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Review

Paclitaxel: What has been done and the challenges remain ahead

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ABSTRACT

In recent years, the nanotechnology has offered researchers the opportunity to solve the problems caused by the vehicle of the standard and first formulation of paclitaxel (Taxol®), while maximizing the proven antineoplastic activity of the drug against many solid tumors. Hence, different types of nanocarriers have been employed to improve the efficacy, safety, physicochemical properties and pharmacokinetic/pharmacodynamic profile of this drug. To date, paclitaxel is the unique drug that is marketed in three different nanoplatforms for its parenteral delivery: polymeric nanoparticles (Abraxane®), liposomes (Lipusu®), and polymeric micelles (Genexol®, Nanoxel® and Paclical®). Indeed, a fourth nanocarrier might be available soon, because phase III studies of Opaxio™, a polymeric-conjugated, are near completion. Furthermore, other several nanoformulations are currently in various stages of clinical trials. Therefore, it is only through the critical analysis of clinical evidence from these studies that we can get a more concrete idea of what has been achieved with pharmaceutical nanotechnology so far.

This review attempts to summarize current information available regarding the clinical status and the physicochemical characteristic of different nanocarriers for paclitaxel delivery in cancer therapy. We present an overview of the preclinical and clinical data of these systems including their pharmacokinetics, dose and administration, adverse events and clinical efficacy.

Contents

Abbreviations: CN, chemotherapy naïve; CR, complete response; CrEL, Cremophor EL; DLT, dose limiting toxicities; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DOTAP, 1,2-dioleoyl-3-Trimethylammonium Propane; DTIC, dacarbazine; ET, Endo-Tag1®; FDA, Food and Drug Administration; GEM, Gemcitabine; GFLG, glycylphenylalanylleucylglycine; HPMA, hydroxypropyl-methacrylamide; i.v., intravenous; LEP, LEP-ETU®; MBS, metastatic breast cancer; MPS, mononuclear phagocyte system; MTD, maximum tolerated dose; MTs, microtubules; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, objective response rates; PEG, polyethylene glycol; PFS, progression free survival; PPX, paclitaxel poliglumex; PR, partial response; PTX, paclitaxel; RECIST, response evaluation criteria in solid tumor; TTP, time to progression; US, Unites States.

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1. Introduction

Paclitaxel (PTX), a member of taxane family, is one of the most useful and effective antineoplastic agents for treatment of many forms of advanced and refractory cancers. The success of PTX in these diseases has been due to its singular properties: a broad spectrum of antitumor activity, effectiveness on both solid and disseminated tumors and a unique mechanism of action. It is a microtubule-stabilizing drug that selectively disrupts the microtubule dynamics, thus inducing mitotic arrest that leads to cell death (Derry et al., 1995; Yvon et al., 1999). This drug has played a crucial role in the treatment of ovarian and breast cancer, even as a single agent (McGuire et al., 1989; Nowak et al., 2004). In addition, PTX has also made important progress in the treatment of patients with non-small cell lung cancer (Ramalingam and Belani, 2004). However, significant side effects produced by the vehicle of conventional formulation of PTX have limited its optimal clinical utility as an anticancer agent (Singla et al., 2002). Recently, alternative PTX nanoformulations have been developed to minimize or overcome these limitations.

The objective of this review is to introduce and examine different novel approaches for delivery of PTX that are under clinical investigation in regards to the therapeutic challenges and achievements of these delivery systems, as reported in the literature. Firstly, we present the main structural features, results from preclinical studies and clinical experience of these nanocarriers. Then, we discuss the clinical data and compare them with clinically approved products. Finally, in order to provide new ideas for the development of new drug delivery systems, challenges and future perspectives are highlighted.

1.1. History and origins

PTX is one of the most widely studied and effective therapeutic agent available against a wide range of solid tumors (McGuire et al., 1989). This drug was discovered in the early 1960's, as a consequence of a plant screening program initiated by the National Cancer Institute (NCI) of the United States to identify new substances with cytotoxic activity. Originally, PTX was isolated from the bark of Pacific yew (*Taxus brevifolia*), a slow-growing evergreen shrub or small tree, by Monroe E. Wall and Mansukh C. Wani. These scientists named it "taxol" and, in 1971, they elucidated its chemical structure (Wall, 1998). Although PTX was originally derived from *T. brevifolia*, it was also reported to be present in other Taxus species like European yew (*T. baccata*) or Japanese yew (*T. cuspidata*). However, botanical studies led to determine that Pacific yew was the best source of taxol, because it showed the least variation in drug content (Itokawa, 2003).

In 1979, Susan Horwitz discovered the mechanism of action of PTX and, some years later, the clinical trials were started (Schiff et al., 1979). However, it was not until 1992 that the Food and Drug Administration (FDA) of the United States authorized its commercialization initially for the treatment of ovarian cancer. This agent was developed commercially by Bristol-Myers Squibb, who trademarked the name "Taxol" and assigned the generic name "paclitaxel". Nowadays, its FDA-labelled indications include: Kaposi's Sarcoma (second line), breast cancer (metastatic or non-metastatic), advanced ovarian cancer (first line), microcytic lung malignant neoplasm (metastatic or non-metastatic). Moreover, since PTX exhibits a potent antineoplasic activity, it is often used off-label to treat oesophageal cancer, bladder cancer, prostate cancer, cervical cancer, gastric cancer, head and neck cancer, endometrial malignancy, brain oligodendroglioma and testicular cancer (Fu et al., 2009).

PTX was originally obtained by extracting peeled bark of the Taxus trees. Since the drug was derived from a non-renewable natural source, the method to obtain PTX was initially the major limitation for the use of this one in cancer treatment. Despite achieving increases in the yields of extraction (~0.04% w/w from dried bark), a complete therapy could require approximately 2 gr of the antineoplasic equivalent to 4 trees (Griffon-etienne et al., 1999). Thus, the content of PTX in the trees was too low to supply a sufficient quantity for clinical use. Lamentably, a completely synthetic method for commercial production of PTX has not yet been developed, due to the structural complexity of the molecule. Consequently, PTX has been produced semi-synthetically by the acylation of 10-deacetylbaccatin III, which is a precursor present in the needles of *T. brevifolia* as well as *T. baccata*. This route allows to obtain higher yields than isolating the drug directly from the tree (1 kg of PTX from 3000 kg of needles) and provides a good choice for PTX production (Panchagnula, 1998). Currently, besides semi-synthesis method, PTX can be obtained by plant cell fermentation process whereby the drug is extracted from *Taxus* cell cultures, purified by chromatography and isolated by crystallization (Guo et al., 2006).

1.2. Properties

PTX has become a major point of interest between researchers due to its unusual structure. It is a tricyclic diterpenoid that contains a "taxane" complex ring and an amide function, thus occasionally is considered as a pseudo alkaloid. Wani et al. presented the first structure-activity data showing that both the taxane ring and the C-13 side chain were essential for their cytotoxic activity (Wall, 1998). Moreover, in order to achieve an adequate drug-receptor interaction, the oxetane ring and the homochiral ester chain are important features (Fig. 1) (Guéritte-Voegelein et al., 1991). Besides, the position 2′ of the hydroxyl group plays a relevant role to increase the activity and represents an ideal position for the insertion of functional groups to create prodrugs or polymeric conjugated. In contrast, the hydroxyl group in position C-7 is not essential for the antitumor activity, as it can be esterified, epimerized or even excluded, without significant loss of the activity. Similarly, the acetilation of the C-10 hydroxyl group does not affect their anti-cancer potency. For example, docetaxel, a synthetic analog of PTX, lacks the acetyl group and is more active than Taxol® (Büssing, 2000).

PTX is a white crystalline powder that melts at a temperature of 216–217 °C (Singla et al., 2002). It is a non-ionic molecule and is practically insoluble in aqueous mediums. However, PTX is soluble in several non-aqueous solvents such as methylene chloride (~17.1 mg/mL), ethanol (~39.4 mg/mL), methanol (~50 mg/mL) and dimethyl sulfoxide (~50 mg/mL) (Adler et al., 1994; Richheimer et al., 1992; Singla et al., 2002). The high lipophilicity (theoretical log P = 3.20) and the elevated net energy of PTX results in a limiting aqueous solubility that has been informed as approximately 0.3–0.5 μg/mL (Bernabeu et al., 2016a).

1.3. Mechanism of action

Since the microtubules (MTs) are the major constituent of the mitotic apparatus for all eukaryotic cells, they have become an interesting pharmacological target for cancer therapy (Fong et al., 2013). PTX acts as a chemotherapeutic agent by binding selectively to the subunit β of tubulin proteins, promoting their polymerization and assembly, thereby stabilizing the formation of the MTs. This effect leads to form a dysfunctional mitotic spindle, which causes profound mitotic arrest at G2/M phase and eventually results in cell death through an apoptosis pathway (Band Horwitz, 1992; Snyder et al., 2001). It has also been informed that PTX restricts tumor angiogenesis and induces the expression of genes and cytokines that lead to the inhibition of cellular growth and apoptosis (Taghian et al., 2005). The combination of both anti-proliferative and cytotoxic properties contributes to antitumor efficacy of PTX (Fauzee et al., 2011).

2. Taxol®: the first formulation

In spite of its promising anticancer activity, the development of intravenous PTX's formulation has showed several difficulties due to its poor solubility in water. According to this, the first commercially available formulation containing paclitaxel (Taxol®) is formulated in a vehicle composed of polyoxyethylated castor oil (Cremophor® EL) and dehydrated alcohol in equal parts (Fig. 1). Thus, the current clinical dosage form contains in each millilitre 6 mg of PTX, 527 mg of Cremophor® EL (CrEL) and 49.7% (v/v) of absolute ethanol. This vehicle is associated with a variety of side effects such as hypersensitivity, nephrotoxicity and neurotoxicity, attributable mainly to Cremophor® EL. Importantly, these effects

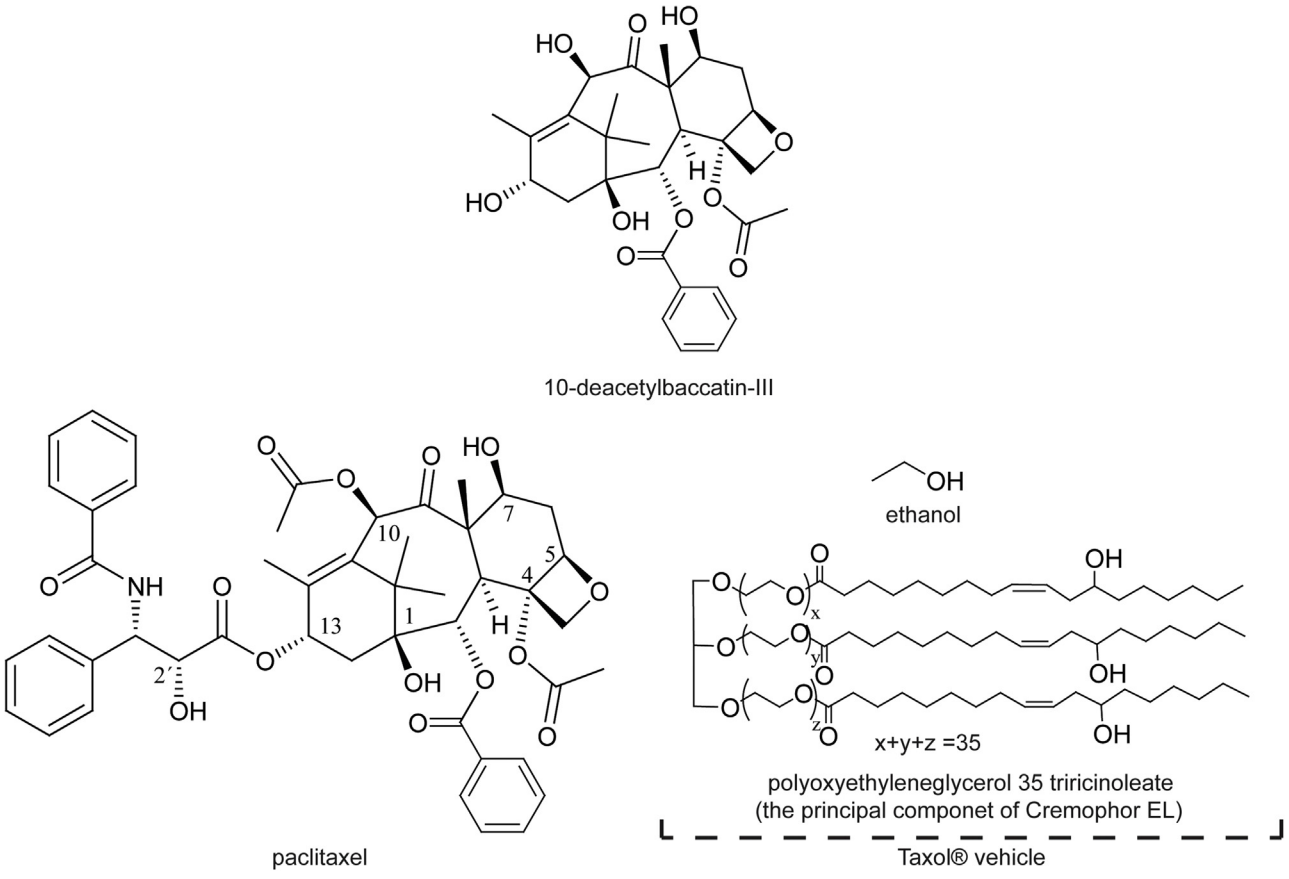

Fig. 1. Chemical structure of 10-deacetylbaccatin-III (a), paclitaxel (b) and Taxol® vehicle (c).

are shown in 25–30% of treated patients (Weiss et al., 1990). This excipient is also used, especially at low concentrations, in the formulation of a wide variety of hydrophobic drugs, such as propofol, cyclosporine A, diazepam and a photosensibilizer, the C8KC (Gelderblom et al., 2001). Thus, the amount of CrEL administered (for an average patient for a single dose administration) with these drugs averages 5 mL, whereas the amount of CrEL in Taxol® per administration is the relatively higher, approximately 26 mL (Gelderblom et al., 2001). Consequently, all patients receiving Taxol® must be premedicated with corticoids, H_2 antagonists and antihistamines to prevent, sometimes fatal, hypersensitivity reactions. Moreover, CrEL has a direct influence over the cells of the pulmonary and vascular endothelium, causing respiratory difficulties and vasodilatation. Severe reactions as bronchospasms and hypotension have been reported (Singla et al., 2002). Finally, since both ethanol and CrEL solubilize the plasticizers, Taxol® requires the use of non-plasticized solution containers such as di(2-ethyl-hexyl) pthalate (DEHP) in the polyvinylchloride (PVC) infusion bags/sets (Rowe et al., 2009).

Since CrEL can cause hypotension and hypersensitive reactions, Taxol® should be slowly infused over a period of 3 to 24 h for doses of 135–175 mg/m^2 every 3 weeks, respectively (Panchagnula, 1998). It should be previously diluted at a final concentration of 0.3 to 1.2 mg/mL, thus depending on the dose volumes ranging from 250 to 1000 mL of physiological solution or dextrose 5% may be required. Also, due the risk of drug precipitation upon dilution, Taxol® should be administered using an in-line filter ($\leq$0.22 μm). A considerable number of clinic studies with Taxol® have been performed to date and have revealed highly variable pharmacokinetics (Gianni et al., 1995; Kearns, 1997). The half-life was found to be in the range of 1.3 and 8.6 h and a large volume of distribution of about 55 L/m^2 was also reported (Wiernik et al., 1986). PTX is more than 90% bound to plasma proteins. The main pathways of elimination are hepatic metabolism followed by biliary excretion. In the liver, metabolism is mediated by the cytochrome P450 (CYP3A4 and CYP2C8) and less than 10% of the dose is excreted intact by urine (Rowinsky and Donehower, 1995). This drug has shown a variable pharmacokinetic pattern depending on the infusion time. Early studies for prolonged infusion times (6 or 24 h) were generally suggestive of linear pharmacokinetics, but become nonlinear for shorter durations infusion (3 h) due to saturable elimination (Sonnichsen and Relling, 1994). The clinical relevance

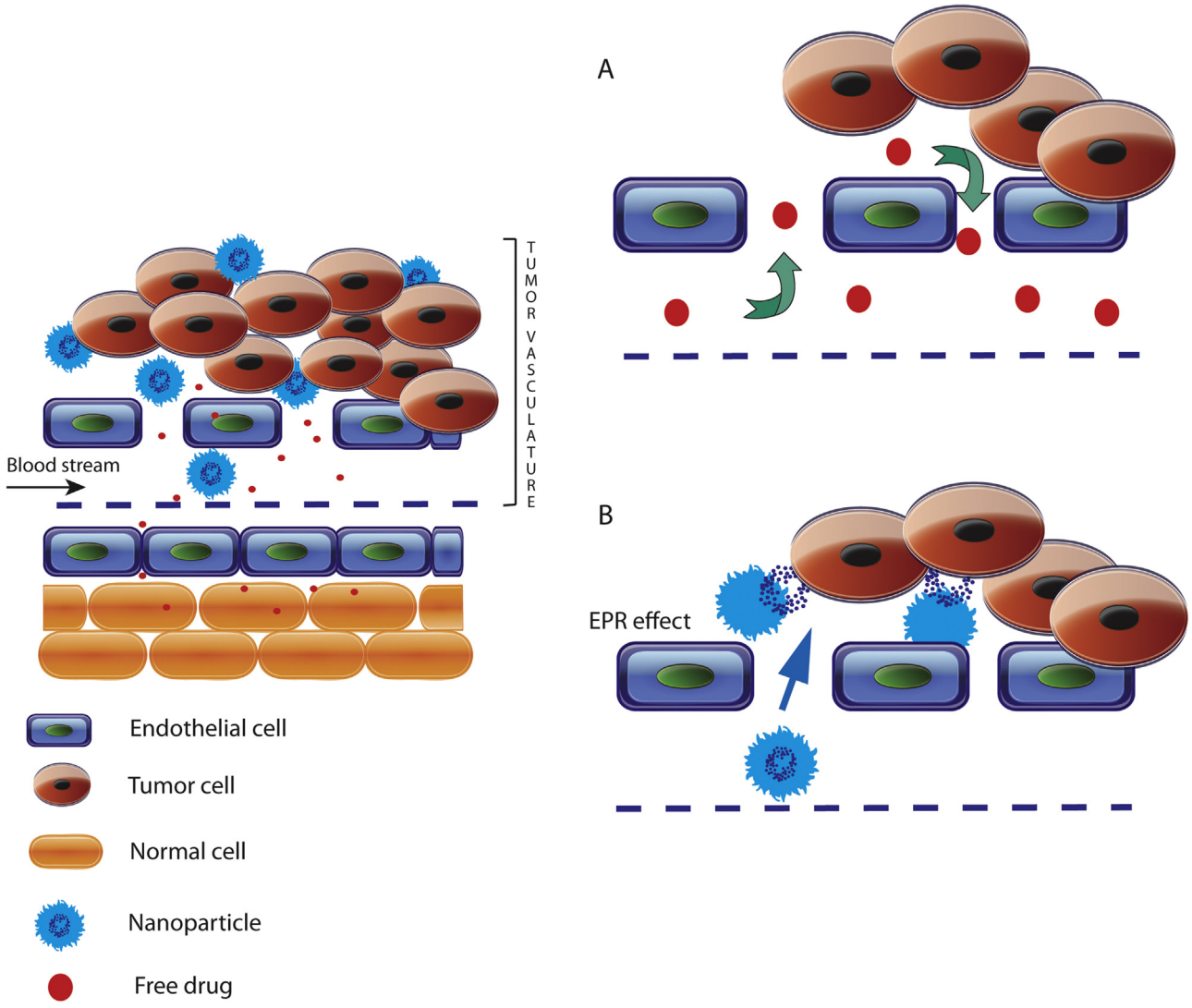

Fig. 2. Schematic representation of enhanced permeability and retention (EPR) effect. Typical blood vessels from solid tumor contain pores of various sizes, which allow nanoparticles and molecules of drug to enter into the interstitium of tumor tissue. (A) However, due to their small size, anticancer drugs can diffuse freely in and out of the tumor site, hence, only low levels of the drug accumulate in tumor. At the same time, significant concentrations of the agent are found in normal tissues. (B) The size of nanoparticles allows them to extravasate through gaps into the extravascular spaces and accumulate inside the tumor where the carrier releases the drug.

of nonlinear deposition of the drug is based on the fact that small changes either in dosage or infusion duration might result in systemic exposure levels of PTX too large, thereby increasing the risk of toxicity. For example, 3-h infusions of PTX at 135 mg/m2 resulted in a mean C_{max} of 3.3 mM and a mean AUC of 10.4 μMh, whereas at 175 mg/m2, the mean C_{max} and AUC values were 5.9 and 18.0 μMh, respectively (Sparreboom et al., 1999). Moreover, various studies have shown that CrEL alters the pharmacokinetics profile of the drug and contribute to the reduction in plasma clearance observed at higher PTX doses. Indeed, PTX may be entrapped within hydrophobic interior of CrEL micelles in plasma, which tend to diminish the free fraction of PTX and, thus making it

Table 1
Main nanocarrier for PTX delivery in clinical trials or on the market.

Platform	Product name/ company	Composition	Size (nm)	Characteristics	Status	Therapeutic indication	Ref.
Liposomes	LEP-ETU®/ NeoPharm Inc.-Insys Therapeutics	DOPC/ cholesterol/ cardiolipin (90:5:5 molar ratio)	150	It shows linear kinetics and allows the administration of higher doses of PTX, with lower adverse effects (lower neuropathy incidence).Premedication is required. It is bioequivalent to the reference formulation of PTX.	Phase II	Breast cancer	Cabanes et al. (1998), Zhang et al. (2005)
	EndoTag-1®/ MediGene	DOTAP/DOPC (cationic liposomes)	180–200	Anti-angiogenic properties against tumoral microvasculature. It targets negatively charged cell-surface molecules expressed by the tumor endothelial cells leading to a reduced tumor growth and perfusion.	Phase II	Breast cancer; Pancreatic cancer; HNSCC	Eichhorn et al. (2010), Schmitt-Sody et al. (2003), Strieth et al. (2008)
	Lipusu®/Luye Pharma Group	Lecithin/ cholesterol	400	Similar *in vitro* and *in vivo* anti-tumoral activity as Taxol®, with lower toxicity. Pharmacokinetics profiles tend to be linear. Premedication is required.	Marketed in China since 2006	Breast cancer NSCLC	Ye et al. (2013)
Nanoparticles	Abraxane; *nab-paclitaxel/Abraxis Bioscience-Celgene*	Albumin	~130	Nab-PTX allow to achieve a 50% higher MTD (300 mg/m^2), and a shorter infusion time (30 min) without the need for premedication. It has linear pharmacokinetics and a greater therapeutic index than Taxol®. Nab (*nanoparticle albumin-bound*) technology, suitable for encapsulation of other drugs (rapamycin, docetaxel).	FDA approval in 2005, EMA approval in 2008	Breast cancer, NSCLC, pancreatic cancer	Ibrahim et al. (2002), Nyman et al. (2005)
Polymer-drug conjugates	Opaxio™; CT-2300; Xyotax®/CTI BioPharma	Poly(glutamic acid)	N.S.	The distribution and the elimination of PTX depend on the cleavage of cathepsin B that catalyzes the release of the drug by the polymer. It is administered as 30-min iv infusion. The $t_{1/2}$ of Opaxio™ is higher than Taxol® (120 h at 233 mg/m^2 and 128 h at 177 mg/m^2).	Phase III/FDA has granted OOD for the treatment of glioblastoma	NSCLC (women); Ovarian cancer	Boddy et al. (2005)
	PNU166945/ Pharmacia-Pfizer	HPMA	N.S.	Severe neurotoxicity observed in rat studies.	Phase I (stopped)	Breast cancer	Terwogt et al. (2001)
	Taxoprexin®; DHA-paclitaxel/Protarga Inc.	docosahexaenoic acid	N.S.	It is formulated in a vehicle containing 80% less CrEL and ethanol on a molar basis than Taxol®. Although PTX AUC values were similar, the conjugate administration produced about 10-fold lower PTX C_{max} values and 5-fold longer apparent half-life compared with Taxol®. Premedication is requested.	Phase III	Metastatic melanoma	Bedikian et al. (2004), Wolff et al. (2003)
Polymeric micelles	Genexol-PM®/ Samyang Biopharmaceuticals	mPEG-b-PDLLA (~3750 Da)	20–50	This formulation permits administration of higher PTX doses than Taxol® without associated increase in toxicities (MTD of 390 mg/m^2). In phase I studies, it showed lower AUC and C_{max} than conventional PTX and a shorter plasma half-life (11.0–12.7 h).	Marketed in South Korea since 2007	Breast cancer NSCLC Ovarian cancer	Kim et al. (2001, 2004)
	Nanoxel®/Dabur Pharma Ltd	PVP-b-PNIPAAM	80–100	It is activated by the low pH level of the tumor microenvironment: in acidic conditions, PNIPAAM is degraded and the release of the free drug occurs. It has linear pharmacokinetics and can be administered without premedication.	DCGI approval in 2008	Breast cancer, NSCLC and AIDS-related KS	Madaan et al. (2013)
	NK105/ NanoCarrier™	PEG-P(aspartate)	85 (20–430)	It is administered as a 1-h i.v. infusion, without premedication. At the recommended phase II dose (150 mg/m^2), NK105 showed more than 15-fold higher plasma AUC and a 26-fold lower clearance than Taxol®.	Phase III	Stomach cancer Breast cancer	Hamaguchi et al. (2007)
	Paxceed®/ Angiotech Pharmaceuticals Inc	mPEG-PDLLA	N.S.	PTX has showed its usefulness as an agent that stops growth of cells and blocks certain types of cell function associated with RA.	Phase II/ completed	Rheumatoid Arthritis	van Gaal and Crommelin (2015)

AUC, the area under the plasma concentration-time curve; C_{max}, maximum drug concentration; DCGI, Drug Controller General of India; DOPC, 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine; DOTAP,1,2-Dioleoyl-3-Trimethylammonium Propane; FDA, Food and Drug Administration; KS, Kaposi sarcoma; EMA, European Medicine Agency; HNSCC, head and neck squamous cell carcinoma; HPMA, *N*-(2-hydroxypropyl) methacrylamide; mPEG-PDLLA, monomethoxy- poly(ethylene-glycol)-*block*-poly(D,L-lactide); N.S., not stated; NSCLC, non-small cell lung cancer; ODD, orphan drug designation; PVP-b-PNIPAAM, poly-(vinylpyrrolidone)-b–poly-(*N*-isopropyl acryl-amide); poly(DL-lactide)-block-methoxy polyethylene glycol.

less available for distribution to tumor (ten Tije et al., 2003; Wall, 1998).

Generally, the main reason for discontinuation of PTX is not the lack of efficacy, but toxicity (Marupudi et al., 2007). Peripheral sensory neuropathy is the most commonly reported neurotoxic effect of PTX which is dose- and infusion-duration related. (Scripture et al., 2006). The symptoms may begin as early as 24–72 h after administration and include numbness, paresthesias and burning pain in a glove and-stocking distribution. Because CrEL can also cause neurotoxicity, PTX-induced neuropathy may be at least, in part, contributed by the vehicle formulation (Gelderblom et al., 2001). The other major adverse effect is myelosuppression, which mainly consists of neutropenia and usually becomes the dose-limiting toxicity (Legha et al., 1986).

3. The advent of nanotechnology in cancer

In the past few years, the application of nanotechnology to the administration and delivery of drugs has caused a special impact in modern medicine, giving rise to a new concept: nanomedicine. The main objective of this new field is employing nano-sized materials to diagnosis, prevention and treatment of diseases. In spite of the fact that the concept of nanomedicine is relatively recent, nanotechnology has been applied in the development of drug delivery systems for decades. Nanosized carrier exhibits countless advantages, some of them related with i) improvements in drug aqueous solubility, chemical stability, efficacy and safety ii) prolonged drug biodistribution after an intravenous administration and iii) reduction of side effects (Bernabeu et al., 2016b).

In cancer chemotherapy, nanomedicine has a special interest, because the nanocarrier enables the preferential delivery of drugs to the tumoral site, introducing the concept of Enhanced Permeability and Retention (EPR) effect, a particular phenomenon of solid tumors as a result of their anatomical and physiopathological characteristics that makes them different from normal tissues (Fig. 2). The endothelial cells from malignant blood vessels present larger gaps than normal blood vessel junctions (5–10 nm), that range from 100 nm to several hundred nanometers between them. In consequence, solid tumors exhibit selective extravasation and retention of drug-loaded nanocarriers. Moreover, these nanosvehicles are cleared by the lymphatics in healthy tissues. However, in solid tumors most of these lymphatic vessels are collapsed and compressed, therefore the nanosystems are selectively retained (Fang et al., 2011; Wang et al., 2012). Ideally, nanocarriers, such as micelles or liposomes, by virtue of their size, can escape from the vasculature through the leaky endothelium overlying the tumor and then accumulating preferentially in solid tumors (Maeda et al., 2009).

As one of the most lethal diseases all over the world, cancer has always been in the limelight of nanomedicine. It is well known that conventional antineoplasic agents exhibit lack of specificity, as they exert their activity on both malignant and healthy tissues. Furthermore, solid tumors present certain physiopathological barriers associated with decreased cellular drug accumulation. Early clinical studies with liposomes as nanocarriers for cancer treatment were promising (Northfelt et al., 1996). In more than ten Phase I/II clinical trials that included patients with AIDS-related Kaposi's sarcoma, higher response rates with significant lower toxicities were observed in the group of doxorubicin loaded liposomes as compared to the free drug (Cagel et al., 2016). For these reasons, nanotechnology has been widely and rapidly integrated to cancer treatment. Additionally, the above mentioned EPR effect, also known as passive targeting, partially justified its quick integration. Data from animal models have shown that the drug concentrations found in tumor after the administration of the nanocarriers are ranged from 10 to 50 times higher than in healthy tissue (Iyer et al., 2006). Of note, these models differ from clinical tumors in several key aspects that seem to make EPR more pronounced than in human patients (Nichols and Bae, 2014).

On the other hand, in order to achieve similar concentrations and to reach the site of action, it is necessary that these vehicles remain an adequate time in the bloodstream. To this end, certain defence mechanisms in the organism, such as the mononuclear phagocyte system (MPS) must be avoided. The MPS participates in the uptake and rapid removal of these nanosystems from the bloodstream, decreasing their circulation time and efficacy

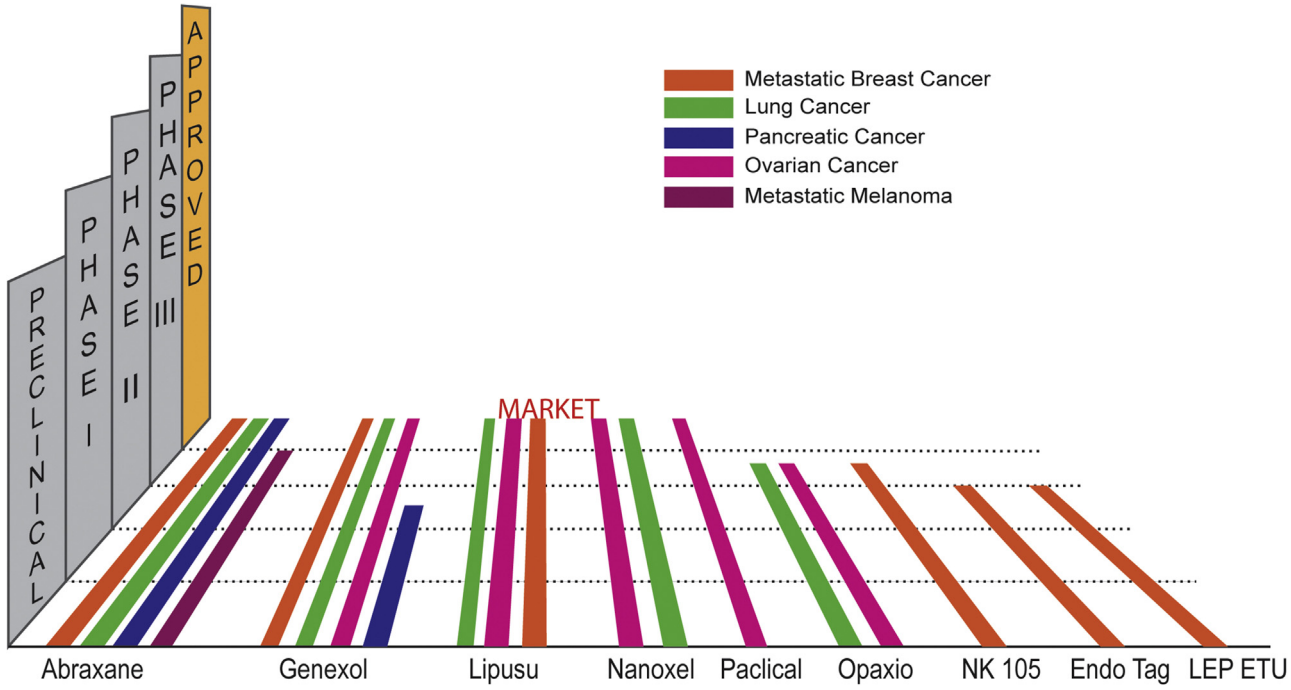

Fig. 3. Examples of nanotechnological platforms for PTX delivery that are either clinically approved, or at various stages of clinical trials for cancer therapy.

(Gustafson et al., 2015). The first step in the clearance of nanocarriers is their recognition as strange particles by plasmatic opsonins, making them visible to the phagocytic cells. After the opsonization, phagocytosis enables to destroy or eliminate the circulating particles. Nonetheless, modifications in the surface of these particles with hydrophilic polymers, such as poly(ethylene) glycol (PEG), poloxamers, poloxamines, *etc.*, may protect them from opsonisation and avoid their elimination by the MPS cells (Owens and Peppas, 2006). In this sense, the camouflage of nanotransporters with PEG or PEGylation is the most utilized and studied strategy to avoid the recognition by the immune system (Hama et al., 2015). PEGylation allows to reduce the absorption of specific proteins on the surface of the particles, delaying their degradation and increasing the mean residence time of the drug in the bloodstream (Molino et al., 2012; Walkey et al., 2012). In this regard, it must be taken into account that the molecular weight of the chosen PEG affects in a different extent the adsorption percentage of these proteins (Gref et al., 2000). The properties of PEG that justify its utilization are: i) its elevated aqueous solubility, ii) high chain flexibility, iii) low toxicity and iv) low immunogenicity. The decoration on the surface of the particle with PEG can be achieved by an adsorption process or by covalent bonding (Owens and Peppas, 2006). So far, numerous nano-sized PEGylated systems have been developed, some of which are already in the pharmaceutical market, evidencing the importance of this type of materials (Etheridge et al., 2013).

4. Nanotechnology-based paclitaxel formulations

Considering the potential of PTX as an antineoplasic agent, several nanosystems were designed to improve its vehiculization (Table 1). Some PTX loaded nanoformulations have achieved an enhancement in the solubility of the drug, while avoiding the use of Cr EL. Different PTX-based nanotechnological platforms can be mentioned: polymeric nanoparticles (Abraxane®), polymeric conjugates (Xyotax), polymeric micelles (Genexol-PM, NK 105) and liposomes (LEP-ETU), some of them approved or still in clinical trials (Fig. 3) (Boddy et al., 2005; Fetterly et al., 2008; Kim et al., 2004; Miele et al., 2009). These formulations will be described below.

One of the most extraordinary characteristics of these systems is their size, giving them unique properties that are not observed in individual molecules. In addition to avoiding the use of Cr EL, the advantages of these nanonystems, when compared to conventional chemotherapy, rely on their possibility of increasing the intratumoral concentration of antineoplasic drugs, decreasing their toxicity and maintaining the therapeutic efficacy for a prolonged period, due to their higher mean residence time in the bloodstream (Fetterly et al., 2008).

4.1. Nanoparticles

4.1.1. Abraxane®: the alternative formulation

PTX is also available in a different form marketed under the name Abraxane®, also known as ABI-007 during development (Abraxis/Celgene). This novel formulation is formed using the nanoparticle albumin-bound (*nab*®) technology that complexes PTX with human albumin without forming covalent bond. Each vial consists of lyophilized cakes containing 100 mg of PTX and approximately 900 mg of human albumin (Celgene, 2016). Upon reconstitution to 50 mg/mL, the albumin-stabilized PTX particles have an average size of 130 nm. After their intravenous administration, however, nanoparticles are quickly dissociated into smaller albumin-PTX complexes whose size is approximately 8 nm (Min et al., 2015). Moreover, due to the negative zeta potential (−31 mv) imparted by the human albumin, Abraxane® shows a high colloidal stability (Celgene, 2016).

4.1.2. Indications of Abraxane®

Abraxane® was initially approved by FDA in 2005 for treatment of metastatic breast cancer. In 2012, the FDA approved Abraxane® to treat locally advanced or metastatic non-small cell lung cancer. More recently, Abraxane® was added to gemcitabine (GEM) for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. This formulation has shown several advantages by eliminating CrEL from its formulation, for example, reducing the infusion volume and administration time (30–40 min), eliminating the need of pre-medication and avoiding the use of special infusion sets (bag, tubing and in-line filters). Furthermore, it permits a higher dose of PTX to be administered with a similar toxicity in comparison to Taxol® (Desai, 2012).

4.1.3. Preclinical assays

The mentioned benefits were supported, at least initially, by preclinical models. In a study using mice bearing human tumor xenograft of lung breast, ovarian, prostate and colon cancers, Abraxane® has shown less toxicity compared with equal doses of CrEL-based PTX (Desai et al., 2006). Moreover, *nab*-PTX had greater antitumor efficacy than Taxol® for breast and ovarian models at equitoxic doses (Abraxane®, 30 mg/kg/d; Taxol®, 13.4 mg/kg/d). Importantly, the intratumoral concentration of PTX was 33% higher for *nab*-PTX than for Taxol® in mice (n = 63 for each arm) with human breast tumors, following equal doses of PTX (20 mg/kg i.v.).

4.1.4. Clinical trials

New medications require substantial evidence of efficacy derived from adequate clinical trials before their approval for use in patients. To evaluate the efficacy and safety of drug in oncology studies, in particular for solid tumors, a number of endpoints are measured. Overall survival (OS), for example, is the time from randomization until death from any cause. FDA considers OS as a direct measure for demonstrating clinical benefit (Pazdur, 2008). Other efficacy endpoints such as Progression Free Survival (PFS) and Time to Tumor Progression (TTP) have also been accepted as markers of clinical benefit for drug approval. PFS is defined as the time from randomization to time of progressive disease or death. The definition of TTP is similar, but this one does not include deaths; thereby, PFS is often the requested primary endpoint by regulatory agencies. On the other hand, TTP is used as the primary endpoint in trials in which the majority of deaths are not expected to be related to the cancer.

Unlike OS and TTP, which must be evaluated in randomized trials, response rates can be accurately assessed using a single-arm trial. Response rate measures the changes in tumor mass, growth (progression) or shrinkage (response) and it is often assessed using the RECIST criteria (Response Evaluation Criteria in Solid Tumor) (Eisenhauer et al., 2009). RECIST guideline provides a simplified set of criteria for identifying four types of tumors response: complete (disappearance of all clinical evidence of disease), partial (at least 30% reduction in size of all measurable tumors), stable disease and progressive disease (≥20% increase in size of tumors). Another commonly used endpoint in oncology trials is objective response rate (ORR). The FDA has defined ORR as the sum of partial responses (PR) and complete response (CR), hence ORR is a direct measure of the drug's antitumor activity (Food and Drug Administration, 2007). In selecting an endpoint for a trial, this one should accurately assess the efficacy of the drug being evaluated.

A first phase I trial was performed by Ibrahim et al. to examine the pharmacokinetic properties, toxicity profile and maximum tolerated dose (MTD) of PTX following Abraxane® administration

(Ibrahim et al., 2002). The study was conducted on 19 patients with melanoma and breast cancer who received doses of Abraxane® ranging from 135 to 375 mg7m^2 over 30-min every 3 weeks. The authors determined the MTD to be 300 mg/m^2, whereby sensory neuropathy and mucositis became the dose-limiting toxicities. In contrast to Taxol®, pharmacokinetic parameters of the nanoparticle formulation display a linear trend. Sparreboom et al. compared the pharmacokinetic of PTX in 27 patients following administration of Abraxane® (260 mg/m^2 over 30 min) and Taxol® (175 mg/m^2 over 3 h) (Sparreboom et al., 2005). In spite of the difference in the PTX doses, AUC_∞ for *nab*-PTX (14 789 ng h/mL) was similar to that for Taxol® (12 603 ng h/mL). Also, both formulations showed similar half-life: 21.6 h for *nab*-PTX and 20.5 h for Taxol®.

On the other hand, clearance and volume of distribution were significantly higher for Abraxane® than for Taxol® (21.13 versus 14.76 L/h m^2, and 663.8 versus 433.4 L/m^2, respectively), indicating that Abraxane® was extensively distributed and bound to tissue and extravascular proteins. Linear pharmacokinetic was also observed after weekly administration of Abraxane® over a dose range of 80–200 mg/m^2 (Nyman et al., 2005). Weekly Abraxane® therapy was relatively well-tolerated and demonstrated antitumoral activity in patients previously exposed to PTX. The MTDs were identified as 100 and 150 mg/m^2 for heavily and lightly pretreated patients, respectively. Grade 4 neutropenia was the dose-limiting toxicity (DLT) for heavily pre-treated group, while grade 3 peripheral neuropathy was the DLT for the other one. The authors concluded that Abraxane® seems to be an ideal agent for use in dose-dense regimens. Interestingly, weekly Taxol® therapy at doses ranging from 80 to 100 mg/m^2 as a 1-h infusion has been well tolerated, causing minimal myelosuppression; however, peripheral neuropathy prohibited dose escalation above 100 mg/m^2 (Chang et al., 1997; Seidman et al., 1998).

In other phase I study, forty-three patients with squamous cell carcinoma of head and neck were treated intra-arterially with Abraxane® to examine a possible locoregional treatment (Damascelli et al., 2001). The dose-limiting toxicity was myelosuppression consisting of grade 4 neutropenia. Importantly, practically the same dose used in systemic treatments can be administrated over 30 min through a microcatheter. Thus, ABI-007 was infused selectively into the branches of the internal carotid artery at the MTD of 270 mg/m^2.

4.1.4.1. Metastatic breast cancer. Because of the well established activity of PTX monotherapy in patients with metastatic breast cancer (MBC), the safety and efficacy of Abraxane® for the treatment of this patient population was initially studied. In an early phase II study, sixty-three women with MBC were treated with Abraxane® at 300 mg/m^2 by intravenous infusion every 3 weeks (Ibrahim et al., 2005). The main toxicities were two: i) grade 4 neutropenia (24%) and ii) grade 3 neuropathy (11%). Median time to progression (TTP) was 26.6 weeks and median survival was 63.6 weeks. Grade 4 neutropenia occurred in 24% of patients, and grade 3 sensory neuropathy occurred in 11% of patients. Overall responses was 48% (2 patients had complete response and 28 patients had partial response) for all patients and 64% for those who received *nab*-PTX as first-line therapy. In addition, responses rates were 20% and 22% for patients who previously failed to respond to 1 or 2 chemotherapeutics regimens, respectively. These response rates are closer to those reported for Taxol® in this setting (Nabholtz et al., 1996; Winer et al., 2004). Thus, phase III trials with Taxol® at a dose of 175 mg/m^2 established response rates from 26 to 29% in patients with MBC who had failed prior chemotherapy for metastatic disease.

Following these results, Gradishar and col. initiated a phase III study in which the primary objective was to demonstrate no inferiority of nab-PTX when compared with Taxol® (Gradishar et al., 2005). This trial randomized 454 patients between the arms, with 229 in the Abraxane® arm. They were treated with either Abraxane® at a dose of 260 mg/m^2 i.v. over 30 min or Taxol® 175 mg/m^2 i.v. over 3 h (both administered every three weeks). . Abraxane® arm demonstrated significantly higher response rate (33% *vs* 19%; $p = 0.01$) and longer median time to progression (23 *vs* 16.9 weeks; $p = 0.006$) than Taxol® arm. Although no significant difference in OS was observed in first-line patients, the difference was statistically significant in those patients who received Abraxane®, compared with Taxol®, as second-line or greater therapy (56.4 versus 46.7 weeks, respectively; P = 0.024). Patients in both group showed similar treatment compliance because they received more than 90% of the planed chemotherapy. Also, the adverse event-related discontinuations were infrequent. Of note, no statistically differences in quality of life were noted between the two treatment groups. Abraxane® arm was associated with significantly fewer grade 4 neutropenia (9% *vs* 22%), but more grade 3 neuropathy (10% *vs* 2%). These clinical data led to the FDA approve Abraxane® for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Also, results from a phase II trial in chinese patients provided additional evidence to demonstrate the efficacy of Abraxane® in this setting (Guan et al., 2009).

Subsequently, several studies have examined different schedules, doses or drug combinations in order to optimize the *nab*-PTX-based therapy for MBC (Blum et al., 2007; Gradishar et al., 2009). In a phase II study, weekly *nab*-PTX administration (100 or 125 mg/m^2) was found to be safety and efficacious schedule for treatment of MBC (Blum et al., 2007). In a recent phase II trial, 300 patients were randomly assigned to receive one of the following four treatments: *nab*-PTX 300 mg/m2 every 3 weeks, 100 mg/m2 or 150 mg/m2 administered weekly or docetaxel 100 mg/m^2 every 3 weeks (Gradishar et al., 2009). The results indicated a trend toward increased ORR, comparing both weekly Abraxane® doses (45% to 49%) with docetaxel (35%), but this did not reach statistical significance. On the other hand, Abraxane® 150 mg/m2 arm showed significantly longer PFS than docetaxel (12.9 *vs* 7.5 months; $P = 0.0065$). OS was 33.8 months with Abraxane® given 150 mg/m2 compared with 22.2, 27.7 and 26.6 months in patients receiving Abraxane® 100 mg/m2, 300 mg/m2 and docetaxel, respectively. Additionally, dose reductions occurred more frequent in Abraxane® 150 mg/m2 arm (47%), compared with the other treatment arms. There were no significant differences between Abraxane® given every 3 weeks and docetaxel arm in terms of ORR and PFS. Weekly administration of Abraxane® was thus more active compared with docetaxel given tri-weekely. Neutropenia occurred more frequently and was more severe in patients who received docetaxel compared with any doses of *nab*-PTX. However, neuropathy was most frequent in patients treated with Abraxane® at 150 mg/m^2 and 300 mg/m^2. The authors concluded that *nab*-PTX 150 mg/m^2 weekly may be an alternative to docetaxel in the first-line treatment for patients with MBC.

These results leaded to the development of a recent phase III study comparing either Abraxane® (150 mg/m^2) or ixabepilone (16 mg/m^2), once-per-week to Taxol® (90 mg/m^2) once per week (Rugo et al., 2015). All agents were given in combination with the monoclonal antibody bevacizumab. In this trial, 799 patients were enrolled and randomly assigned. Curiously, Abraxane® was inferior to Taxol® for tumor response (27% *vs* 38%), OS (23.5 months *vs* 26.5 months) and PFS (9.3 months *vs* 11 months), but these difference did not reach the lowest level of significance. Treatment with *nab*-PTX showed significantly greater haematological and non-haematological toxicity than Taxol®. Thus, the dose of Abraxane® used in this study is clearly not feasible and resulted in dose reductions and discontinuation. The authors

concluded that toxicity with Abraxane® was unacceptably high and there is no evidence that this newer agent is superior.

Traditionally, the administration of neoadjuvant chemotherapy is often associated with a rapid reduction in tumor size in order to facilitate surgical removal (Connolly and Stearns, 2013). A phase III trial was initiated in 2012 to evaluate Abraxane® as adjuvant therapy for patients with early breast cancer (Untch et al., 2016). A total of 1206 patients received *nab*-PTX 125 mg/m^2 (reduced from the initial dose of 150 mg/m2 after a protocol amendment due to neurotoxicity) or Taxol® 80 mg/m^2, each given weekly, followed by epirubicin/cyclophosphamide. Abraxane® achieved significantly higher pathological CR than Taxol® (38% *vs* 29% $P = 0.001$). More importantly, the largest difference was noted in the triple negative breast cancer subpopulation (n = 276, 23%) in which nab-PTX showed 48.2% versus 25.7% with Taxol®. Abraxane® was associated with significantly more grade 3/4 peripheral sensory neuropathy compared with Taxol® (10% *vs* 3%). In order to confirm whether the higher pathological CR translates into improved disease-free survival, long-term follow-up data are needed, but they will not be available before 2018 (Untch et al., 2016).

4.1.4.2. Lung cancer. Lung cancer accounts for more deaths than any other cancer in both men and women, with a five-year survival rate of about 17% (American Cancer Society, 2016). PTX, as a single agent, is an active drug in advanced non-small-cell lung cancer (NSCLC). A phase II study evaluating single-agent Abraxane® at 260 mg/m^2 in chemotherapy-naïve, advanced-stage NSCLC patients (n = 43) demonstrated an ORR of 16% (Green et al., 2006). TTP was 6 months, and median time survival was 11 months. Abraxane® produced minimal hematologic toxicity. In addition, based on the results of a phase I trial that evaluated the weekly administration of *nab*-PTX, Rizvi et al. conducted a small study in patients with untreated advance NSCLC (Rizvi et al., 2008). A total of 40 patients were treated with Abraxane® at 125 mg/m^2. In this trial the response rate was 30% and the median survival was 11 months. They also reported sensory neuropathy and fatigue as the most common non hematologic toxicities. A compressive review of Taxol® in the treatment of advanced NSCLC at doses ranging from 175 to 225 mg/m2 every three weeks showed that it is effective with an ORR of 28.5% and median survival of 6–11 months (Socinski, 1999).

Since the combination of Taxol® and carboplatin has been reported to be safe and have high activity in NSCLC, some phase II studies employing Abraxane® and carboplatin have been performed (Reck et al., 2003). Recently, Okuma et. al conducted a phase II trial to explore the efficacy of first line chemotherapy with Abraxane® (100 mg/m^2) plus carboplatin in 37 elderly patients with NSCLC (Okuma et al., 2016). However, the study was early interrupted, because two treatment-related deaths and 1 life-threatening severe adverse event. Similarly, another phase II trial for elderly patients with advanced small cell lung cancer was closed, because of slow accrual and frequent doses adjustment (Grilley-Olson et al., 2015). Similar results were also obtained in other phase II study in patients with advanced urothelial cancer. The combination of Abraxane® (220 mg/m^2), carboplatin and GEM was poorly tolerated showing severe adverse events, which required removed 11 patients from study (Alva et al., 2014).

4.1.4.3. Ovarian cancer. On the other hand, PTX is also commonly used in conjunction with platinum (cisplatin or carboplatin) during initial treatment of advanced ovarian cancer (McGuire et al., 1989). Despite a favourable response to combined survery-chemotherapy approach, the majority of women will experience relapse (Teneriello et al., 2009). Patients with recurrent ovarian cancer who previously responded to platinum therapy can be re-challenged with the same agent, but for these patients there is no agreed-on second line treatment. Teneriello et al. sought to determine the response rate to re-challenge with taxane based on therapy using Abraxane®. Thus, 44 patients with platinum-sensitive disease (any stage) were treated with Abraxane® 260 mg/m^2 by intravenous infusion over 30 min every three weeks for six cycles (Teneriello et al., 2009). The ORR was 64% with 15 patients achieving complete responses CR and 13 of them had partial responses PR. The most frequent grade 3 to 4 treatment-related toxicities were neutropenia (24%) and neuropathy (9%). The estimated median PFS was 8.5 months. In a study using Taxol® as second-line chemotherapy for platinum-sensitive patients with recurrent disease, the median PFS was 9 months and median survival 25.8 months (Cantù et al., 2002). Importantly, development of multiple drug resistance is responsible for the majority of deaths among patients with advanced stages (Kampan et al., 2015).

Coleman et al. conducted a single arm phase II study investigating the efficacy of Abraxane® (100 mg/m^2) monotherapy in patients who had platinum- and taxane-resistant ovarian cancer (Coleman et al., 2011). Of the forty seven patients evaluated for response, 11 were indentified with confirmed response (1 complete response and 10 partial responses). The median PFS was 4.5 months and OS was 17.4 months. There were no grade 4 toxicities and grade 3 neurotoxicity occurred in 1 patient (2%). The most common reason for treatment discontinuation was disease progression occurring in 42 (82%) patients, while treatment associated toxicity was reported in three women. The investigators concluded that these parameters are quite notable since 70% of the study population had recurred within 3 months of primary treatment completion. Similarly, Markman et al. studied weekly administration of Taxol® (80 mg/m^2) in patients with ovarian cancer refractory to platinum and PTX (Markman et al., 2002). The ORR was 25% (13 patients) and median OS was 58 weeks. Grade 3 to 4 peripheral neuropathy was developed by 3 patients, while five women were forced to discontinue therapy because excessive toxicity.

4.1.4.4. Melanoma. Currently, melanomas are the most severe form of skin cancer with high incidence of metastasis and resistance to conventional chemotherapy (Fauzee et al., 2011). Taxol® has showed beneficial, although limited, effects over this disease. In four clinical trials in mostly chemotherapy-naive (CN) patients with metastatic melanoma, Taxol® was found to be effective with a response rate of 16% (Bedikian et al., 2004).

Hersh et al. conducted a phase II study investigating the use of weekly Abraxane® (100 mg/m^2) in previously treated (n = 37) and CN (n = 37) patients with melanoma (Hersh et al., 2010). The median PFS were 3.5 and 4.5 months in the group of pre-treated and CN patients, respectively. The median OS was 12.1 months for previously treated patients and 9.6 months for CN patients. The OR rate was 2.7% (1 of 37 patients) for the previously treated cohort and 21.6% (8 of 37patients) for the CN cohort. These results demonstrated that Abraxane® had antitumoral activity in CN patients, but failed to show this activity in patients who have been previously treated. Similarly, Kottschade et al. presented the results from phase II trial utilizing a combination of carboplatin and Abraxane® (100 mg/m^2) administered on a weekly regimen (Kottschade et al., 2011). The response rates were 25.6% (1 CR and 9 PRs) and 8.8% (3 PRs) in the CN and pre-treated patients, respectively. The most common toxicities were sensory neuropathy, leukopenia, and neutropenia.

A subsequent randomized phase III study compared the efficacy of *nab*-PTX versus dacarbazine (DTIC) in 529 CN patients with stage IV. Abraxane® was given at 150 mg/m^2 on days 1, 8 and 15 every 4 weeks and DTIC was given at 1000 mg/m^2 every 3 weeks. The results were reported at the Society for Melanoma Research

meeting in 2012 and showed that *nab*-PTX significantly improved the median PFS compared to DTIC arm (4.8 *vs* 2.5 months; $p = 0.044$). In contrast, the ORR (15% for *nab*-PTX arm *vs* 11% for DTIC arm) and OS (12.8 with *nab*-PTX and 10.7 months with DTIC) did not show statistical difference between the two arms. Similar to other pivotal Abraxane® clinical trials, the most common grade 3 toxicity was neuropathy (Abraxane®: 25% *vs* DTIC: 0%) and neutropenia (Abraxane®: 20% *vs* DTIC: 10%) (Hersh et al., 2012).

4.1.4.5. Metastatic pancreatic adenocarcinoma. Metastatic pancreatic adenocarcinoma is an aggressive and lethal disease. Unfortunately, more than half of patients are diagnosed at a distant stage, for which 1- and 5-years survival is 15% and 2%, respectively (American Cancer Society, 2016). GEM-based therapy has been considered the standard first-line treatment for several years (Von Hoff et al., 2013, 2011). Results from randomized phase III trials using this agent have reported 1-years survival of 17 to 23% (Burris et al., 1997; Moore et al., 2007).

Von Hoff et al. conducted a phase I/II study to determine the efficacy and safety of GEM (1000 mg/m^2 on day 1, 8, and 15 every 28 days) in combination with Abraxane® as first-line therapy for metastatic pancreatic cancer (Von Hoff et al., 2011). In the patients treated at the MTD of 125 mg/m^2 of Abraxane® (n = 44), the median PFS and OS were 7.9 and 12.2 months, while the 1-year survival was 48%. Of note, these results are among the highest reported, even when comparing to those from newer chemotherapy regimens. For example, a median OS of 11.1 months was observed in patients who were treated with fluorouracil, leucovorin, irinotecan, and oxaliplatin regimen (FOLFIRINOX) (Conroy et al., 2011).

These phase II data were further supported by a phase III trial comparing the combination of GEM and Abraxane® versus GEM monotherapy. A total of 861 patients were randomized to receive Abraxane® plus GEM (n = 431) or GEM (n = 430) alone. Abraxane®/GEM arm showed clinically meaningful improvements in three efficacy endpoints: median OS (8.5 *vs* 6.7 months), PFS (5.5 *vs* 3.7 months) and rate of PFS at 1 year (35% *vs* 22%) (Von Hoff et al., 2013). Unfortunately, quality-of-life was not measured. The most common grade ≥3 toxicities with Abraxane®/GEM versus GEM were neutropenia (38% *vs* 27%) and neuropathy (17% *vs* 1%). On the basis of these results, Abraxane® plus GEM has become in a standard treatment option for patients with advanced pancreatic cancer.

4.1.5. Advantages and disadvantages of Abraxane®

Abraxane® was developed to take advantage of the antitumoral activity of PTX while minimizing or eliminating the toxicity typically associated with Cremophor®. Consequently, the patients receiving treatment with Abraxane® do not need hypersensitive premedication or long duration infusions, making an easier and safer way to administer the drug. This is not a minor point, because patients spend less time in hospital and the risk of hypersensitive reactions is markedly reduced. In fact, this has been the main purpose of a great number of research studies for many years. At this point, we therefore agree with the assertion that states that Abraxane® is a successful solution. This novel formulation has shown to be efficacious in the treatment of various cancers, but its superiority over standard PTX formulation has not yet been totally demonstrated.

As mentioned above, Phase III studies have showed that Abraxane® required a 50% higher dose than Taxol® to achieve a better tumor response and PFS (Gradishar et al., 2005). Also, no differences in OS were observed in patients with MBC (Fig. 4). The OS is the gold standard primary end point to evaluate the outcome of any drug that is assessed in oncologic clinical trials (Driscoll and Rixe, 2009). Of note, nanotechnology platforms such as Abraxane®, have been designed to facilitate drug delivery to the tumor site by exploiting the EPR effect. However, because it is a highly variable pathophysiological phenomenon with large inter- and intra-individual differences, the treatments with nab-PTX and other nanomedicines have had little impact in terms of prolongation of OS in patients with cancer (Ojha et al., 2015; Shen et al., 2015). In addition, while this mechanism has certainly been established in small animal models, similar evidence is lacking from human. This evidence comes mostly (if not exclusively) from implanted tumors with limited data on EPR in metastatic lesions in both mice and patients (Prabhakar et al., 2013). Thus, to know whether a tumor is likely to respond to an EPR effect-based therapy, complete understanding of EPR process and its biological implications are needed (Prabhakar et al., 2013). Moreover, since cancer is a highly heterogeneous set of diseases, there is significantly variation within and between different tumor types (Know et al., 2012). In this sense, an image-guided patient selection

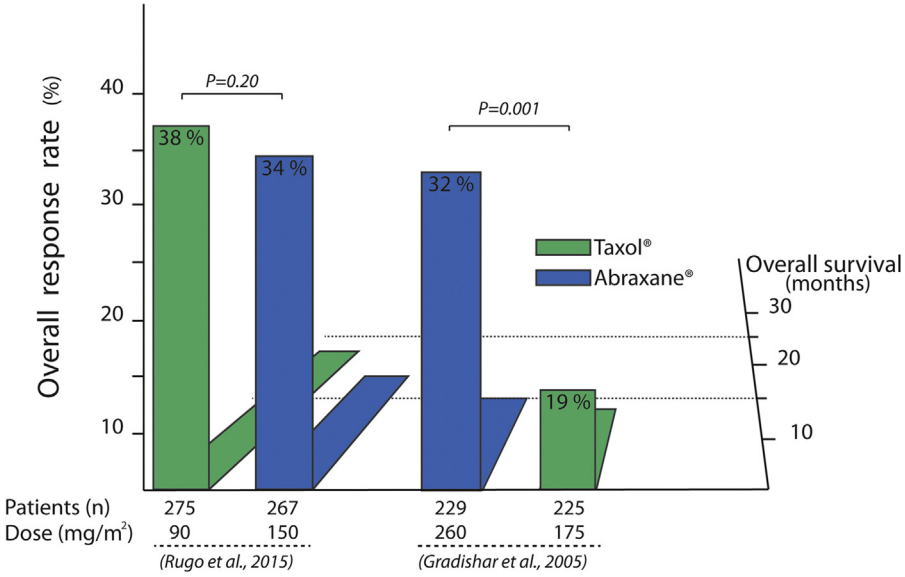

Fig. 4. Overall response rate and overall survival of two randomized Phase III comparative studies of Abraxane® versus Taxol® in patients with metastatic breast cancer.

and diagnosis process could be an useful tool to profile and select tumor types that would respond better to a therapy based on nanoparticles.

On the other hand, the data show that Abraxane® cannot avoid the peripheral neuropathy induced by PTX. Ongoing randomized controlled trials are investigating the efficacy and safety of Abraxane® for the treatment against different cancers types, alone or as combination therapy.

4.2. Liposomes

The first nanoplatform commercialized as a drug delivery system was a liposomal formulation. The clinical success of liposomes is based on their potential to improve the therapeutic index and the safety profile of several drugs (van Elk et al., 2016).

4.2.1. Lipusu®: the first PTX liposomal formulation commercialized

In the case of PTX, Lipusu® (Luye Pharma Group) is the first liposomal preparation on the market by i.v. administration that transports this drug. It has been commercialized in China for the treatment of ovarian, breast, NSCLC, gastric and head and neck cancer since 2006 (Zhang et al., 2009). This liposomal formulation was developed to overcome the toxicity problems related with the use of conventional PTX vehicle. However, like Taxol®, premedication protocols for Lipusu® are needed to reduce the vehicle related toxicity (Zhang et al., 2009). The liposomes composed of lecithin and cholesterol, are prepared by film dispersion method followed by a lyophilization technique (Ye et al., 2013). They exhibited a final size of about 400 nm. In order to compare the safety profile of Taxol® and Lipusu®, Wang et al. performed an anaphylaxis study in mice using bioequivalent dosage to those used in the clinic (Wang et al., 2013). The majority of the animals treated with Taxol® showed anaphylactic responses such as piloerection, anhelation and syncope, which were not observed in the Lipusu®-injected animals. Also, Lipusu® induced milder hypersensitivity reactions than Taxol®. Additionally, the antitumoral effect of Lipusu® and PTX injection was evaluated by using rats implanted with NuTu19 ovarian cancer cells (Ye et al., 2013). Results showed that Lipusu® exhibited similar antitumoral effects to Taxol®. However, both formulations were intraperitoneally administered, which is not their conventional administration route. A clinical study has been conducted to investigate the feasibility, pharmacokinetics, efficacy and toxicity of intrapleural Lipusu® injection for the treatment of NSCLC patients with malignant pleural effusions (Wang et al., 2010). Liposomes or standard formulation of PTX were instilled into the pleural cavity through the catheter in 30 min at 125 mg/m^2. As regard the efficacy, no significant difference between Lipusu® and conventional PTX solution was observed. Interestingly, anaphylaxis and neurotoxicity were never observed in patients treated with PTX liposomal, while these ones were the major side-effects in patients treated with Taxol®. In addition, there were a few mild symptoms (diarrhoea, anaemia, neutropenia, thrombocytopenia, hepatotoxicity and chest pain) after intrapleural Lisupu® administration that were all easily controlled. The authors reported that the mean $T_{1/2}$ and $AUC_{0\rightarrow 96IP}$ in the pleural fluid of PTX liposomal formulation were about 2-fold and over 2.5-fold higher than those of Taxol®, respectively. However, the number of individuals in each group were small (nine were treated with Lipusu® and 2 with free PTX) to provide acceptable statistical significance. In order to compare the efficacy and safety of Lipusu® with Taxol® when administered in combination, Xu et al. conducted a phase I study in fifty eight patients with advanced gastric cancer (Xu et al., 2013). Patients were treated either with tegafur, oxaliplatin and PTX liposomes at a dose of 135 mg/m^2 or tegafur, oxaliplatin and Taxol® at the same dose with the same timing. All patients received steroid premedication. The authors reported that Lipusu® (47%) had similar ORR compared to available PTX (46%). The incidence rate of allergy, nausea and vomiting, rash, muscle pain in the group receiving PTX liposomes was lower than those receiving Taxol®. However, no significant differences were observed in haematological and neurologic toxicities between the treatments. Other preclinical and clinical studies have been performed, but they were reported in chinese. Therefore, these were excluded of this review.

4.2.2. PTX-liposomes in clinical trials

Although this drug delivery system has been discovered more than 30 years ago, liposomal formulations of PTX have yet to come to the market in Europe and USA. At present time there are two liposomal platforms in clinical trials: i) LEP-ETU® and ii) EndoTag-1® (ET).

4.2.2.1. LEP-ETU®. The first is known as LEP-ETU® for the abbreviation of Liposome-entrapped paclitaxel easy to use, which was designed to obviate the need for premedication, shorten infusion time and reduce toxicity (Zhang et al., 2005). Curiously, there are few preclinical models to support the theorized benefit of LEP-ETU®. In fact, some results reported from animals models were made with a similar liposomal preparation of PTX (known as LEP). LEP formulation was composed by cardiolipin, egg phosphatidyl choline, cholesterol, and D-α-tocopheryl acid succinate (Cabanes et al., 1998). However, phase I study of LEP was discontinued, because an assessment of the pharmacokinetics and clinical dates suggested that LEP was unlikely to have any advantages over Taxol® (Soepenberg et al., 2004). Some years later NeoPharm Inc. developed LEP-ETU®, which is formulated with a mixture of 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine (DOPC)/cholesterol/cardiolipin (90:5:5 molar ratio) and 33:1 molar ratio lipid:drug with a concentration of 2 mg/mL of PTX. The liposome size was about 150 nm before and after lyophilisation (Zhang et al., 2005). In spite of the disappointing results from a previous trial, Fetterly and coworkers conducted a phase I study to evaluate the primary toxicity, the MTD and the dose-limiting toxicities (DLT) of LEP-ETU® in 30 patients (Fetterly et al., 2008). The majority of the enrolled patients had a histologically diagnosis of locally advanced or metastatic carcinoma. The most common tumor types included breast (16%) and ovary (10%) cancers. The liposomal formulation was administered over 1.5 h at doses ranging from 135 to 375 mg/m^2 every 3 weeks in 30 patients. Importantly, prophylactic premedication was only administered to patients who received doses less than 175 mg/m^2. In this sense, 23% of the patients experienced infusion related-reactions, which required interruption of LEP-ETU® infusion. The DLT were peripheral neuropathy and myelosuppression, moreover, neurotoxicity occurred in 5 of 12 patients treated at $\geq$325 mg/m^2. The higher MTD (325 mg/m^2) indicated that LEP-ETU® is better tolerated than Taxol® (175 mg/m^2). Therefore, LEP-ETU® might offer an improved therapeutic index at a dose of 275 mg/m^2. Slingerland et al. recently reported the results of clinical bioequivalence study comparing the pharmacokinetics of LEP-ETU® and Taxol® by i.v. administration, in 58 patients with advanced cancer (Slingerland et al., 2013). Eligible patients were randomized to receive either LEP-ETU® at a dose of 175 mg/m ^{2} followed (wash out 3 week) by the same dose of Taxol® or vice versa. All patients received steroid and antihistamine premedication. The mean areas under the curve (AUC) of LEP-ETU® and Taxol® were 15,853.8 and 18,550.8 ng H/mL, respectively and means of C_{max} were 4955.0 and 5108.8 ng/mL. Therefore, LEP-ETU® was bioequivalent to the reference formulation of PTX. In addition, the most frequently reported adverse events with the liposomal formulation were fatigue, alopecia and myalgia. A phase II clinical trial has been conducted to determine the safety and efficacy of LEP-ETU® in thirty-five patients with advanced breast cancer (NeoPharm, 2016). Enrolled

subjects received LEP-ETU® doses of 275 mg/m^2 administered over 90 min every 21 days for 6 cycles without routine premedication. This multicenter, open-label trial was conducted at 5 centres in India. Unfortunately, results have not been published yet.

4.2.2.2. EndoTAG-1®. The another formulation, EndoTAG-1® (Medigene Inc.), also known as MBT-0206 or LipoPac®, consists of 1,2-Dioleoyl-3-Trimethylammonium Propane (DOTAP), DOPC and PTX in 50:47:3 molar ratio, solubilizing 0.5 mg/mL of PTX (Soo et al., 2009). These liposomes have a final size of 180–200 nm and a zeta potential of approximately +25 to +100 mV in a 0.05 mM KCl solution at pH 7.5 (Schmitt-Sody et al., 2003). Because endothelial cells lining the tumor blood vessels tend to have negative charge, these cationic liposomes can be targeted toward the neovascularisation area at the tumoral site (Kunstfeld et al., 2003). Thus, positive charged liposomes could be an option to promote the PTX uptake into the tumor endothelial cells. This causes significant antivascular effects within the treated tumors and an increase in tumor microvessel permeability (Strieth et al., 2014). These targeting properties have been demonstrated in several animal models (Strieth et al., 2008, 2004). In comparison to Taxol®, ET significantly retarded the growth of subcutaneously-inoculated tumors after i.v. administration (Bode et al., 2009; Lohr et al., 2011). In addition, immunohistological analysis confirmed a significant reduction of microvessel density in ET treated tumors, showing a strong anti-vascular effect on the pre-existent tumor vasculature (Eichhorn et al., 2006). In contrast, animals treated with Taxol® at equal drug dose did not show any significant difference in vascular parameters, as compared to controls. Despite the fact that positively charged substance may be usually therapeutically active, unloaded cationic liposomes demonstrated a slight antitumoral effect (Bode et al., 2009). Similarly, Kunstfeld et al. showed that ET prevents tumor angiogenesis and retards melanoma growth in humanized mouse melanoma model (Kunstfeld et al., 2003). In rats bearing subcutaneous rat prostatic adenocarcinoma cells (MatLu), four injections of ET significantly retarded the growth rate of the tumors compared to Taxol treatment (Bode et al., 2009). In this sense, remarkable antitumoral effects can be achieved by combining antivascular tumor therapy with conventional chemotherapy. Thus, the efficiency of ET therapy in combination with conventional chemotherapy was investigated by Eichhorn et al. in an orthotopic pancreatic cancer model in nude mice (Eichhorn et al., 2006). The combination of ET and GEM resulted in significantly higher inhibition of primary tumor growth compared to both monotherapies. Interestingly, there was an additive effect between ET and GEM chemotherapy. Moreover, only combination treatment with the two drugs was able to inhibit the pancreas metastasis. Therefore, ET could be combined with standard antineoplasic agents to treat some tumors that are normally taxane- resistant, such as pancreatic cancer. A phase II clinical trial evaluating the safety and efficacy of ET in combination with GEM in 212 pancreatic cancer patients was recently presented (Lohr et al., 2011). Patients received either GEM monotherapy or ET at doses ranging from 11 to 44 mg/m^2 in combination with GEM. Median time to progression was longer for all ET doses plus GEM compared with GEM alone. In the group of patients receiving the higher doses of ET, the median time for OS was 9.3 months compared with 6.8 months in the GEM group. It is important to note that pancreatic cancer is not taxane sensitive. Median survival rates were 30% in patients who received the higher doses of ET compared to 15% in those given GEM alone. Neutropenia and thrombocytopenia were the main haematological toxicities reported and they appeared to be dose related. Awada et al. recently reported the results of a phase II clinical trial comparing the safety and efficacy of ET with Taxol® in 140 patients diagnosed with triple negative breast cancer (Awada et al., 2014). Patients were randomized assigned to weekly ET (22 mg/m^2) plus Taxol® (70 mg/m^2) (group 1), ET (44 mg/m^2 twice a week) (group 2) or weekly Taxol® (90 mg/m^2) (group 3). Tumor responses were assessed after four cycles (16 weeks). The median OS did not differ significantly between the treatment (13.0, 11.9 and 13.1 months for groups 1, 2 and 3, respectively). Ten patients (17.8%) permanently discontinued ET monotherapy due to adverse events. Infusion-related reactions (pyrexia and chills) were most frequent on ET-based treatments, but severity was predominantly mild/moderate. In 2013, a phase II trial evaluating the efficacy and safety of neoadjuvant ET in combination with Taxol® in patients with HER2-negative breast cancer has been completed, although the result has not been published yet (ClinicalTrials.gov NCT01537536, 2013). Additionally, a phase III study evaluating the efficacy of ET in combination with PTX and GEM is currently recruiting triple negative breast cancer patients (ClinicalTrials.gov NCT03002103, 2016).

4.3. Polymeric micelles

As with liposomes, micelles have also grown in popularity for use as drug delivery systems in cancer therapy. Currently, three polymeric micellar formulations of PTX devoid of CrEL-solvent are applied in the clinic: i) Genexol-PM®, ii) Nanoxel® and iii) Paclical®.

4.3.1. Polymeric micelles approved by clinical use

4.3.1.1. Genexol-PM®. Genexol-PM® (Samyang Corporation) is marketed in South Korea, India, Vietnam, Philippines and Indonesia for the treatment of metastatic breast cancer and locally advanced or metastatic NSCLC. It is also commercialized in some Asia countries as Paxus™. This product has recently been approved by Korean FDA as first line treatment for ovarian cancer in combination with others chemotherapeutics agents. In the US, it is in development for MBC and NSCLC under the name Cynviloq™ (IG-001, Sorrento Therapeutic Inc.). Genexol-PM®, as it is most commonly known in the literature, comprises monomethoxy- poly (ethylene-glycol)-*block*-poly(D,L-lactide) diblock copolymer containing physically entrapped PTX. Micelles exhibit a size of 20–50 nm and a drug loading of 16.7% w/w (Kim et al., 2001). Preclinical studies in two animal models showed enhanced efficacy and reduced toxicity of Genexol-PM® when compared with Taxol® at the MTD of each agent (Kim et al., 2001). In a phase I monotherapy study performed by Kim at al., Genexol-PM® was administered i.v. over 3 h at doses ranging from 135 to 390 mg/m^2 every 3 weeks in 21 patients with advanced solid malignancies (Kim et al., 2004). The authors determined the MTD to be 390 mg/m^2. Despite that all of treatments were administered without premedication, no hypersensitive reactions were reported. The DLTs were neutropenia and neuropathy. Interestingly, reduction of Genexol-PM® administration to 1 h infusion weekly for 3 weeks reduced the MTD at 180 mg/m^2 (Lim et al., 2009). Although the incidence of neutropenia was similar in both regimens, the non-hematologic toxic effects were less severe with the weekly regimen (Kim et al., 2004; Lim et al., 2009). A number of phase II clinical trials have been conducted to explore the efficacy and tolerability of Genexol-PM® in patients with MBC, NSCLC and pancreatic cancer. Thus, Lee et al. reported the results of a multicenter single-arm study using Genexol-PM® at a dose of 300 mg/m^2 in 41 women with MBC (Lee et al., 2008). Genexol-PM® reached a response rate of 58.5% (5 complete responses and 19 partial responses) and the median time to progression was 9 months. It is worth noting that Taxol® was approved for the treatment in patients with MBC with a response rate of 25% at the

same dose regimen; however, this value was calculated on 224 patients (Jones et al., 2005). Additionally, a high rate of grade 3 of neuropathy (51.2%) and grade 3/4 of neutropenia (68.3%) were also observed. Moreover, hypersensitivity reactions were seen in the 19.5% of patients.

A combination of Genexol-PM® (230 mg/m^2) and cisplatin (60 mg/m^2) on day 1 of a 3-week cycle was investigated as first-line therapy in patients (n = 69) with NSCLC (Kim et al., 2007). Patients were pre-medicated with steroid and antihistamines. ORR was 37.7% (all responses were partial responses), the median time to progression was 5.8 months. Although these data were similar than those observed in the most of phase II or phase III clinical trials using Taxol® combined with higher doses of cisplatin, Genexol-PM® plus cisplatin showed a more favourable result in term of survival period (21.7 months) (Giaccone et al., 1998; Rosell et al., 2002). In the same way, the efficacy and safety of Genexol-PM® as a non-platinum combination in advanced NSCLC patients were also explored (Ahn et al., 2014). Forty-three patients were treated with Genexol-PM® (230 mg/m^2) on day one and GEM (1000 mg/m^2) on day 1 and day 8 of a 3-week cycle. Patients received a median of 4 cycles (range one to six). The ORR was 46.5% (20 partial responses). Median PFS and OS were 4.0 and 14.8 months, respectively. Moreover, compared with platinum-based regimen, this one induced lower rates of hematologic toxicities and peripheral neuropathy. In other phase II clinical studies, Genexol-PM® was found to be safe and effective in patients with pancreatic cancer and gastric cancer (Park et al., 2004; Saif et al., 2010). For instance, phase II trial using single agent Taxol® yielded a response rate of 8% and a median OS of 5 months in forty-five patients, while Genexol-PM® monotherapy obtained a ORR of 6.7% and median OS of 3.2 months in 56 patients with advanced pancreatic cancer (Saif et al., 2010; Whitehead et al., 1997). Because of results of phase II studies, the FDA agreed that the 505(b)(2) approach (a pathway to provide fast-track approval based on previously approved agents), using Abraxane® as the reference drugs, is the appropriate regulatory approach to gain marketing approval for Cynviloq® in the U.S. The pivotal bioequivalence study (TRIBECA™) between Cynviloq® and Abraxane® in MBC patients was initiated in 2014.

4.3.1.2. Nanoxel®. Another micellar formulation, Nanoxel® (Dabur Pharma Ltd.), has been available in the India market for the treatment of MBC patients since 2006 (Ranade et al., 2013a,b). Later, Nanoxel® was approved for additional indications of ovarian cancer, NSCLC and AIDS related Kaposi's sarcoma by the India regulatory authority. This product is also known under the name DO/NDR/02. This micellar formulation consists of a pH sensitive co-polymer of *N*-isopropyl acrylamide and vinylpyrrolidone monomers. At physiological pH, micelles remain stable but in acidic conditions such as the tumor microenvironment, the polymer is degraded and the release of PTX occurs (Giodini et al., 2016).

While other formulations of PTX such as Abraxane® and Genexol-PM® are lyophilized products approved for room temperature storage, Nanoxel® is a liquid formulation approved for 2–8 °C storage. These nanomicelles have a size between 80 and 100 nm with a narrow size distribution (Madaan et al., 2013). In order to determine the MTD, safety and pharmacokinetic profile, a phase I clinical study was conducted in patients (n = 23) with metastatic solid tumors (Ranade et al., 2008). Nanoxel® was administered as a one-hour infusion at doses ranging from 135 to 375 mg/m^2 for a maximum of six cycles. All enrolled patients did not receive premedication. The authors determined the MTD to be 375 mg/m^2. The most frequent toxicities were grade 3 diarrhea (n = 2) and grade 4 neutropenia (n = 2). The authors also reported that Nanoxel® has a linear pharmacokinetic. On the basis of this trial, Ranade et al. initiated a phase II, open-label, three-arm study in anthracycline failed advanced MBC patients (Ranade et al., 2013a,b). Patients were randomized to receive either Taxol® at 175 mg/m2 (n = 64) administered intravenously over 3 h along with standard premedication, Nanoxel® at 300 mg/m2 (n = 64) or 220 mg/m^2 (n = 66), administered intravenously over 1-h, without premedication. Treatments were administered at three-week intervals for 6 cycles. The ORR was 40% for the both Nanoxel® arm versus 32.3% for the Taxol® arm. Progressive disease for Nanoxel® was 27.3% at the higher dose level compared to 38.7% with Taxol®. No hypersensitive reactions were observed with the polymeric micellar formulation. In addition, the incidence of neutropenia of Nanoxel® (56.3%) was higher than that of Taxol® (50%). Grade 3 sensory neuropathy was observed in 12.5% and 1.5% of patients with Nanoxel® at high and low dosages respectively and 6.3% with Taxol®.

4.3.1.3. Paclical®. The third formulation is Paclical® (OAS-PAC-100), which is developed by Oasmia Pharmaceuticals. This product is composed of PTX encapsulated in the compound XR-17, which consist of two isomeric retinoyl derivates. Paclical® consists of a freeze-dried powder dissolved in conventional solution for infusion. In 2015, Paclical® received a marketing authorization for treatment of ovarian cancer in combination with carboplatin in the Russian Federation (Oasmia, 2015). A Phase III open-label, randomized, multicentre study was designed to compare the efficacy and safety profile between Paclical® and Taxol® in patients (n = 789) with epithelial ovarian cancer (Oasmia, 2016). Both formulations were administered in combination with carboplatin. Paclical® was administered as a 1-h intravenous infusion at 250 mg/m^2 while Taxol® was administered as a 3-h intravenous infusion at 175 mg/m^2. Patients received each agent every 21-days, up to six cycles. Patients in the Taxol® arm received premediation. The study showed a PFS of 10.3 months for Paclical® plus carboplatin compared to 10.1 months for Taxol® plus carboplatin.

4.3.2. Polymeric micelles in clinical trials

4.3.2.1. NK105. NK105 is another micellar formulation that is still at clinical studies. It consists of PEG and modified polyaspartate as hydrophobic block. This product was obtained as a freeze-dried formulation, containing 23% (w/w) of PTX and a median diameter of the micelles of 85 nm. In mouse cancer models, NK105 showed higher antitumoral activity compared with Taxol® ($p < 0.01$) (Hamaguchi et al., 2005). MTD for intravenous administration *via* 1–h infusion every 3-week without premedication was determined to 180 mg/m^2 in a phase I study involving 19 patients (Hamaguchi et al., 2007). DLT was grade 3 of neutropenia. The plasma AUC (369.8 μgh mL^{-1}) of NK105 at 150 mg/m^2 (recommended phase II dose) was 15-fold higher and 32-fold higher than those of Taxol® (210 mg/m^2) and Genexol® (300 mg/m^2) respectively. Although NK105 exhibited excellent pharmacokinetic parameters, it showed modest antitumor activity and tolerability in a in a subsequent phase II clinical trial (Kato et al., 2012). In this study, 56 patients with advanced gastric cancer were enrolled and received NK105 every three weeks. The ORR was 25% (2 responses complete and 12 partial responses) and the OS was 14.4 months. Grade 3 or 4 of neutropenia was the main toxicity, occurring in 37 (64.9%) patients. In the US, NK105 is being evaluated in a phase III trial in patients with MBC against Taxol® (NCT01644890).

4.3.2.2. Paxceed®. Another micellar formulation currently under clinical investigation is Paxceed® (micellar paclitaxel). It consist of poly(DL-lactide)-block-methoxy polyethylene glycol diblock copolymer with entrapped PTX (25 mg PTX/75 mg polymer) (van

Gaal and Crommelin, 2015). These micelles are prepared by the film hydration technique. Unlike the other formulations, this product was developed by Angiotech Pharmaceuticals Inc, for rheumatoid arthritis treatment by intravenous administration. In addition, these micelles are also being studied in patients with psoriasis. Use of PTX in patients with nonlife-threatening diseases, would be reasonable only if treatments are safe and well tolerated. Paxceed® has completed the phase II studies for both diseases (NCT00055133; NCT00006276). The formulation was well tolerated and demonstrated therapeutic activity (Ehrlich et al., 2004).

4.4. Polymeric-conjugates

Another way to provide a water soluble alternative to the standard PTX formulation is based on the covalent conjugation of the drug to biodegradable polymers. Polymeric conjugation eliminates the need of CrEL from the pharmaceutical preparation, avoiding the described toxicity of this solubilising agent.

4.4.1. HPMA copolymer–PTX (PNU166945)

Because the 2′ hydroxyl group of PTX can be easily hydrolysed by enzymatic or chemical means, many C2′ esters have been investigated for their suitability as water-soluble prodrugs. From a wide range of natural or synthetic polymers currently available, hydroxypropyl-methacrylamide (HPMA) has been extensively utilized for conjugation to hydrophobic antineoplastic drugs. PNU166945 (developed by Pharmacia Corporation) was the first polymer-PTX conjugate that entered phase I trial (Ma and Mumper, 2013). It consisted of PTX conjugated to HPMA by a tetrapeptidil linker of glycylphenylalanylleucylglycine (GFLG). In order to minimize drug release in circulation, the peptidyl linker is stable into the bloodstream. However, it is effectively cleaved by the lysosomal thiol-dependant proteases (especially cathepsin B) following lysosomal uptake. This formulation showed adequate aqueous solubility (>2 mg/mL) and had a drug content of ~5 wt%. This drug loading is relatively low; in fact, impractical, because a large amount of polymer is needed to deliver a clinically relevant dose of PTX. Additionally, although PTX can be theoretically released from PNU166945 by hydrolysis, enzymatic cleavage or combinations of both mechanisms, drug release is predominantly driven by hydrolysis (Duncan, 2009). Consequently, the drug will be released from the HPMA copolymer so rapidly after administration that conjugation could impart no pharmacokinetic benefit (Duncan and Vicent, 2010; Terwogt et al., 2001).

Although preclinical work in rodents and dogs showed no signs of toxicity, the phase I study was discontinued prematurely before reaching the DLT due to severe neurotoxicity observed in additional preclinical studies (Terwogt et al., 2001). To date, these results have never been published.

4.4.2. Opaxio™

Opaxio™ (CTI BioPharma), a macromolecular polymer-drug conjugate of PTX with α-poly-L-glutamic acid (PG), was developed in order to improve the safety profile of Taxol®. It is also known under the names of Paclitaxel Poliglumex (PPX), CT-2300 or Xyotax®. In this new chemical entity, PTX is conjugated to PG through its 2′-hydroxil group *via* ester linkage. As this site is essential for β-tubulin binding, the resultant product is biologically inactive. Similar to PNU166945, the mechanism by which PPX is metabolized, at least in part, includes endocytosis of the drug-conjugate followed by released of PTX by lysosomal proteases, particularly cathepsin B (Shaffer et al., 2007; Singer, 2005).

It is supplied as a lyophilized powder for solutions for infusion consisting of approximately 269 mg of PPX, containing 94 mg of PTX (drug loading ~36% w/w) (Chipman et al., 2006). The median molecular weight of PPX is 38.5 KDa and is negatively charged at physiological pH. Curiously, *in vitro* studies to determine the antitumoral activity of PPX against cancer cells have not been performed. However, *in vivo* data seem to support the theoretical benefits of this formulation. In several animal tumoral models, PPX showed significantly grown tumor delay, compared to conventional PTX formulation and, in some cases, the conjugate produced complete tumor regression (Li et al., 1999, 1998). Similar results were reported by Singer et al. in mice bearing multidrug resistant tumors (Singer et al., 2003). In contrast, no superiority was found in mice bearing lung carcinoma between PPX-treated and Taxol®-treated animals (Li et al., 1999). Importantly, for the most of tested model PPX was administered at much higher doses than Taxol®. Early pre-clinical studies of biodistribution in rodents bearing human ovarian carcinoma showed that the accumulation of PPX in tumoral tissue was at least 5 times higher than that with the same dose of standard PTX (Li et al., 2000). Interestingly, the amount of drug present in the tumoral site persisted for up to 144 h after i.v. administration of PPX. The concentrations of PPX were also higher than Taxol® in all studied tissues, especially those with more abundant reticular endothelial system.

Several phase I trials have been performed to examine toxicity, MTD and toxicities associated with the administration of PPX. Boddy et al. conducted a clinical study in thirty patients with refractory solid tumors. The MTD was 233 mg/m^2 with a 3-weekly schedule and 177 mg/m^2 with a 2-weekly schedule (Boddy et al., 2005). The DLT were typically of the taxanes (neuropathy and neutropenia). Importantly, after 7 days of PPX first administration, the death of one patient was attributed to drug-related toxicity. Similarly, high rates of neurotoxicity were observed in other phase I study after the administration of PPX at two dose level, 235 and 270 mg/m^2 (Veronese et al., 2005). In order to determine a regimen with better toxicity profile, Neumunaitis *and colleague* conducted other phase I trial which PPX was weekly administered at a dose of 70 mg/m^2 (Mita et al., 2009). This weekly dosage was well tolerated, although this dosing schedule did not show antitumoral response.

Because direct comparisons between the pharmacokinetic properties of PPX and Taxol® have not been performed, pharmacokinetic profiles compared in phase I trials are based on literature data of Taxol®. Clinical pharmacokinetics studies of PPX showed prolonged half life (>100 h) and low renal elimination (Clearance <10 mL/min) for conjugated taxanes (Boddy et al., 2005; Morgan et al., 2009; Verschraegen et al., 2009). In spite of the fact that PPX is administered as a 10 min infusion compared to 3 h infusion of Taxol®, the C_{max} values are over 3-fold lower for PPX, even when this one was administered at higher doses than Taxol® (Boddy et al., 2005; Verschraegen et al., 2009).

In order to characterize the MTD and safety of PPX in combination with carboplatin or cisplatin, two phase I trials were performed in patients with refractory malignant tumor (Nemunaitis et al., 2005; Verschraegen et al., 2009). The MTDs were determined to be 225 mg/m^2 and 210 mg/m^2 for PPX/carboplatin or PPX/cisplatin combinations, respectively. The most common toxicities were neutropenia and neurotoxicity. In the group of patients (n = 22) treated with PPX/carboplatin combination, partial responses were observed only in three patients, all of whom had previously undergone unsuccessful Taxol® treatment (Nemunaitis et al., 2005). The authors concluded that PPX may override resistant mechanism to taxanes. However, in the group receiving PPX/cisplatin (n = 44), of the 16 assessable patients resistant to taxane chemotherapy only four had a partial response (PR), six had a stable disease and five had progressive disease (Verschraegen et al., 2009).

Numerous phase II studies have been conducted to determine the efficacy of PPX in patients with ovarian cancer, NSCLC and

breast cancer. In these trials PPX was administered intravenously over 10–30 min at recommended doses of 175 mg/m^2 every three weeks, without routine premedication. Sabbatini et al. reported the results of two single arm studies in heavily pre-treated patients with recurrent ovarian, fallopian tube, or peritoneal cancer (Sabbatini et al., 2004). In the first study, out of ninety-nine evaluable patients, ten (10%) demonstrated PR with median time to progression of 2.1 months. Despite the lack of CrEL in the formulation, hypersensitive reactions (grade 1 or 2) occurred in 13% of patients. Similarly, high rates of clinically significant allergic reactions were observed in other phase II study (Lin et al., 2007). This trial was stopped early, because of unexpected high incidence of those reactions. In addition, neurotoxicity was higher than predicted from previous phase I trials (Lin et al., 2007; Sabbatini et al., 2004). Similar results were obtained in a second study of 45 patients with ovarian cancer (Sabbatini et al., 2008). Interestingly, when PPX was administered to patients who had previously showed resistance to taxane chemotherapy, only one patient demonstrated PR (2%) (Nemunaitis et al., 2005). Thus, PPX might not have clinical activity on patients with taxane refractory disease. Finally, the authors conclude that PPX at 175 mg/m^2 every 21 days has modest activity of limited duration when given as second or third line therapy in patients with ovarian cancer (Sabbatini et al., 2008, 2004). Richards et al. reported the results of phase II study of single-agent PPX in the treatment of twenty eight patients with advanced-stage NSCLC. Response rates were modest, because only two patients exhibited a PR (7%, both with stage IV) (Richards et al., 2005). Consistent with the expected pharmacology of PTX, neuropathy was the most common drug-related adverse event to result in patient withdrawal (n = 5).

Although the previously reported evidence in phase II studies in patients with NSCLC is limited, three multi-center, randomized, open-label, phase III studies of PPX designed to determine the efficacy and safety of PPX have been initiated (Langer et al., 2008; Paz-Ares et al., 2008). They were conducted in more than 1700 CN patients with Eastern Cooperative Oncology Group performance status of 0–2. Those trials are also known as Selected Targeted Efficacy in Lung Cancer to Lower Adverse Reactions 2, 3 or 4 (STELLAR). In the STELLAR 3 trial, 400 patients received carboplatin and either PPX (210 mg/m^2) or Taxol® (225 mg/m^2) every three weeks (Langer et al., 2008). The median survival was similar in both arms with 7.8 months for PPX versus 7.9 months for Taxol®. Notably, a survival benefit was only observed for female, but not in male patients, treated with PPX. Thus, survival rates for women at 12, 18 and 24 months were better on PPX compared with Taxol® (37 *vs* 25%, 26 *vs* 5%, and 13 *vs* 5%, respectively). Recent studies have reported a relationship between oestrogen levels and cathepsin B activity (Chipman et al., 2006; Shaffer et al., 2007). In this sense, the oestrogen-mediated activity of enzyme suggests that PPX metabolism may vary depending on hormonal status of patients (Albain et al., 2006; Langer et al., 2008).

The OR rate was significantly favoured for the Taxol® arm (37%) with 2% complete responses, compared to PPX arm (20%) with 1% complete responses.

Patients enrolled in PPX arm were significantly more likely to experience nausea and vomiting. In addition, the incidence of grade 3/4 thrombocytopenia was significantly higher in the PPX arm ($p < 0.001$). On the other hand, those patients in the Taxol® arm experienced significantly more myalgia, arthralgia and cardiac events ($p < 0.05$). In STELLAR 2 study a total of 849 patients were randomized to receive PPX or docetaxel (Paz-Ares et al., 2008). There was no difference in the median overall survival between two arms (6.9 months). The OR rate was 8% with no complete responses for the PPX arm and 12% with two CRs for docetaxel arm. Severe neuropathy (grade 3/4) was observed in 19% and 3% of the patients treated with PPX or docetaxel, respectively. In addition, PPX failed to show a more favourable toxicity profile than docetaxel. In a subsequent STELLAR 4 (also known as PGT304), PPX (175 mg/m^2) was compared with GEM or vinorelbine as a first line therapy (O'Brien et al., 2008). Median survival did not differ significantly between two arms treatment (7.3 versus 6.6 months). Response rates were 11% for the PPX arm versus 15% for the comparator arm and median time to progression was also similar between treatment groups (87 days for PPX versus 107 days for the comparator). All these phase III studies demonstrated similar efficacy and more convenient administration of PPX compared with the control treatment arms. Since this conjugate eliminates the need of CrEL, this formulation decreases the infusion time (10 min) and the risk of hypersensitive reactions. However, the conjugated failed to show superiority in overall survival, which was the primary objective. As result, the interest in the use of PPX for lung cancer treatment has largely subsided. In 2009, the laboratory officially notified the Committee for Medicinal Products for Human Use (European Medicine Agency) that it wished to withdraw its application for a marketing authorisation for Opaxio™, because the studies did not show that this formulation was more effective than the standard treatments (Cell Therapeutics, 2009). On the other hand, retrospective analysis of clinical data from the STELAR 3 and 4 trials showed improvement in OS for women less than 55 years old (presumably pre-menopausal) or women with normal oestrogen levels receiving PPX compared with standard chemotherapy (9.5 *vs* 7.8 month; $p = 0.03$). Additional studies in women with advanced NSCLC to evaluate the efficacy of PPX in relation to estrogen levels are needed.

PPX is also currently being evaluated in a phase III trial (GOC 212) of maintenance chemotherapy comparing 12 monthly cycles of single Taxol® or PPX versus no treatment in women with advanced ovarian cancer (Clinical Trials NCT00108745, 2016).

4.4.3. Taxoprexin®

Taxoprexin®, also known as DHA-paclitaxel (from Protarga Inc), is a lipid-PTX conjugate which has completed several phase II studies for treatment of gastric cancer, lung cancer, and non-uveal melanoma (Homsi et al., 2009; Jones et al., 2008; Payne et al., 2006). Although it can be confused with a polymeric conjugate, Taxoprexin® is a small prodrug formed by covalently linking the fatty acid docosahexaenoic acid (DHA) to the 2′-OH position of the PTX molecule. Thus, in contrast to PPX, Taxoprexin® has not been designed to assemble into a nanostructure (Feng and Tong, 2016). This formulation is supplied as a concentrate which is reconstituted with a vehicle containing Cremophor® (10%) and ethanol (10%) (Bradley et al., 2001). Like Taxol® vehicle, this one allows micellar solubilization of the drug. Therefore, patients who receive this formulation require steroid and antihistamine premedication to reduce the risk of vehicle-related hypersensitive reactions. This drug showed promising results in preclinical animal models. In order to characterize the pharmacokinetic profile and MTD, a phase I trial was conducted in 24 patients with advanced refractory solid tumors. At the MTD (1100 mg/m^2), DHA-PTX demonstrated a low systemic clearance (0.11 L/h), a long terminal $t_{1/2}$ (112 h), and a small Vd (1.9 L/m^2) at the steady state (Wolff et al., 2003). In addition, PTX plasma concentrations remained ≥0.01 μM for an average of 6–7 days. The authors concluded that this prolonged exposure to low PTX concentrations might produce greater antitumor activity. However, clinical effects observed during these studies were quite modest (Homsi et al., 2009; Jones et al., 2008; Payne et al., 2006). Recently, phase III study compared Taxoprexin® to dacarbazine in 393 patients with malignant melanoma (Bedikian et al., 2011). No significant difference in terms of OS, TTP and duration of response was noted between both treatment arms. Moreover, haematological toxicity is comparable to that previously shown with Taxol®.

5. Ligand-based PTX-loaded nanoformulations

Active targeting refers to the conjugation of a biologically active molecule, such as monosaccharides (mannose, glucose, fructose), small peptides, aptamers, antibodies and other proteins to the surface of the carrier, in order to be recognised by its receptor at the target site (Cagel et al., 2016; Wu and Zheng, 2016). Applying this technology, a nanocarrier loaded with PTX might be ideally directed to the tumoral site only through surface modifications with different ligands that interact specifically with receptors on the tumoral cells. Some of the apparent benefits of active-targeting delivery may be an increased cellular uptake of the drug in the tumor cells, diminished toxicity towards healthy tissues and better pharmacokinetic parameters, when compared to the "untargeted" counterparts. It results tempting to think that a system may combine all these characteristics. However, it is clearly more complicated to achieve such development, considering that a successful actively-targeted formulation requires a delicate balance between the ligand content and the exposed surface, in contemplation of minimizing immunological recognition and clearance and providing an adequate nanocarrier circulation time to reach the target cell, while maintaining an appropriate binding affinity with the receptors expressed on these cells (Zamboni et al., 2014). In practice, some actively-targeted nanosystems have not really shown improve delivery to target tumors (Know et al., 2012). Moreover, the nanoparticles need to preserve their structure intact when administered into the bloodstream, at least until they arrive to the respective target site. Otherwise, the encapsulated drug is prematurely released. From the examples cited above, while Genexol-PM® and Abraxane® quickly dissociate upon dilution in blood plasma, only NK105 remains unharmed during systemic circulation (Svenson, 2014). On the other hand, such modifications lead to a time-consuming and difficult fabrication process, which will result in a high cost of production. Although several nanoformulations of PTX for active targeting have been investigated *in vitro* and *in vivo*, there are still no "magic bullets" for PTX delivery (Hillery and Park, 2016). Moreover, there are currently no targeted formulations of PTX under clinical trials and the only targeted formulation containing the second-generation taxane docetaxel (BIND-014, *BIND Therapeutics, Inc*), has surprisingly failed in phase I clinical trials against cervical and head-and-neck cancers, with no apparent superiority over docetaxel in lung cancer (Ledford, 2016; Von Hoff et al., 2016). BIND-014 was originally targeted to tumor tissues by binding to prostate-specific membrane antigen (PSMA), which is a protein abundantly expressed on the surface of cancer cells of many solid tumors. These nanoparticles carried docetaxel within a matrix of polylactic acid covered with a coating of PEG and decorated with PSMA. In April 2016, BIND-014 has completed a phase II clinical phase in patients with metastatic castration-resistant prostate cancer (Autio et al., 2016) (NCT01812746). However, that same year the company announced the cutback of the product and a 38% reduction in the personnel and a month later the firm filed for bankruptcy (Ledford, 2016). Considering this background, it results clear that the clinic implementation of PTX-based targeted therapy remains a challenging topic for the coming years.

6. PTX loaded nanoparticles for use in theranostic applications

The concept of "theranostic" merges the fields of therapeutics and diagnostics, evolving towards new improved treatments with enhanced safety and efficacy. In this sense, nanotechnology has brought diagnosis and therapy closer, developing nanocarrier-based theranostic agents, which can be defined as nanoplatforms than can deliver both therapeutic and imaging moieties (Liu et al., 2007). Despite the numerous research groups studying theranostic nanosystems, it must be considered that this kind of technology is still in the early stages of development and the vast majority of them are focused in cancer (Xie et al., 2010). In the case of PTX, different nanotechnological platforms have been investigated and all these theranostic nanoformulations are still in preclinical studies.

In this regard, Tran et al. have recently prepared PTX-loaded theranostic nanoparticles of silica-coated iron oxide magnetic core and oleic acid and gelatin shell (Tran et al., 2017). They reported an *in vivo* significant improvement in efficacy of their nanoparticles versus Taxol®, measuring the change in tumor volume in C57BL/6 melanoma tumor-bearing mice after 21 days. Moreover, they obtained a higher median lethal dose with their formulation (65.78 ± 2.82 mg/kg) than with Taxol®. Employing different biomaterials, Mangaiyarkarasi and co-workers developed chitosan-functionalized magnetite doped luminescent rare earth nanoparticles as a carrier for PTX (Mangaiyarkarasi et al., 2016). They confirmed an improvement in the cytotoxicity and enhanced apoptotic effect of their theranostic formulation against lung cancer cells A549 after 24 h incubation ($IC_{50} = 6.37$ μg/mL), compared to free PTX ($IC_{50} = 11.24$ μg/mL). Interestingly, Kim et al. prepared albumin-based nanoparticles containing PTX, indocyanine green and siRNA aiming for both therapy and photoacoustic imaging (Kim et al., 2016). The *in vivo* therapeutic effect was evaluated measuring the change in tumor volume against B16F10 melanoma tumor-bearing Balb/c nude mice and the researchers observed that their formulation (~5000 mm3) suppressed the tumor volume in a greater extent than the nanoparticles containing only PTX (~3000 mm3), indicating the synergistic effect of siRNA and PTX. Moreover, the photoacoustic effect of their theranostic nanomedicine was 1.5-fold higher than free indocyanine green (Kim et al., 2016).

In regard to other nanoplatforms different from nanoparticles, Hollis and co-workers developed hybrid nanocrystals containing PTX and two bioactivable near infrared fluorophores (MMPSense® 750 FAST and Flamma Fluor® FPR-648), in order to evaluate this formulation in a breast cancer murine model (MCF-7 tumor-bearing female nude outbred mice) (Hollis et al., 2014). They defined treatment efficacy and toxicity as decrease in tumor volume and percent of body weight change, respectively and observed no significant differences in efficacy, but obtained reduced toxicity with their hybrid nanocrystals, in comparison to Taxol® ($p > 0.05$). For their part, Ferber et al. designed a drug-polymer nanotheranostic conjugate composed of fluorescent dye Cy5 and PTX, both conjugated to *N*-(2-Hydroxypropyl)methacrylamide (HPMA) copolymer *via* the lysosomally degradable GFLG linker (Ferber et al., 2014). The researchers observed selective tumor accumulation with their formulation against cathepsin B-overexpressing T41 murine mammary adenocarcinoma-bearing mice, as compared to free Cy5, indicating that their system would be suitable for non-invasive *in vivo* monitoring simultaneous to PTX delivery in breast cancer. Finally, Liu and co-workers prepared PTX-loaded polymeric micelles assembled employing PLA-PEG-poly(L-lysine)-diethylenetriaminepentaacetic acid and PLA-PEG-poly(L-lysin)-biotin, targeted with biotinylated alpha-fetoprotein antibodies (Liu et al., 2015). *In vivo* results in female Kunming mice implanted with hepatocarcinoma cells (H22) exhibited a more than 3-fold greater increase in the tumor imaging intensity and prolonged imaging time (1–6 h), in comparison to Magnevist®. Furthermore, their targeted polymeric micelles showed higher anti-tumor efficiency than Taxol® ($p > 0.05$).

7. Opinion

Although Taxol® and its generics have played an important role in conventional chemotherapy for cancer treatment, it is far from

being totally satisfactory due to problems related with their formulation and toxicity. However, since PTX possesses significant cytotoxicity against a wide range of malignancies, it remains an attractive drug for cancer therapy. Research in nanomedicine has led to the development of several PTX delivery systems looking forward to take advantage of nanomaterial's unique properties. Therefore, various nanoplatforms have been investigated to create new CrEL-free formulations of PTX, such as nanoparticles, liposomes, polymeric micelles and polymeric-conjugates. Abraxane® is recognised as the first nanotechnology-based drug approved by FDA on the market. Results from clinical trials demonstrated that this nanoparticle formulation generally has equivalent or improved therapeutic effectiveness compared to Taxol®. Even in the case where Abraxane® has shown no superiority in OS, it offers additional benefits like absence of premedication and easier administration. Also, as nab-PTX is well tolerated in metastatic setting, improves patient compliance and consequently therapeutic response (Bosselmann and Williams, 2012). Dranitsaris et al. conducted a study to compare cost and benefits of three regimens for the treatment of MBC: Abraxane®, Taxol® and docetaxel (Dranitsaris et al., 2009). The majority of oncologic nurses and pharmacist, who were used as patient surrogates, chose Abraxane® as the preferred treatment. The economic analysis, however, estimated that the overall cost per treatment using Abraxane® is about five fold higher than with Taxol®. Alternative PTX nanoformulations such as Lipusu®, Genexol-PM® and Nanoxel® are already commercially available in several countries. Still, none of them has yet succeeded in obtaining approval from the FDA.

Coming back to the title of this review, what has made the nanotechnology for PTX? Based on the examples discussed here, nanotechnology has provided a partial solution improving the solubility and the safety profile of PTX. Overall, the main clinical benefits resulting from treatment with these newer formulations have largely been associated whit a decrease in toxicity, while no dramatic benefits in term of therapeutic efficacy have been achieved. Several drug delivery nanotechnological strategies are still in pre-clinical studies aiming for bridging up the gap between this stage and clinical phases, in order to finally reach the market. This so called "Valley of Death" seems really hard to be overcome, considering the need for predictive animal models, the costly, extensive and technically uncertain development process of nano-based therapies, consumer's distrust and the lack of alignment and communication between academics, the pharmaceutical industry and the clinic (Kulve and Rip, 2013; Würmseher and Firmin, 2017). In this sense, even after 20 years of numerous publications on the nanomedicine field, it appears to befar from being a fact that a new formulation of PTX can provide additional clinical benefits in terms of effectiveness (Bölükbas and Meiners, 2015). In summary, nanotechnological platforms still remain a future promise as drug delivery systems for improving clinical efficacy in cancer therapies. In order to achieve this, an interdisciplinary approach with the cooperation of all the actors of this scenario (*e.g.* the pharmaceutical industry, chemists, pharmacists, biologists, clinicians) is needed.

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