Review

Advances in the formulation and delivery technology of paclitaxel for injection

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Abstract: Paclitaxel is a promising antineoplastic agent against a variety of human solid tumors, such as ovary, breast, lung, head and neck tumors, and melanoma. Owing to its poor solubility, the first available formulation of paclitaxel (Taxol®) exists as a non-aqueous concentrate composed of Cremophor EL (polyethoxylated castor oil) and ethanol. It must be diluted to a suitable aqueous solution prior to long time intravenous infusion. Based on the components and usage, Taxol® has serious adverse effects and is inconvenient for clinical use. To address these problems, the development of a less-toxic, better-tolerated, Cremophor EL-free formulation of paclitaxel has been attempted. In recent years, new drug delivery systems (DDS) including albumin-based nanoparticles, micelles, liposomes, etc. have been investigated. In this review, we present the formulations and delivery technologies of paclitaxel for injection and focus on some of preclinical and clinical experience on the formulations which are already on the market or under clinical stages. Finally, possible nanotechnology advantages, existing challenges and future perspectives of paclitaxel delivery are highlighted.

Keywords: Paclitaxel, Taxol®, Preclinical and clinical studies, New drug delivery system

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1. Introduction

Among the chemotherapeutic agents for cancer, taxanes constitute one of the most important classes of drugs over the past decades. In 1960s, paclitaxel was first extracted from the bark of *Taxus brevifolia* (Pacific yew) by National Cancer Institute (NCI). The molecular formula of paclitaxel is $C_{47}H_{51}NO_{14}$, corresponding to a molecular weight of 853 Da (Fig. 1). Its chemical name is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one, 4,10-diacetate 2-benzoate13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. The physicochemical property shows that paclitaxel is highly lipophilic, and especially insoluble in water.

As a potent inhibitor of cell replication, paclitaxel acts by blocking cell cycle in the late G2 or M phase. In detail, by promoting tubulin polymerization and stabilizing the resulting microtubules towards depolymerization, paclitaxel triggers mitotic arrest and cell apoptosis in sensitive cancer[1]. This mechanism is widely recognized as its mode of action for cell cytotoxicity and interest is further stimulated when impressive activity was demonstrated in NCI tumor screening.

Taxol® (Bristol Myers Squibb GmbH), the first formulation of paclitaxel, was approved by Food and Drug administration (FDA) in 1992. Taxol® is a transparent, viscous solution with achromatic or slightly yellow color, which is composed of 1:1 blend of Cremophor EL (polyethoxylated castor oil) and ethanol. In the clinical instructions, this solution must be diluted with normal saline or 5% glucose before intravenous infusion. Taxol® has now been a potent chemotherapeutic drug in clinic against epithelial ovarian carcinoma, breast cancer, colon, head, non-small cell lung cancer, and AIDS-related Kaposi's sarcoma. In the clinical application, Taxol® is usually administered as a 3-hour and 24-hour infusion representing a total dose of 135–175 mg/m^2 of the body every 3 weeks.

Although the development of Taxol® has significantly improved patient's survival compared to past, the relevant adverse effects are still not to be ignored. Cremophor EL, the core component of Taxol® used for solubilizing paclitaxel, can cause toxic effects by inducing hypersensitivity reaction, which affects 25%–30% of treated patients[1]. Due to the significant percentage, all Taxol® treated patients have to be pre-administrated with corticosteroids, diphenhydramine, and H_2 antagonists to prevent hypersensitivity reaction. Furthermore, it is reported that Cremophor EL influences the pharmacokinetics of paclitaxel[2]. In additions, the container is a non-ignorable issue, in which both ethanol and Cremophor EL in Taxol® might leach toxic di(2-ethylhexyl) phthalate (DEHP) from the polyvinylchloride (PVC) infusion bags and administration sets, causing hepatotoxicity, carcinogenicity and teratogenicity[3].

Based on hereinbefore problems, pharmaceutical researchers have been developing a less-toxic, better-tolerated, Cremophor EL-free formulation of paclitaxel in the recent two decades. Presently, new pharmaceutical methods based on nanotechnology bring light to the development of Taxol® substitute agents. As shown in Figure 2, multiple drug delivery systems such as albumin-based nanoparticle, micelle, liposome and nanogel show good prospects to improve antitumor efficiency[4,5]. Table 1 displays different nanotechnology-based paclitaxel formulations that are on the market or in the clinical trials presently.

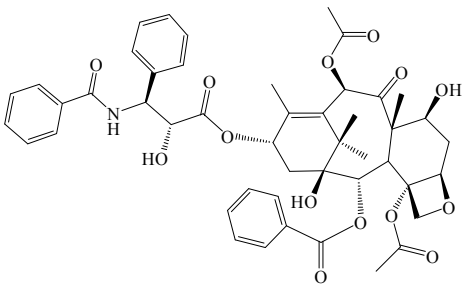

Figure 1. The structure of paclitaxel (5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one, 4,10-diacetate 2-benzoate13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine).

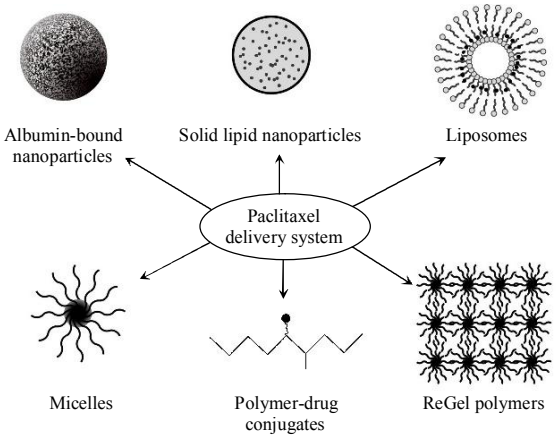

Figure 2. A sketch of various formulations of paclitaxel.

Table 1. New formulations on the market or under clinical evaluation

Product	Formulation	Storage form	Application	Route of injection	Developer	Status
Abraxane®	Albumin-bound nanoparticle	Powder	Metastatic breast cancer and NSCLC and Pancreatic cancer	Intravenous	Celgene Corp.	Marketed
Genexol®-PM	PEG-poly(D,L-lactide) with paclitaxel micelle	Powder	Breast cancer and NSCLC	Intravenous	Samyang Pharmaceuticals	Marketed
Lipusu®	Liposomal paclitaxel	Powder	Metastatic breast cancer and NSCLC	Intravenous	Sike Pharmaceuticals	Marketed
NK105	mPEG-poly(aspartic acid) with paclitaxel micelle	Powder	Recurrent or metastatic breast cancer	Intravenous	Nippon Kayaku Co., Ltd.	Phase 3 NCT01644890[a]
LEP-ETU	Liposomal paclitaxel	Powder	Metastatic pancreatic cancer	Intravenous	Insys Therapeutics	Phase 2 NCT01190982[a]
EndoTAG-1	EndoTag-1 plus Paclitaxel	Suspension	HER2-negative breast cancer	Intravenous	Medigene AG	Phase 2 NCT01537536[a]
OncoGel™	ReGel/paclitaxel	Low viscosity solution	Superficially accessible solid tumors and esophageal cancer	Local intratumoral	Macro MedInc.	Terminated

NSCLC: non-small cell lung cancer; [a] Clinical Trials. gov identifier.

In the review, we firstly present the structure characteristics of these new paclitaxel formulations, then discuss part of preclinical studies (such as cytotoxicity, antitumor efficiency, pharmacology and toxicities) and clinical experiences, hoping to provide new ideas for the development of new drug dosage forms. Finally, nanotechnology advantages, the existing challenges and future perspectives of paclitaxel drug delivery system (DDS) are highlighted.

2. New drug delivery system

2.1. Nanoparticle engineerring

Recently, there are numbers of reports about polymeric nanoparticles on DDS to increase antitumor efficiency of encapsulated anti-carcinogens[6]. Nanoparticle technology offers a potential solution associated with the solvent-based formulations, such as the instability and toxicity of solvent. In particular, protein-based nanoparticle DDS shows remarkable market prospect due to the endogenous feature and highly concentration of paclitaxel in tumor[7].

Abraxane® (albumin nanoparticle-bound paclitaxel, Celgene Corporation) has been approved since 2005 for the treatment of breast cancer in patients who failed combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy and has meanwhile been approved in 41 countries around the world[8]. In 2012, Abraxane® was approved for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with carboplatin. Moreover, in 2013, Abraxane® was added as a new medication for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas in combination with gemcitabine.

Abraxane® is a lyophilized nanoparticle formulation by nab-technology[9], with a mean particle size of approximately 130 nanometers, containing 100 mg of paclitaxel and approximately 900 mg of human albumin, which is devoid of any solvents or ethanol. Figure 3 illustrates its formation process. The particles of paclitaxel are in a non-crystalline, amorphous, readily bioavailable state, allowing for rapid drug release from the particles following intravenous administration. By eliminating Cremophor EL from its formulation, Abraxane® reduces the risk of hypersensitivity reaction and does not require premedication, and can be given over a shorter period (30 min) without special intravenous tubing. The following is some of preclinical and clinical information.

Preclinical studies: In a comparative preclinical study[10], Abraxane® and Taxol® were given by intravenous injection (i.v.) to Harlan Sprague-Dawley male rats at the same dose to determine the pharmacokinetics and drug disposition. The result showed that CL (total body clearance) and Vz (volume of distribution) of paclitaxel were ~50% higher for Abraxane® compared with Taxol®. In addition, the endothelial binding and transcytosis of paclitaxel were significantly (P<0.0001) higher (9.9- and 4.2-fold) with Abraxane® than Taxol® in vitro. These phenomena can be explained as follows: (a) paclitaxel is captured by Cremophor EL micelles originating from Taxol® in plasma, which reduces the bioavailability of paclitaxel[11]; (b) transport of Abraxane® through the epithelium is facilitated by the gp-60 albumin receptor[6,12]; and (c) accumulation of Abraxane®

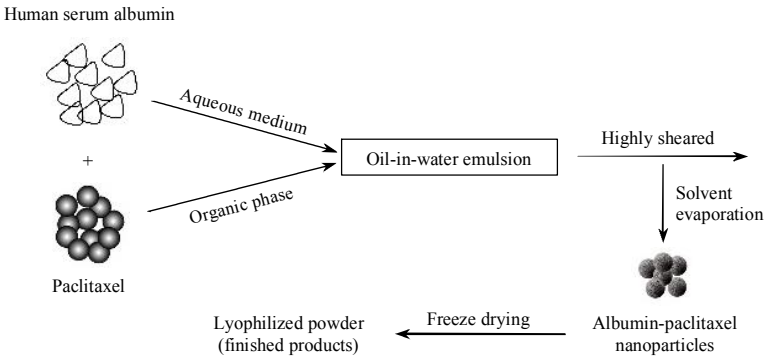

Figure 3. Schematic of Abraxane® prepared by nab-technology. Abraxane® consists of particles of paclitaxel in nanometer-size range, stabilized with human albumin.

is enhanced by the action of albumin binding secreted protein acidic and rich in cysteine (SPARC)[7].

In another preclinical study[13], researchers used human tumors H522 (lung), MX-1 (breast), SK-OV-3 (ovarian), PC-3 (prostate), and HT29 (colon) as models to evaluate the antitumor activity and mortality. The results showed that doses resulted in 50% mortality (LD_{50}) for Abraxane® and Taxol® with the dose schedule were 47 and 30 mg/kg/d, respectively. At the 30 mg/kg/d dose, mortality for Abraxane® and Taxol® were 4% (3 of 72) and 49% (23 of 47), respectively ($P<0.0001$, Fisher's exact test). The MTD (maximum tolerated dose) was defined as the body weight of animals for trial lost 15% over the control. The MTDs were 30 and 13.4 mg/kg/d for Abraxane® and Taxol®, respectively. In anti-tumor efficacy, no statistically significant differences were observed in the lung tumor xenografts; the proportion of tumor-free survivors was higher for the Abraxane® groups compared with Taxol® in breast and ovarian tumor xenografts at equitoxic doses. For the prostate tumor xenograft and the colon tumor xenograft at the equitoxic doses, the Abraxane® group showed a trend toward slower tumor growth and longer median tumor doubling times.

Clinical studies: A phase I study[14] was performed to examine the toxicity profile, MTD of Abraxane® with advanced solid tumors (n = 19). The MTD of Abraxane® was 300 mg/m^2, 70% to 80% higher than that reported for Taxol®, which was 175 mg/m^2 for both an every-3-weeks regimen and a weekly regimen (150 mg/m^2 versus 80 mg/m^2). Dose-limiting toxicities (DLTs) occurring at a dose of 375 mg/m^2 included sensory neuropathy, stomatitis and superficial keratopathy. No hypersensitivity reaction occurred, despite the absence of premedication. Another phase I clinical study was performed in 39 patients with advanced non-hematological malignancies. This study determined the MTD of Abraxane® monotherapy administered weekly and the results were consistent with above results[15].

In a multicenter phase II trial of Abraxane® in metastatic breast cancer, 63 women received 300 mg/m^2 Abraxane® by intravenous infusion over 30 min every 3 weeks without premedication[16]. Overall response rates were 48% for all patients. Median time to disease progression was 26.6 weeks and median survival was 63.6 weeks. No severe hypersensitivity reactions were reported.

A randomized, phase III trial with metastatic breast cancer was carried out. The researchers compared equitoxic doses of Abraxane® (260 mg/m^2) and Taxol® (175 mg/m^2) in 454 patients[17]. Response rates were significantly higher for Abraxane® than for Taxol®.

There are also some trials in NSCLC and metastatic adenocarcinoma of the pancreas. For example, a multicenter phase III clinical trial enrolled 1052 chemo-naive patients with stage IIIB-IV NSCLC[18,19]. The result of the study showed that Abraxane® achieved significant overall response rate (ORR, 33%) in all patients with squamous histology as compared to solvent-based paclitaxel (25%) and Abraxane® showed a 10% improvement in OS (overall survival) compared to Taxol®. A recent phase III trial was done on a total of 861 patients[20] to treat metastatic pancreas. The result showed that Abraxane® plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased.

The data above demonstrate the increased antitumor activity of Abraxane® and lower toxicity. However, Abraxane® cannot solve the peripheral sensory neuropathy induced by DLTs or cumulative toxicity; besides, some show drug resistance[21].

2.2. Liposome technology

Liposome is a versatile and advanced DDS for a wide range of biologically active compounds. The application of a liposome technology resolves the issue of paclitaxel insolubility. In additions, it reduces the toxic side-effects. Three liposomal formulations, Lipusu®, LEP-ETU and EndoTAG-1are discussed below.

2.2.1. Lipusu®

Lipusu® (paclitaxel liposome for injection, Luye Pharma Group) was developed by Sike Pharmaceutical (Nanjing, Jiangsu, PRC) as freeze-dried powder for injection in glass vials containing 30 mg of active drug which is approved by the State FDA of China. Lipusu® is prepared by using film dispersion method followed by a lyophilization technique (Fig. 4). It is composed of paclitaxel (6.0 g), lecithin (72 g) and cholesterol (10.8 g)[22]. These materials were dissolved in ethanol, after a series of processing, organic solvent will be formulated. The resulting membrane was dissolved by the addition of 5% mannitol solution containing lysine (1.4 g) to obtain a paclitaxel liposome solution. The solution was filtered through a 0.22 μm filter and lyophilized to a dried paclitaxel liposome (Lipusu®). The mean diameter is about 400 nm. It is the first paclitaxel liposome injection which comes into the clinical market in China. It has been applied for the treatment of ovarian, breast, NSCLC, gastric and head and neck cancer by i.v. administration.

Preclinical study: The research performed in vitro and in vivo experiments was to compare the safety profiles of Lipusu® and Taxol®[23]. Results showed that there was no significant difference between Taxol® and Lipusu® in vitro cytotoxicity against KB oral carcinoma cells. Single dose acute toxicity assays were performed on Swiss mice and the results demonstrated that Lipusu® exhibited a greater safety margin than Taxol®. The LD_{50} values for Lipusu® and Taxol® were calculated to be 69.82 and 33.0 mg/kg respectively. The animals in the Taxol® group were all observed to have acute hypersensitivity reaction and all the animals in the Lipusu® group, however, showed much milder reaction. Similar results had also showed that the cytotoxic effects and antitumor activities of Lipusu® were lower compared with Taxol®[24].

In order to find potential benefits of intraperitoneal injection (i.p.) of Lipusu®, Liang Ye et al[25] performed an experiment in NuTu19 ovarian cancer-bearing rats and normal mice. Antitumor effects and kinds of toxicity and biodistributions were evaluated. Results showed that Lipusu® exerted antitumor effects similar to Taxol®, but much lower bone marrow toxicity and cardio-toxicity. Furthermore, Lipusu® exhibited similar plasma drug exposure, higher exposure in tumor and pelvic lymph nodes and lower exposure in bone marrow and heart compared with Taxol®.

Clinical studies: A phase I clinical and pharmacokinetic study of Lipusu® has been done by X.H. et al[26]. Thirteen of NSCLC patients with malignant pleural effusions and three treated with Taxol® were enrolled into the phase I clinical study. It turned out that the toxicity of Lipusu® was much lower than that of Taxol®; no significant differences were observed between Lipusu® and Taxol® in treatment effect. Pharmacokinetics were analyzed by ultra-performance liquid chromatography (UPLC) and the pharmacokinetic parameters revealed that Lipusu® was eliminated more slowly than Taxol® from pleural fluid and had delayed release action[26,27].

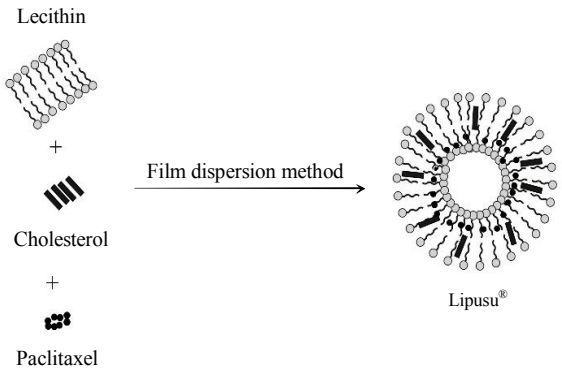

Figure 4. Lipusu® composed of paclitaxel, lecithin and cholesterol. It is prepared by using film dispersion method followed by a lyophilization technique.

In a research about treatment with metastatic gastric cancer in 2013[28], 58 patients were enrolled to evaluate for efficacy. The overall response rate was 47% in group Lipusu® in combination with tegafur and oxaliplatin, 46% in group Taxol® in combination with tegafur and oxaliplatin, a slightly superior to conventional paclitaxel. The incidence rate of allergy, nausea and vomiting, rash, muscle pain in the Lipusu® group was lower than that in the Taxol® group.

In other clinical studies, for example, Chen et al[29] compared Lipusu® with Taxol® on treatments of breast cancer and NSCLC; Jinguan Lin et al[30] performed an analysis of Lipusu® in treatment for 54 cases with advanced NSCLC compared with Taxol® (49 cases). The experiments both showed no difference in therapeutic effect, but lower hypersensitivity and toxicity with Lipusu®. Still, like Taxol®, there is a need to obtain an optimal premedication protocol for Lipusu®[31].

So far, phase IV clinical study in metastatic breast cancer is currently recruiting participants. Dose escalation and pharmacokinetic study of Lipusu® in treating patients with advanced solid tumor after failure from conventional treatments in phase IV is currently recruiting participants.

2.2.2. LEP-ETU

A novel lyophilized paclitaxel formulation marked as LEP-ETU (INSYS THERAPEUTICS, easy-to-use liposome-entrapped paclitaxel) is composed of 2-dioleoyl-sn-glycero-3-phosphocholine (DOPC)–cardiolipin–cholesterol (9:0.5:0.5, v/v/v) and α-tocopheryl acid succinate (α-TAS) with paclitaxel (1:33, v/v)[32], among these materials, DOPC, cardiolipin and cholesterol are served as hydrophobic excipients. LEP-ETU formulations are prepared by the modified thin-film hydration method. The mean particle size of the liposome is about 150 nm and the drug entrapment efficiency is greater than 90%; stability data indicated that the lyophilized LEP-ETU was physically and chemically stable for at least 12 months at 2–8 °C and 25 °C[33].

Pre-clinical data suggested that paclitaxel in LEP-ETU and paclitaxel in Taxol® had comparable pharmacokinetic properties[34].

A multi-institutional, open-label phase I study of LEP-ETU have been finished by Gerald J. Fetterly et al[34]. Results showed that the MTD of LEP-ETU for 1.5 h infusion every 3 weeks was defined as 325 mg/m^2, higher than that of Taxol® at 175 mg/m^2. In addition, the neuropathy caused by LEP-ETU appeared to be no worse than that for Taxol®.

In another phase I study, 23% of the patients treated with LEP-ETU experienced IRRs (infusion-related reactions) and this incidence appeared to be no worse than that observed with Taxol® at similar doses[35].

The researchers conducted a multicenter, open-label II trial of LEP-ETU at 5 centers in India. 35 patients were enrolled into the trial for the metastatic breast cancer treatment. The trial showed that the tumor response rate reached 45.7%, higher than that in Taxol®.

Whether to extend the trial phase II of LEP-ETU or to start phase III of randomized trials with Taxol® used in metastatic breast cancer patients needs to be well evaluated[32].

2.2.3. EndoTAG-1

As mentioned above, liposomes are widely known as potent drug delivery system. In particular, there are already some reports about cationic liposomes[36]. Cationic liposomal formulations are confirmed to be positively charged, which can specifically target tumor vasculature (Fig. 5) as promising carriers for therapeutic substances[37,38].

EndoTAG-1 (Medigene Martinsried, Germany), also known as LipoPac® or MBT-0206, is a novel formulation of charged liposomes, carrying paclitaxel embedded in the cationic liposome membrane. The formulation involves a series of reactions of pure paclitaxel (0.006 mmol) and the cationic lipids 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP, 0.1 mmol) and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC, 0.094 mmol)[39]. They were dissolved in chloroform. The resulting mixture was warmed

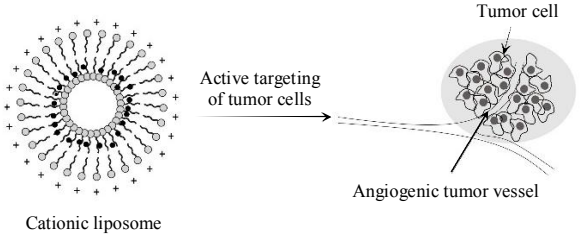

Figure 5. Cationic liposomes targeting tumor vasculature.

to 40 ºC and the solvent was evaporated under vacuum to produce a lipid film. Drying of the film eliminated solvent traces, and multilamellar liposomes formed spontaneously upon addition of 10 mL of 5% glucose. The resulting suspension was stored at 4 ºC under argon; analysis of the liposomes revealed particles measuring 180 to 200 nm.

In the case of cationic lipids, the relationship between zeta potential and cationic component concentration fits a hyperbolic curve. To enable selective targeting of a vascular site, the liposomes should be made up of cationic lipids in the range of 25 to 50 mol %, with a zeta potential of approximately +25 to +100 mV in a 0.05 mM KCl solution at pH 7.5[40].

Preclinical studies: Vascular targeting of Rhodamine-labeled EndoTAG-1 and its tissue distribution ratio were confirmed in Syrian golden hamsters bearing A-Mel-3 (amelanotic hamster melanoma)[41]. Tumor-bearing animals were treated by continuous i.v. infusion over 90 min with 5% glucose, Taxol®, unloaded cationic liposomes, or EndoTAG-1, respectively. The results revealed that injection of EndoTAG-1 led to a significantly enhanced accumulation in intratumoral micro-vessels and was not detectable in the tumor extravascular compartment, which showed an evident vascular targeting compared with normal tissue by image analysis. In contrast, injection of the control groups did not produce significant differences between normal tissue and tumor tissue. Tumor volumes in animals treated with EndoTAG-1 were significantly smaller than those in any other group and lower toxicity was seen. Besides, the appearance of regional lymph node metastases was significantly delayed by the treatment with EndoTAG-1 in comparison with all other groups. Similar reports were verified in another research[39]. The report demonstrated a 3:1 uptake ratio for tumor to normal tissue over a period of 360 min after injection of EndoTAG-1.

Preclinical data were also collected in humanized SCID mouse melanoma model[42]. EndoTAG-1 could retard melanoma growth and invasiveness and improve survival of mice. Moreover, vascularization of tumor margins at the interface to the human dermis was diminished by EndoTAG-1; besides, the mitotic index of endothelium was also reduced. However, the Taxol® group showed insignificant effects. Neovascular targeting was also tested for the treatment of prostate cancer[43].

Clinical studies: Clinical data are available for pancreatic cancer and triple-negative breast cancer and neck squamous cell carcinoma (HNSCC). Pharmacokinetic and a phase I/II study have been done.

A phase II trial to evaluate the effect of EndoTAG-1 in combination with Gemcitabine was to be conducted at 20 clinical centers in four European countries and to investigate EndoTAG-1 for the first-line treatment of advanced pancreatic cancer[44]. The result showed that improved OS (overall survival) and PFS (progression-free survival) happened when combined gemcitabine with EndoTAG-1 (compared with gemcitabine only). The EndoTAG-1–gemcitabine combination had a better toxicity profile than what had become the current standard of care in advanced pancreatic cancer.

A randomized controlled phase II study on TNBC (triple-negative breast cancer)[45] showed that treatment of advanced TNBC with a combination of EndoTAG-1 and Taxol® was well tolerated and showed antitumor efficacy. PFS with EndoTAG-1 was improved when compared with that on using either agent alone. Another phase II study in the same setting is currently ongoing (NCT00377936). A phase III trial with EndoTAG-1 in TNBC is planned for 2014.

Some data have also been received in human head and HNSCC[46]. Through this study, it seems to be safe and further phase II and III studies are warranted to prove efficacy in the treatment of HNSCC.

2.3. Polymeric micelle technology

Polymeric micelle-based anti-cancer drugs are originally developed by Prof. Kataoka et al. in the late 1980s or early 1990s[47]. Polymeric micelles are expected to increase the accumulation of drugs in tumor tissues utilizing the EPR effect and incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability[48].

2.3.1. Genexol®-PM

Genexol®-PM (Fig. 6) is a polymeric micelle formulation of paclitaxel free of Cremophor EL which is developed

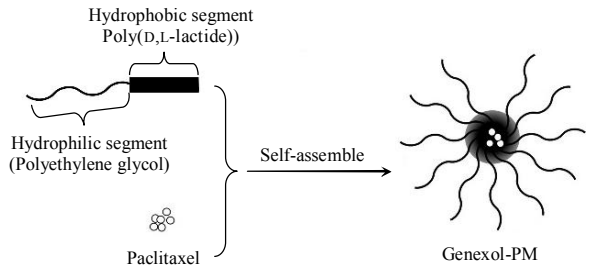

Figure 6. The formulation of Genexol®-PM.

by Samyang Biopharmaceuticals Corporation (Genexol, Samyang Genex Co., Seoul, Korea) and has been successfully applied in the clinic and approved in Korea in 2006 as the first line therapy for recurrent or metastatic breast cancer and NSCLC through i.v. administration for 3 h once every 3 weeks[49,50].

Genexol®-PM is reserved in a form of lyophilized powder by a freeze dryer system (Labconco, USA)[51]. It is newly developed by using a low molecular weight, nontoxic and biodegradable amphiphilic diblock copolymer, monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) and paclitaxel. The particles are measured 20 nm to 50 nm[52].

Preclinical studies: Breast cancer cell line MCF-7 and human ovarian cancer cell line OVCAR-3 were used in vitro study[51]. T/C (treatment over control) values for the cell survival and IC_{70} values (concentration of drug resulting in T/C values of 70%, or 70% growth inhibition) were considered as the indexes to evaluate the results of cytotoxicity of Genexol®-PM and Taxol®. The results showed that Genexol®-PM and Taxol® had the same cytotoxicity at the same drug concentration in vitro against OVCAR-3 and MCF-7. Three treatments of healthy female mice were used to investigate the MTD by receiving daily i.v. injections, dosage escalation of Taxol® and Genexol®-PM and saline as a control. The results showed that MTD of Genexol®-PM was recommended 60 mg/kg, a higher dosage than Taxol® (20 mg/kg).

Another study was done to evaluate efficacy of Genexol®-PM using NSCLC and human ovarian cancer mouse xenograft models in vivo[53]. It was indicated that the treatment with Genexol®-PM led to significantly delayed tumor growth compared with Taxol® in H460 cells. The efficacy studied in vivo showed that Genexol®-PM was more effective for treatment of NSCLC than Taxol®. On the other hand, Taxol® only delayed tumor growth in human ovarian cancer mouse xenograft models at dose of MTD, but tumors regrew as quickly as without treatment after 48 d. While Genexol-PM® was observed a striking antitumor response for reducing the tumor at its MTD, whose efficacy was threefold higher than that of Taxol®.

Clinical studies: In a phase I clinical study, Kim TY et al[50] finished an open-label dose-escalation on twenty-one patients (fifteen male and six female). The MTD of Genexol®-PM administered as a 3-h infusion every 3 weeks was determined to be 300 mg/m^2, two times higher than that Taxol® (175 mg/m^2). On the other hand, Genexol®-PM was able to overcome taxane resistance by enhancing the dose of paclitaxel in tumor tissues due to the superior delivery system.

A multicenter single-arm phase II study was done by Lee KS et al[54] to evaluate the efficacy and safety of Genexol®-PM in patients with metastatic breast cancer (MBC). Genexol®-PM reached an overall response rate of 59.5% which was more beneficial compared either the response rate of 47.6% produced by Abraxane® or Taxol® with response rates of 21%–54% as a first-line therapy with MBC at the same dose regimen.

Another multicenter phase II study of Genexol®-PM was conducted by Kim DW et al[54] on the patients with advanced NSCLC (n = 69). The data of overall response rate, time to progression and survival period of Genexol®-PM plus cisplatin were more favorable than that in most phase II or phase III clinical trials of Taxol® using 175–200 mg/m^2 (3-h infusion) combined with higher dose of cisplatin. Owing to a higher paclitaxel tumor concentration produced by Genexol®-PM than Taxol®, Genexol®-PM showed more significant antitumor activity than Taxol®.

The status of an open-label, randomized, parallel, phase III trial (n = 212) of Genexol®-PM compared to Taxol® in subjects with recurrent or metastatic breast cancer is unknown and a phase IV trial (n = 90) against taxane-pretreated recurrent breast cancer is underway.

2.3.2. NK105

NK105[55] (Nippon Kayaku Co., www Ltd.), a novel amphiphilic block copolymer, which has a passive

targeting ability based on the EPR effect and is still at clinical studies, is a paclitaxel-incorporating 'core-shell-type' polymeric micellar nanoparticle formulation. Like Genexol®-PM forming process, NK105 polymer is constructed using PEG as the hydrophilic segment and modified polyaspartate as the hydrophobic segment. NK105 is obtained as a freeze-dried formulation. Molecular weight of the polymers is determined to be approximately 20 000 (PEG block: 12 000; modified polyaspartate block: 8000). It has a single and narrow size distribution, the average diameter of the nanoparticles is approximately 85 nm. Due to its absence of Cremophor EL and ethanol, it can reduce adverse effects and increase safety; besides, it can be injected without premedication to cure recurrent or metastatic breast cancer.

Preclinical studies: The pharmacokinetics study[55] was used in 26 colon tumor-bearing CDF1 mice. It revealed that plasma concentration at 5 min ($C_{5\ min}$) and *AUC* of NK105 were 11–20-fold and 50–86-fold higher for NK105 than for Taxol®, respectively; furthermore, the half-life at the terminal phase ($t_{1/2z}$) was 4–6 times longer for NK105 than for Taxol®. In vitro cytotoxicity was tested on 12 human tumor cell lines, similar dose response curves were noted for Taxol® and NK105. Furthermore, the IC_{50} (half maximal inhibitory concentration) values of NK105 were similar to those of Taxol® at 48 h and 72 h, indicating that both NK105 and Taxol® show equivalent cytotoxic activity in vitro.

NK105 exhibited superior antitumor activity compared with Taxol® (P<0.001) in BALB/c mice bearing s.c. HT-29 colon cancer tumors[55]. In addition, less weight loss was induced in mice who were given NK105. In another antitumor study[56], growth rate was evaluated in LLC (Lewis lung carcinoma). No antitumor activity was observed following treatments with either Taxol® or NK105 alone, because LLC is primarily a paclitaxel-resistant tumor. Combined NK105 therapy with radiation yielded superior antitumor activity as compared to both radiation alone (P = 0.0047) and combined Taxol® therapy with radiation (P = 0.0277) on the day 9 after the treatment initiation. No significant difference in body weight changes were noted among the groups tested. Besides, its adverse effects were lower than Taxol®[55–57].

Clinical studies: A phase I study was designed to determine the MTD, DLTs, and recommend dose (RD) of NK105 for phase II, as well as its pharmacokinetics. Hamaguchi et al[58] performed the experiment on 19 patients without anti-allergic premedication and with no any taxanes. The results showed that DLTs occurred in two patients who were given 180 mg/m^2. The MTD in this study was defined as the level at which two out of six patients experienced dose-limiting toxicities, 180 mg/m^2 in this study was designated as the MTD. The plasma *AUC* of NK105 at 150 mg/m^2 was approximately 15-fold higher than that of Taxol®. NK105 was well tolerated, and the RD for the phase II study was determined to be 150 mg/m^2 every 3 weeks. No local pain or toxic response occurred on patients, nor did related hemolytic reaction.

A phase II study of NK105 is now underway against advanced stomach cancer as a second line therapy. Chin et al[59] recruited 56 patients to evaluate the efficacy and safety of NK105 in patients with advanced gastric cancer after failure of first-line chemotherapy. NK105 was proved to be effective in this phase II study: 2 patients were completely relieved and 12 patients were partially relieved, there were no treatment-related deaths. The *AUC* of NK105 at 150 mg/m^2 was about 9-fold larger than that of Taxol® at dose of 210 mg/m^2 (conventional dose for every 3 weeks). These PK parameters were almost similar to those observed in the phase I study. Further clinical studies should be continued.

This first study with NK105 at 150 mg paclitaxel equivalent/m^2 provides positive proof of concept for high activity and tolerability of a new DDS formulation for paclitaxel. To clarify the survival benefit, a phase III will be evaluated.

2.4. ReGel™ technology

OncoGel™, developed by MacroMed Inc. (Sandy, Utah), incorporates paclitaxel into ReGel™ to provide an injectable, controlled-release (approximately 6 weeks), biodegradable vehicle for paclitaxel local delivery and to enhance efficacy and limit systemic toxicity[60,61]. ReGel™ is a thermal gel depot–based delivery system

developed by Protherics, a Salt Lake City, Inc. which is a tri-block copolymer comprised of poly (D,L-lactide-co-glycolide) (PLGA) and polyethylene glycol (PEG) with the basic structure of PLGA-PEG-PLGA[61,62]. ReGel™ can spontaneously form polymeric micelles containing ahydrophobic core. ReGel™ polymers transform from low viscosity solution (sol-state) to a viscous, water insoluble biodegradable controlled-release gel (gel state) when the temperatures change from 2 °C or 15 °C to body temperature[62].

Preclinical studies indicated that OncoGel™ had an acceptable safety profile when administered intralesionally into various tumors and animal models. Studies on the safety of OncoGel™ in normal tissue have been conducted in three species: rat, dog and pig. These studies demonstrated the tolerability of OncoGel™ in normal tissue, and the ability to deliver and sustain high local concentrations of paclitaxel at tumor site[62].

OncoGel™ have been evaluated in three completed clinical studies in superficially-accessible solid tumors and in combination with radiotherapy in esophageal cancer[63,64]. Further clinical trials have been terminated by sponsors based on business decision, not on safety or efficacy data.

3. Discussion

We highlight the unique features of new drug delivery systems. Compared with Taxol®, these formulations have a number of advantages resulted from the following possible reasons.

3.1. Nanotechnology endows paclitaxel with the potential of targeting delivery to tumors owing to the enhanced permeability and retention effect[65–72]

The enhanced permeability and retention (EPR) effect is very common for most of the solid tumors which does not occur in normal tissues and is regarded as a 'gold standard' in the design of new anticancer agents[73,74]. Because of the extensive angiogenesis, defective vascular architecture and impaired lymphatic drainage/recovery systems in solid tumors[75], nanoparticles, such as liposomes, micelles, by virtue of their smaller size, can cross biological barriers getting directly delivered to their sites of action by the EPR effect. Conventional chemotherapeutics, such as Taxol® mentioned in this review directly undergoes a process of elimination and need to cross biological barriers other than directly gather in the intended target sites, contributing to adverse effects and low efficiency[76]. Nanotechnology has the potential to overcome these problems.

3.2. Nanotechnology prolongs the half-life period of paclitaxel due to decreased clearance by reticuloendothelial system

Reticuloendothelial system (RES), also called macrophage system or mononuclear phagocyte system, is a class of cells which are part of the body's defense mechanisms[65,75,77]. To hide from macrophages of RES, different reports demonstrate that this could be significantly reduced by modifying their surface with PEG[75,78–80]. PEG polymers have low toxicity and no immunogenicity and are approved by FDA for clinical use. Nanoparticles functionalized with PEG chains have been described as long circulating drug delivery systems on the basis of most widely accepted theory: PEG reduces the protein interactions on the surface by preventing opsonin binding[81,82]. Evidently, the formulations above such as Genexol®-PM, NK105, OncoGel™ can prolong circulation time in the blood stream. As to Taxol®, the immunogenicity of Cremophor EL may reduce its bioavailability.

3.3. Nanotechnology renders paclitaxel to effectively overcome drug resistance compared with conventional formulations

Cancer cells are intrinsically resistant to growth arrest and can further acquire multidrug resistance (MDR). MDR is predominantly mediated by ATP-driven multidrug resistance efflux transporters[83], so it remains one of the most significant factors impeding the progress of cancer treatment for conventional chemotherapeutics including paclitaxel. However, new formulations based on nanotechnology provide a way of targeted drug delivery by being localized in the cytoplasm or lysosomes after being endocytosed, thereby resulting in enhanced efficiency and reduced side effects, avoiding MDR[84,85].

3.4. Intralesional delivery of paclitaxel based on nanotechnology improves both safety and efficacy due to the long-term localized release of drug

As mentioned above, some delivery technologies such as intravenous liposomes and micelles can enhance anti-tumor efficiency and reduce toxicity. Another delivery system called locally intralesional delivery is also attractive because it could result in the maintenance of cytotoxic drug levels within the tumor over a long-term period and high intratumoral concentration of paclitaxel, as well as attenuating systemic toxicity[86]. Besides, anti-cancer agents can be delivered throughout the tumor and separated from normal tissue. OncoGel™ is an example of a local drug delivery technology that uses both physical targeting to the target body site and controlled release of drug.

Our research group, for example, Lin et al., constructed a combination drug delivery system based on in situ gel entrapment of insoluble drug nanocrystals[5]. The main compositions are paclitaxel, Pluronic® F127 (F127, one of the most widely studied temperature sensitive polymers and has been approved by the FDA). The gel is a free-flowing liquid at 4 °C and instantly forms a gel depot upon injection. The research showed that it has a high drug-loading property and a longer localized retention time when mice received an intratumoral injection compared with Taxol®.

Despite of these improvements, there may still exist problems. Although nanotechnology can change the particle sizes to improve the EPR to some extents, the author thinks that it is still an international problem to overcome the accumulation in liver and spleen induced by RES, especially for the particles with diameter greater than 200 nm[87,88].

There also exist other problems. Paclitaxel is complex to synthesize and is difficult to obtain. The scale up of new formulations may be another problem. Besides, the development of new indications is also a focus problem. Furthermore, despite extensive research and development in nanotechnology, only a few nanoparticle drug delivery systems have been approved and are available for cancer treatment.

Therefore, a deeper understanding of cancer diseases, tumor targets and novel ligands, and new strategies for targeting and particle stabilization are needed. We believe that these limitations and drawbacks of earlier agents as well as efficacy and safety will be properly addressed in the future.

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注射用紫杉醇在剂型和递送技术方面的进展

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摘要: 紫杉醇用于治疗人体各种实体瘤比如卵巢癌, 乳腺癌, 头颈部癌和黑色素瘤, 是一个很有前景的抗癌药物。由于它的疏水性, 紫杉醇的第一个给药剂型泰素是以非水浓缩液的形式存在, 成分主要含有聚氧乙烯蓖麻油和乙醇, 它在长时间的输注前必须用合适的水溶液稀释。基于它的成分和用法, 泰素存在严重的不良反应并造成临床应用的不便。为了解决以上问题, 科学家们开始致力于开发低毒、较好耐受性、不含聚氧乙烯蓖麻油的紫杉醇新剂型。最近几年, 新的药物递送系统如白蛋白纳米粒、胶束、脂质体等已经处于研究中。在这篇综述中, 我们提出了注射用紫杉醇的一些新剂型及递送技术, 并且重点研究已经上市的或处于临床研究阶段的几个制剂的部分临床前和临床研究成果。最后, 阐述纳米技术优势的几个原因及紫杉醇给药系统现存的挑战和展望。

关键词: 紫杉醇; 泰素; 临床前和临床研究; 新型药物给药系统

Prof. Qiang Zhang graduated from Beijing Medical College in 1982. Studied in Belgium in 1985 and worked in Japan from 1990 to 1991, he got his Ph.D degree at West China University of Medical Sciences in 1995 and have been working in School of Pharmaceutical Sciences, Peking University since then.

Currently he is the Chair of Pharmaceutics Committee of Chinese Pharmaceutical Association (CPA), Founder and Vice-Chair of Nanomedicines Committee of CPA, Vice-Chair of Pharmaceutics Committee of Chinese Pharmacopoeia, Vice-Editor of *Acta Pharmaceutica Sinica* (Eng) and *Journal of Chinese Pharmaceutical Sciences* (Eng), Expert for Center of Drug Evaluation of China FDA, Editorial board member of *J. Control. Release*, *Nanomedicine*: *NBM* and so on. He has been the first President of CRS-China Chapter and the Vice-Dean of School of Pharmaceutical Sciences, Peking University for 12 years.

Most of his research is engaged in the field of the molecular pharmaceutics of nanomedicines, especially the molecule-targeted delivery system for antitumor therapy and the transcytosis mechanism of nanomedicines. He began his study in nanomedicine in 1992 when he read for his PH.D degree. Now more than 260 SCI papers, more than half in the field of nanomedicines, were published, including *J. Control. Release*, *Biomaterials*, *Nanomedicine*: *NBM*, *Molecular Pharmaceutics* and so on, with more than 4000 citations. Besides, as the DDS people, he has developed at least 7 DDS into market, including an oral nanoemulsion system, and some others into clinical study, including 2 types of nanomedicine, one for injection and one for local use.

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长期从事创新药物制剂的研究与开发, 主要研究方向包括: 蛋白多肽药物的给药系统研究、新型纳米给药系统研究、新型抗肿瘤靶向给药系统的研究等。目前承担国家973、自然科学重点、重大专项等重大项目的研究工作。在*J. Controlled Res*., *Biomaterials*, *Nanomedicine*, *Molecular Pharmaceutics* 等本领域国际一流学术杂志上发表论文200多篇, 被引用4000多次; 主编或参编专著与教材15部; 获教育部自然科学一等奖、中国药学会科学技术一等奖、吴阶平-保罗·杨森医药奖一等奖、教育部科学技术奖或自然科学二等奖、中国药学发展奖、教育部跨世纪人才基金奖等, 是全国优秀科技工作者和国务院特殊津贴获得者。带领北京大学药剂学科获得全国第一个药剂学创新团队。负责完成创新制剂研究30余项, 申请国内外发明专利40多项; 开发上市多个新型释药系统, 上市后产生重大经济效益与社会效益。