has been obtained by the conjugation of trastuzumab, a stable linker, and the cytotoxic drug maytansine-derivate (DM1) [49]. Numerous clinical trials have proven its superiority in the treatment of breast cancer [50–53]. ADC design seldom involves linking taxanes, such as methotrexate, doxorubicin, and vinblastine directly to trastuzumab. Moreover, ADCs have failed to demonstrate therapeutic benefits, with the shortcomings of (a) poor in vitro potency, (b) modest in vivo activity, and (c) localization in human tumors [53], which result in bare ADCs containing PTX.

5 Conclusions

Breast cancer pose a great threat to women, and current cancer treatment modalities are based on chemotherapy, radiotherapy, targeted therapy, biological therapy, and comprehensive treatment modes. Hence, patients could benefit from the application of new strategies and technologies. In this paper, we find that new formulations of PTX are associated with better therapeutic efficacy and fewer side effects. A variety of ongoing basic and clinical trials are developing more and more formulations of PTX for precise theranostic for breast cancer.

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References


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