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Review
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A Review of Paclitaxel and Novel Formulations Including Those Suitable for Use in Dogs

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Paclitaxel is a commonly used chemotherapeutic agent with a broad spectrum of activity against cancers in humans. In 1992, paclitaxel was approved by the U.S. Food and Drug Administration (FDA) as Taxol® for use in advanced ovarian cancer. Two years later, it was approved for the treatment of metastatic breast cancer. Paclitaxel was originally isolated from the bark of the Pacific yew tree, *Taxus brevifolia* in 1971. Taxanes are a family of microtubule inhibitors. As a member of this family, paclitaxel suppresses spindle microtubule dynamics. This activity results in the blockage of the metaphase-anaphase transitions, and ultimately in the inhibition of mitosis, and induction of apoptosis in a wide spectrum of cancer cells. Additional anticancer activities of paclitaxel have been defined that are independent of these effects on the microtubules and may include the suppression of cell proliferation as well as antiangiogenic effects. Based on its targeting of a fundamental feature of the cancer phenotype, the mitotic complex, it is not surprising that paclitaxel has been found to be active in a wide variety of cancers in humans. This review summarizes the evidence in support of paclitaxel's broad anticancer activity and introduces the rationale for, and the progress in development of novel formulations of paclitaxel that may preferentially target cancers and that are not associated with the risks for hypersensitivity in dogs. Of note, a novel nanoparticle formulation of paclitaxel that substantially limits hypersensitivity was recently given conditional approval by the FDA Center for Veterinary Medicine for use in dogs with resectable and nonresectable squamous cell carcinoma and nonresectable stage III, IV and V mammary carcinoma.

Key words: Chemotherapeutics; Chemotherapy; Oncology; Pharmacology; Taxol.

Isolation and Mechanism of Action of Paclitaxel

Paclitaxel, the prototype of the taxane class of chemotherapeutics, was originally isolated from the bark of the Pacific yew tree as part of a National Cancer Institute screen of plants and natural products with putative anticancer activity that occurred during the 1960s.[1–3] The development history for paclitaxel and the emergence of a detailed understanding of its molecular mechanisms have been recently summarized and reviewed elsewhere.[1]

The primary mechanism of action of paclitaxel is the suppression of microtubule spindle dynamics.[4] This results in the blockage of metaphase-anaphase transitions, and ultimately the inhibition of mitosis and induction of apoptosis. Unlike other microtubule disrupting drugs (eg, the vinca alkaloids), paclitaxel specifically stabilizes microtubules by binding to the polymeric tubulin, thereby preventing tubulin disassembly (Fig 1).[5] The broad-spectrum activity of paclitaxel was predicted by this mechanism of action (ie, control of cell proliferation and DNA repair),[6,7] which targets the very basic elements of the cancer phenotype.

Abbreviations:

EPR	enhanced permeability and retention
FDA	Food and Drug Administration
Pgp	P-glycoprotein
PK	preclinical pharmacokinetic

Pharmacology and Mechanisms of Resistance

Paclitaxel has been studied and used extensively in several species including rodents, dogs, nonhuman primates, and humans.[8] The pharmacology of paclitaxel is similar among most species; clearance occurs primarily by nonrenal routes with hepatic metabolites excreted in feces.[9] Despite primary hepatic metabolism, no greater risk of toxicity is observed in human patients with liver dysfunction provided their serum bilirubin concentration is <2× the upper reference limit.[10]

The mechanisms of cancer resistance to the taxanes primarily involve modifications to their cellular target, tubulin. Such modifications include mutations, tubulin isotype selection, and post-translational alterations in tubulin and associated regulatory proteins.[11,12] In vitro studies have also identified paclitaxel-mediated upregulation of the MDR1 gene in cell lines as a possible mechanism for resistance, and paclitaxel is a substrate for ABC-transporter cellular drug efflux pumps.[13] It remains unclear if and how drug efflux proteins contribute to clinical cancer resistance to paclitaxel.[13]

Paclitaxel's Broad Spectrum of Activity in Human Cancer

Paclitaxel is one of the most widely used cancer therapeutic agents in human patients with broad activity in

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Taxol is a registered trademark of BMS.

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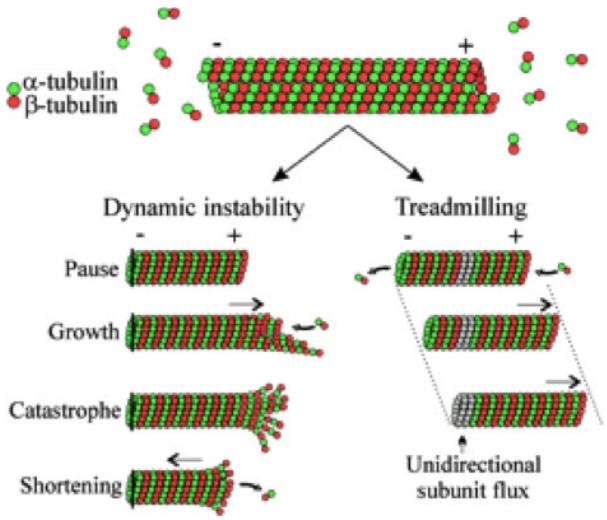

Fig 1. The mature microtubule is assembled from tubulin subunits. The microtubule exists in a dynamic state where tubulin subunits are added (assembly) and removed (disassembly) from the mature microtubule. The result can be growth, shortening in one or both directions, or a state referred to as dynamic instability or treadmilling. These dynamic states, and the multiple functions for microtubules in eukaryotic cells predict that the microtubule would be a valuable cellular target when the microtuble is growing and after it has matured.

several cancer histologies ranging from the sarcomas to several epithelial cancers and melanoma (Table 1). Specifically, paclitaxel is active in breast cancer, endometrial cancer, nonsmall-cell lung cancer, bladder cancer, and cervical carcinoma.[7] Combinations of paclitaxel with other cytotoxic agents have also been explored and it has been found to be a useful addition that has enhanced efficacy[14]; most notably combinations of paclitaxel with doxorubicin in breast cancer, and with cisplatin and carboplatin for lung cancer.[15] Paclitaxel, based primarily on its propensity to arrest cancer cells in the G2/M phase of the cell cycle, has also been used as a radio-sensitizer in several cancers including head and neck carcinoma.[16] The activity of paclitaxel was reported in the context of an early phase case series that included 25 dogs with a variety of cancer histologies and accordingly should be cautiously interpreted as evidence of efficacy. Specifically, partial responses were seen in 5 dogs from this case series, including 2 dogs with osteosarcoma, 2 dogs with mammary carcinoma and a single dog with malignant history of histiocytosis.

Paclitaxel is active as a first-line (adjuvant) treatment for breast cancer. Phase 3 trials have demonstrated a clear survival advantage for women receiving adjuvant (postsurgical) paclitaxel-anthracycline combination protocols compared to similar patients receiving nonpaclitaxel anthracycline-based protocols.[15,17,18] Interestingly, the paclitaxel benefit is greatest in patients with more aggressive, hormone receptor-negative tumors.[19] Furthermore, paclitaxel is also active as a second line agent in breast cancer, with response rates that range from 30 to 57% depending on the stage of the disease.[20–22] Common adverse events predicted by the mechanism of action of paclitaxel include nausea and vomiting, loss of appetite, and myelosuppression (specifically neutropenia and thrombocytopenia).[23] In addition to these expected adverse effects that are directly related to the mechanism of action of paclitaxel and its effects on rapidly dividing

Table 1. The Taxanes are a widely active chemotherapy class with demonstrated broad-spectrum activity in many human cancer types.

Cancers of Humans and Settings in Which the Taxane Class is Active	Nature of Evidence	Description of Use and Effectiveness
Breast Cancer	Phase III studies-single agent adjuvant	Improved overall survival (HR 0.83; 0.74–0.86)[46]
Lung Cancer	Phase III studies-single agent adjuvant	Improved survival alone and in combination with platinum chemotherapy[47]
Prostate Cancer	Phase III studies-single agent adjuvant	Single agent activity in hormone resistant prostate cancer and improved survival as an adjuvant to surgery[48]
Pancreatic Cancer	Phase III studies-combined with gemcitabine	Front-line option in metastatic patients and adjuvant treatment alone and with gemcitabine[49]
Ovarian Cancer	Phase III studies-single agent adjuvant	Response rates 20–48%[50]
Bladder Cancer	Phase II studies	Single agent overall disease control rate 18%[50]
Endometrial Cancer	Phase I studies-in platinum resistant endometrial cancer	Single agent response rate 86%, including platinum resistant patients[51]
Squamous Cell Carcinoma	Phase II studies	Single agent response rates 66–96%: benefit seen when combined with bevacizumab[52]
Melanoma	Phase II studies	6-month PFS 29%: response rate 0–14%[34]
Soft Tissues Sarcoma and Kaposi Sarcoma	Phase II studies	Single agent response rate of 14.3%[53]
Lymphoma	Phase II studies-single agent	Combined with vinorelbine, etoposide with cisplatin (vtepa) response rate 33%[54]

cells, paclitaxel is also recognized to be associated with neurotoxicity in humans. It is unclear whether this neurotoxicity is the result of the drug's effect on microtubule stabilization, or if alternative mechanisms for axonal degeneration may be involved. Regardless of the mechanism, paclitaxel exposure results in neuronal damage and the clinical observation of peripheral neuropathy. This peripheral neuropathy is more influenced by the paclitaxel schedule than the dosage, and occurs in 4–16% of treated human patients.[24] Neurotoxicity associated with paclitaxel exposures has not been observed in dogs. It is, however, reasonable that as the duration of exposures increases, such neuropathies may become evident. The absence of clinical neuropathy in dogs is not surprising given the difficulty in defining peripheral neuropathy using clinical assessment alone.

Because of the low aqueous solubility of paclitaxel, Taxol® formulations include Cremophor® EL (polyoxyethylated castor oil) and ethanol as an excipient. Such formulations overcome poor solubilization of paclitaxel for parenteral use. However, Cremophor®-induced complement activation is believed to be the cause of common hypersensitivity reactions related to Taxol® use in humans and other species.[25,26]

Cremophor® formulations are especially troublesome in dogs and are associated with a high incidence of hypersensitivity reactions. In 1 study, of 36 dogs with cancer receiving Taxol®, 64% developed substantial hypersensitivity reactions despite premedication with antihistamines and corticosteroids.[27] Because Taxol® is contraindicated in human patients with a history of past Taxol® hypersensitivity reactions, by standards used in humans Taxol® would be contraindicated in most dogs.[25,28] In addition to these Cremophor®-associated hypersensitivy reactions, paclitaxel's use in dogs was associated with expected toxicities based on its mechanism of action. These included neutropenia and other signs of myelosuppression as well as gastroenteritis. The brevity of exposures in dogs in published studies to date likely explains why the chronic neurotoxicities seen in human patients have not been observed in dogs thus far.

Novel Paclitaxel Formulations

The promising activity of Taxol® alone and in combination with other cancer treatments in such a wide spectrum of cancer histologies has led to interest in the development of alternative (ie, nonCremophor®) formulations designed to decrease or eliminate hypersensitivity reactions, thereby increasing the therapeutic index of this drug class.[26,29] Most alternative formulations focus on enhanced water solubility (ie, safer excipients), tumor-targeting properties, drug biodistribution, and more practical extraction or synthesis (Fig 2).

Historically, alternative formulations were developed as a means to decrease the difficulty with extraction and purification of paclitaxel from its natural source. Indeed, Taxotere® (docetaxel), is a semisynthetic form of paclitaxel, that avoids these issues while maintaining a similarly broad spectrum of activity in cancers of humans.[30]

Examples of recently developed alternative formulations of paclitaxel that are noncremophorylated and may preferentially target tumors include:

- Abraxane®: Paclitaxel that is bound to human albumin. Abraxane is associated with a decreased rate of hypersensitivity and may be associated with increased intratumoral uptake. Abraxane has been proven to be active in advanced and metastatic prostate cancer and is approved as monotherapy in metastatic breast cancer.[31] The inclusion of human albumin results in this formulation being less acceptable for use in dogs.
- Taxoprexin® is a prodrug of paclitaxel bound to the fatty acid, docosahexaenoic acid. Fatty acid cleavage occurs slowly within tumor tissues with the desired outcome of sustained tumor accumulation.[32,33] Phase II studies have demonstrated favorable results with this new paclitaxel formulation in human patients with lung melanoma and other cancers.[34]
- Paclical® poliglumex: Paclitaxel conjugated to poly-(L-glutamic acid). This compound similarly results in drug accumulation in tumor and tumor vasculature.[35] Phase II studies in nonsmall cell lung cancer, ovarian, and breast cancers are underway with encouraging early results.[36]
- ANG1005: Paclitaxel linked to angiopep-2 (brain peptide vector). This formulation allows paclitaxel to be transported across the blood brain barrier and to decrease active cellular efflux by evading the P-glycoprotein (Pgp) transport efflux pump.[37] This ultimately results in higher drug concentrations within the brain parenchyma after systemic delivery and a decrease in Pgp-mediated resistance.
- Paccal® is a novel, Cremophor®-free formulation of paclitaxel. The key component of this new formulation is the use of a novel excipient composed of a surfactant-based derivative of retinoic acid (XR-17) that results in a nanoparticle micellar preparation (Fig 2) with high water solubility that eliminates the need for Cremophor®.[38] This Cremophor®-free formulation avoids the serious hypersensitivity issues observed with Taxol® and other cremophorylated taxane formulations. In addition, the nanoparticle formulation is of a size (20–40 nm diameter) that may take advantage of the enhanced permeability and retention (EPR) effect.[39] The EPR effect occurs when the nanosized macromolecules evade renal clearance resulting in prolonged elimination half-lives and exploit leaky tumor vasculature, which may result in selective and specific extravasation and accumulation within the tumor tissues. Although the size and molecular characteristics of Paccal® predict it to be a formulation that would yield the EPR effect, there are insufficient data to confirm the EPR effect with this specific agent.

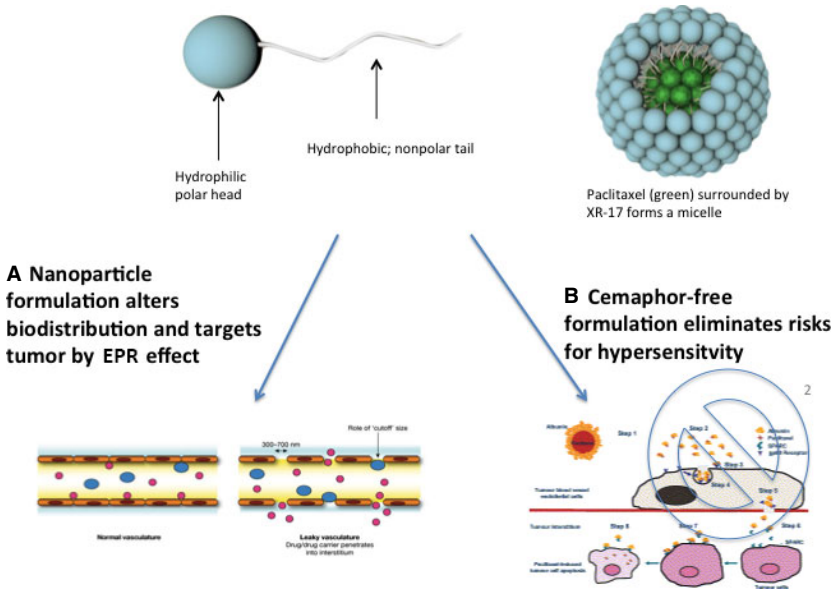

Fig 2. Recently developed novel formulations of paclitaxel have the desired goals to increase tumor uptake, and to alter pharmacokinetics and biodistribution so as to collectively improve the therapeutic index. These formulations often take advantage of nanoparticle delivery and (**A**) the associated enhanced permeability and retention (EPR) effect. The EPR effect occurs when nano-sized (20–40 nm) molecules evade renal clearance resulting in prolonged elimination half-lives so as to exploit leaky tumor vasculature, which results in selective and specific extravasation and passive accumulation of drug within tumor tissues. A critical additional advantage of novel paclitaxel formulations is to be cremophor-free which (**B**) avoids the hypersensitivity reactions associated with Taxol® use. As an example of such novel formulations, Paccal Vet-CA1® includes a retinoic acid excipient (XR-17) which allows water solubilization of paclitaxel in a nanomolecular particulate formulation.

- Other nanoparticulate or liposomal Cremophor® free formulations of paclitaxel have been the subject of early preclinical pharmacokinetic (PK) studies, dose-finding investigations, or both in normal laboratory dogs, but their use in tumor-bearing client-owned dogs has not, as of yet, been reported. These include CTI 52010, a nanoparticulate paclitaxel evaluated in a small intracohort phase I dose-finding study in normal dogs.[40] MTC-220, a conjugate of paclitaxel and the immunomodulatory analog of muramyl dipeptide has been evaluated in a small number of laboratory beagle dogs to establish PK properties.[41] Liposomes composed of Tween-80/HSPC/cholesterol and paclitaxel were evaluated in a small number of normal dogs for their PK and lung-targeting properties[42] and Lipusu®, another paclitaxel liposome, has been evaluated in laboratory dogs.[43]

Preclinical Development of Paccal Vet®

In repeat dosing studies in rats, no systemic toxicities were seen after the administration of the novel excipient (XR-17) of Paclical®. A preclinical study showed that rats could tolerate higher doses of Paclical® compared to Taxol®. As predicted by the novel Cremaphor®-free formulation, the safety profile for Paclical® was favorable in several animal species and in the recently completed early trials in humans.[27,44] In rats, Paclical® was found to have no unique organ toxicities when directly compared to Taxol®. Expected toxicities included bone marrow atrophy, lymphoid atrophy, and degenerative changes in the male genital tract and mammary gland. The occurrence of acute toxicity is decreased when comparing the results of the studies using Paccal® with those using Taxol®. Pharmacokinetic assessment demonstrated a rapid distribution of paclitaxel to the tissues. More importantly, no hypersensitivity reactions were observed and no unexpected adverse effects were noted after repeated administration of Paclical®.

Clinical Development of Paccal Vet® for Dogs with Cancer

Based on the safety profile of Paclical® in other species and its Cremophor®-free formulation, studies of an identical formulation of Paclical® called Paccal Vet® were initiated. An initial Phase I/II study was performed to investigate the tolerability of Paccal Vet® in dogs with solid tumors.[38] In a rapid dose escalation study design, Paccal Vet® was well tolerated at a dosage of up to 150 mg/m^2.[38] In this population of dogs, the most common adverse events included transient neutropenia, inappetence, and mild vomiting and diarrhea. Pharmacokinetic studies identified a rapid tissue distribution of paclitaxel. The elimination half-life was 3 hours (median). One dog experienced a mild hypersensitivity reaction in this study.

Results from this phase I/II study of Paccal Vet® led to a multi-center European, open label, single-arm study of Paccal Vet® to determine the efficacy and safety in dogs with grade II or III mast cell tumors.[45]

The study resulted in the accrual of 29 dogs with mast cell tumors. Paccal Vet® was given as an infusion at a dosage of 150 mg/m^2 every 3 weeks for 3 treatment cycles. No unexpected adverse effects were seen in this phase II study in dogs. These data prompted the launch of an international, multi-center, randomized, controlled, Phase III study to determine the efficacy and safety of Paccal Vet® compared with lomustine (CeeNU®) in dogs with grade II and III mast cell tumors.[44] In the 169 dogs that received Paccal Vet® as part of this study, the adverse event profile observed was similar to that of most currently used cytotoxic chemotherapy agents in veterinary oncology. Therefore, standard clinical management practices did not require modification when using Paccal Vet®. The majority of adverse events attributed to Paccal® were transient and clinically manageable. No unexpected adverse events with a VCOG score of 3 or greater were observed. The most common adverse events, with a VCOG score of 3 or greater included neutropenia (73%); emesis (20%), and anorexia (10%). A full description of the observed adverse events are included in a recent manuscript. The reader is referred to the original manuscript for a complete and tabular listing of the adverse events observed in this randomized trial.[44] Importantly, replacement of the Cremophor® excipient with the much safer excipient (XR-17) was a clear benefit because hypersensitivity reactions were significantly decreased.

As predicted by paclitaxel's mechanism of action (which targets the very basic elements of the cancer phenotype) and its broad spectrum of activity in human patients, Paccal Vet® likely will be active against a number of veterinary cancer histologies. This recognition contributed to the conditional approval of Paccal Vet-CA1® in dogs with nonresectable grade III, IV and V mammary tumors and dogs with resectable and nonresectable squamous cell carcinoma. The '-CA1' suffix designates Food and Drug Administration (FDA) conditional approval status. The actual benefit of the drug in these and other veterinary cancers remains unclear. Conditional approval allows the sponsor of a new drug to make a drug available to the market before collection of all effectiveness data but after proving the drug is safe in accordance with the full FDA approval standard and showing that there is reasonable expectation of effectiveness. The reader is directed to the FDA website defining conditional approval as set forth in the Minor Use and Minor Species Animal Health Act of 2004 (http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm2007133.htm). Under conditional approval, Paccal® may be marketed and used to treat animals that strictly meet the approved label, that is, the treatment of dogs with resectable and nonresectable squamous cell carcinoma and nonresectable stage III–V mammary tumors that have not received previous chemotherapy or radiotherapy. Importantly, it is a violation of federal (USA) law to use conditionally approved drugs other than as directed in the labeling. Discussion of data, whether published or otherwise, that extends beyond the conditional approval label, may be considered by regulatory groups to be inappropriate. As such, further discussion in this manuscript of Paccal®'s use on cancers, whether published or not, that do not fall under this conditionally approved label has been limited. We nonetheless recognize the reasonable interest of the oncology community in these published studies,[38,44,45] that include early phase studies in several cancer types, and more prominent later phase randomized studies in dogs with mast cell tumors. Briefly, the activity of Paccal® in dogs with a variety of measurable cancers in early phase studies was demonstrated and may be considered to be reasonable evidence of its expected activity in a variety of canine cancers in dogs.[38] In the clinical studies of Paccal® use in mast cell tumors, the demonstrated benefit compared to the CCNU comparator was statistically significant for the primary endpoint of best overall response.[44] However, the magnitude of this significant advantage may be considered to be small. Clinical trials are now underway to define the efficacy of Paccal Vet®-CA1 in dogs with mammary tumors and in dogs with squamous cell carcinoma, with each population of dogs having no previous exposure to chemotherapy or radiotherapy.

In summary, there are now opportunities to develop safer, more effective, and potentially tumor-targeting paclitaxel compounds. Indeed, currently there are investigations in humans and in laboratory and tumor-bearing dogs underway with these agents. Current veterinary preclinical trials are evaluating the pharmacokinetics and pharmacodynamics of these agents, whereas 1 compound with FDA conditional approval (Paccal Vet®-CA1), is currently being investigated for its efficacy in client-owned dogs with squamous cell carcinoma and mammary carcinoma. It is hoped that safe, effective, and fully approved paclitaxel formulations will soon become more available to practicing veterinarians.

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Cragg GM. Paclitaxel (Taxol): a success story with valuable lessons for natural product drug discovery and development. Med Res Rev 1998;18:315–331.

2. Suffness M. Is taxol a surrogate for a universal regulator of mitosis? In Vivo 1994;8:867–878.

3. Walsh V, Goodman J. From taxol to Taxol: the changing identities and ownership of an anti-cancer drug. Med Anthropol 2002;21:307–336.

4. Manfredi JJ, Horwitz SB. Taxol: an antimitotic agent with a new mechanism of action. Pharmacol Ther 1984;25:83–125.

5. Amos LA, Lowe J. How Taxol stabilises microtubule structure. Chem Biol 1999;6:R65–R69.

6. Foa R, Norton L, Seidman AD. Taxol (paclitaxel): a novel anti-microtubule agent with remarkable anti-neoplastic activity. Int J Clin Lab Res 1994;24:6–14.

7. Hajek R, Vorlicek J, Slavik M. Paclitaxel (Taxol): a review of its antitumor activity in clinical studies Minireview. Neoplasma 1996;43:141–154.

8. Sparreboom A, Scripture CD, Trieu V, et al. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). Clin Cancer Res 2005;11:4136–4143.

9. Furtlehner A, Schueller J, Jarisch I, et al. Disposition of paclitaxel (Taxol) and its metabolites in patients with advanced breast cancer (ABC) when combined with trastuzumab (Hercpetin). Eur J Drug Metab Pharmacokinet 2005;30:145–150.

10. Rowinsky EK. Clinical pharmacology of Taxol. J Natl Cancer Inst Monogr 1993;15:25–37.

11. Horwitz SB, Cohen D, Rao S, et al. Taxol: mechanisms of action and resistance. J Natl Cancer Inst Monogr 1993;15:55–61.

12. Kavallaris M, Kuo DY, Burkhart CA, et al. Taxol-resistant epithelial ovarian tumors are associated with altered expression of specific beta-tubulin isotypes. J Clin Investig 1997;100:1282–1293.

13. Distefano M, Scambia G, Ferlini C, et al. Antitumor activity of paclitaxel (taxol) analogues on MDR-positive human cancer cells. Anticancer Drug Des 1998;13:489–499.

14. Ozols RF. Paclitaxel (Taxol)/carboplatin combination chemotherapy in the treatment of advanced ovarian cancer. Semin Oncol 2000;27:3–7.

15. deMagalhaes-Silverman M, Hammert L, Lembersky B, et al. High-dose chemotherapy and autologous stem cell support followed by post-transplant doxorubicin and taxol as initial therapy for metastatic breast cancer: hematopoietic tolerance and efficacy. Bone Marrow Transplant 1998;21:1207–1211.

16. Zhao Y, Wang SM, Zhang J. [Combination chemotherapy with Taxol and cisplatin for 57 patients with non-small cell lung cancer by intra-artery and intravenous infusion]. Ai Zheng 2002;21:1365–1367.

17. Yamazaki S, Sekine I, Saijo N. [Paclitaxel (taxol): a review of its antitumor activity and toxicity in clinical studies]. Gan to Kagaku Ryoho 1998;25:605–615.

18. Bishop JF, Dewar J, Toner GC, et al. Paclitaxel as first-line treatment for metastatic breast cancer. The Taxol Investigational Trials Group, Australia and New Zealand. Oncology (Williston Park) 1997;11:19–23.

19. Camirand A, Fadhil I, Luco AL, et al. Enhancement of taxol, doxorubicin and zoledronate anti-proliferation action on triple-negative breast cancer cells by a PTHrP blocking monoclonal antibody. Am J Cancer Res 2013;3:500–508.

20. Borovik R, Steiner M, Atad J, et al. Taxol (paclitaxel) as second-line therapy in breast and ovarian cancer. Harefuah 1998;134:605–608, 671.

21. Pazos C, Mickiewicz E, Di Notto MR, et al. Phase II of doxorubicin/taxol in metastatic breast cancer. Argentine Multicenter Taxol Group. Breast Cancer Res Treat 1999;55:91–96.

22. Perez-Manga G, Lluch A, Alba E, et al. Gemcitabine in combination with doxorubicin in advanced breast cancer: final results of a phase II pharmacokinetic trial. J Clin Oncol 2000;18:2545–2552.

23. Lang I, Rubovszky G, Horvath Z, et al. A comparative analysis on the efficacy and safety of intaxel(R) and taxol(R) in advanced metastatic breast cancer. J Clin Diagn Res 2013;7:1120–1124.

24. Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. Curr Neuropharmacol 2006;4:165–172.

25. Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. Clin Rev Allergy Immunol 2014 AOR 17, [Epub ahead of print] PMID:24740483.

26. Nehate C, Jain S, Saneja A, et al. Paclitaxel formulations: challenges and novel delivery options. Curr Drug Deliv 2014;11:666–686.

27. Poirier VJ, Hershey AE, Burgess KE, et al. Efficacy and toxicity of paclitaxel (Taxol) for the treatment of canine malignant tumors. J Vet Intern Med 2004;18:219–222.

28. Banerji A, Lax T, Guyer A, et al. Management of hypersensitivity reactions to Carboplatin and Paclitaxel in an outpatient oncology infusion center: a 5-year review. J Allergy Clin Immunol Pract 2014;2:428–433.

29. Mu L, Feng SS. A novel controlled release formulation for the anticancer drug paclitaxel (Taxol): PLGA nanoparticles containing vitamin E TPGS. J Control Release 2003;86:33–48.

30. Braga SF, Galvao DS. A structure-activity study of taxol, taxotere, and derivatives using the electronic indices methodology (EIM). J Chem Inf Comput Sci 2003;43:699–706.

31. Neesse A, Michl P, Tuveson DA, et al. nab-Paclitaxel: novel clinical and experimental evidence in pancreatic cancer. Z Gastroenterol 2014;52:360–366.

32. Koo H, Min KH, Lee SC, et al. Enhanced drug-loading and therapeutic efficacy of hydrotropic oligomer-conjugated glycol chitosan nanoparticles for tumor-targeted paclitaxel delivery. J Control Release 2013;172:823–831.

33. Fracasso PM, Picus J, Wildi JD, et al. Phase 1 and pharmacokinetic study of weekly docosahexaenoic acid-paclitaxel, Taxoprexin, in resistant solid tumor malignancies. Cancer Chemother Pharmacol 2009;63:451–458.

34. Homsi J, Bedikian AY, Papadopoulos NE, et al. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. Melanoma Res 2010;20:507–510.

35. Wang H, Wu Y, Zhao R, et al. Engineering the assemblies of biomaterial nanocarriers for delivery of multiple theranostic agents with enhanced antitumor efficacy. Adv Mater 2013;25:1616–1622.

36. Northfelt DW, Allred JB, Liu H, et al. Phase 2 trial of paclitaxel polyglumex with capecitabine for metastatic breast cancer. Am J Clin Oncol 2014;37:167–171.

37. Kurzrock R, Gabrail N, Chandhasin C, et al. Safety, pharmacokinetics, and activity of GRN1005, a novel conjugate of angiopep-2, a peptide facilitating brain penetration, and paclitaxel, in patients with advanced solid tumors. Mol Cancer Ther 2012;11:308–316.

38. von Euler H, Rivera P, Nyman H, et al. A dose-finding study with a novel water-soluble formulation of paclitaxel for the treatment of malignant high-grade solid tumours in dogs. Vet Comp Oncol 2013;11:243–255.

39. Hendricks WP, Yang J, Sur S, et al. Formulating the magic bullet: barriers to clinical translation of nanoparticle cancer gene therapy. Nanomedicine 2014;9:1121–1124.

40. Axiak SM, Selting KA, Decedue CJ, et al. Phase I dose escalation safety study of nanoparticulate paclitaxel (CTI 52010) in normal dogs. Int J Nanomed 2011;6:2205–2212.

41. Liu X, Zhao M, Mi J, et al. Simultaneous quantification of MTC-220 and its metabolites in beagle dog plasma by liquid chromatography-tandem mass spectrometry. J Pharm Biomed Anal 2014;99:1–7.

42. Zhao L, Ye Y, Li J, et al. Preparation and the in-vivo evaluation of paclitaxel liposomes for lung targeting delivery in dogs. J Pharm Pharmacol 2011;63:80–86.

43. Wang X, Song L, Li N, et al. Pharmacokinetics and biodistribution study of paclitaxel liposome in Sprague-Dawley rats and Beagle dogs by liquid chromatography-tandem mass spectrometry. Drug Res 2013;63:603–606.

44. Vail DM, von Euler H, Rusk AW, et al. A randomized trial investigating the efficacy and safety of water soluble micellar paclitaxel (Paccal Vet) for treatment of nonresectable grade 2 or 3 mast cell tumors in dogs. J Vet Intern Med 2012;26:598–607.

45. Rivera P, Akerlund-Denneberg N, Bergvall K, et al. Clinical efficacy and safety of a water-soluble micellar paclitaxel (Paccal Vet) in canine mastocytomas. J Small Anim Pract 2013;54:20–27.

46. Gines J, Sabater E, Martorell C, et al. Efficacy of taxanes as adjuvant treatment of breast cancer: a review and meta-analysis of randomised clinical trials. Clin Transl Oncol 2011;13: 485–498.

47. Ramalingam S, Belani CP. Taxanes for advanced non-small cell lung cancer. Expert Opin Pharmacother 2002;3:1693–1709.

48. Schutz FA, Buzaid AC, Sartor O. Taxanes in the management of metastatic castration-resistant prostate cancer: efficacy and management of toxicity. Crit Rev Oncol Hematol 2014;91:248–256.

49. Arslan C, Yalcin S. Current and future systemic treatment options in metastatic pancreatic cancer. J Gastrointest Oncol 2014; 5:280–295.

50. Balar AV. The impact of taxanes on the management of genitourinary cancers. Anticancer Drugs 2014;25:555–560.

51. Cho H, Nam BH, Kim SM, et al. A Phase 2 trial of radiation therapy with concurrent paclitaxel chemotherapy after surgery in patients with high-risk endometrial cancer: a Korean Gynecologic Oncologic Group Study. Int J Radiat Oncol Biol Phys 2014; 90:140–146.

52. Wanebo HJ, Lee J, Burtness BA, et al. Induction cetuximab, paclitaxel and carboplatin followed by chemoradiation with cetuximab, paclitaxel and carboplatin for stage III/IV head and neck squamous cancer: a Phase II ECOG-ACRIN trial (E2303). Ann Oncol 2014;25:2036–2041.

53. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer 2010;116:3969–3977.

54. Shraddha R, Pandit PN. Role of taxanes in the treatment of advanced NHL patients: a randomized study of 87 cases. Gulf J Oncolog 2014;1:7–11.