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Paclitaxel: a review of adverse toxicities and novel delivery strategies

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Better known as Taxol® (Bristol-Myers Squibb), paclitaxel is the first member of the taxane family to be used in cancer chemotherapy. The taxanes exert their cytotoxic effect by arresting mitosis through microtubule stabilization, resulting in cellular apoptosis. The use of paclitaxel as a chemotherapeutic agent has become a broadly accepted option in the treatment of patients with ovarian, breast and non-small cell lung cancers, malignant brain tumors, and a variety of other solid tumors. However, significant toxicities, such as myelosuppression and peripheral neuropathy, limit the effectiveness of paclitaxel-based treatment regimens. This review addresses the toxicities associated with paclitaxel treatment and describes existing and future strategies of paclitaxel administration directed at limiting these toxicities.

Keywords: adverse effects, cancer, paclitaxel, safety, toxicity

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1. Introduction

Paclitaxel and the related taxanes have received considerable attention due to their antitumor activity against a variety of tumors, including breast cancer, ovarian cancer, AIDS-related Kaposi's sarcoma, non-small cell lung cancer (NSCLC), head and neck cancers, and brain tumors. Paclitaxel is a taxoid drug extracted from the bark of the Pacific yew. The extract of *Taxus brevifolia* bark tissue was discovered to have significant antitumor activity during a massive screening of 35,000 plant extracts in 1963. In 1971, researchers elucidated the structure of paclitaxel (**Figure 1**) and reported on its cytotoxicity against the human KB carcinoma cell line and mouse leukemia cells [1].

2. Chemistry and production of paclitaxel, and implications for drug delivery

Paclitaxel is a complex diterpene and taxane derivative that is composed of a four membered oxetane ring and an ester side chain at position C-13 (**Figure 1**) [1]. Structural studies of paclitaxel eventually led to the identification of the diterpenoid as the active component responsible for its antitumor activity [1]. The drug exists in small amounts in the bark of the natural yew tree, which limits the natural amount available for production. It is estimated that extraction of paclitaxel from three mature, 100-year-old trees produces only one gram of active drug.

In addition, synthesis of paclitaxel is a complex and expensive multistep process. Paclitaxel's lack of aqueous solubility poses another problem, contributing to difficulty of therapeutic delivery. Due to the unreasonable costs of production and purification of the drug, alternative and novel methods of paclitaxel production are being developed

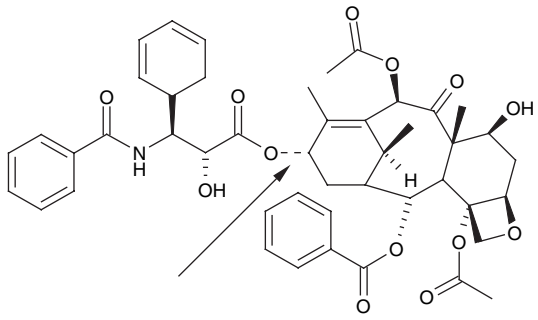

Figure 1. Chemical structure of paclitaxel. The arrow indicates position C-13.

in order to meet the growing demands. Alternatively, improving delivery methods based on paclitaxel's chemical properties may lower the actual amount of drug needed for clinical use and help decrease severity and/or incidence of associated toxicities.

The production quantity of paclitaxel has improved with new methods of production, such as hemisynthesis and plant cell culture. Instead of extracting the drug from tree bark, semisynthetic paclitaxel and analogs, such as docetaxel, are now being derived from 10-deacetylbaccatin III, a paclitaxel precursor isolated from *T. baccata* [2]. The needles from this plant possess the ability to regenerate, providing a continuous source of precursor for paclitaxel. *T. chimesis* suspensions have been stimulated in various ways to increase production of paclitaxel, by organic solvents, sucrose feeding, fungal elicitation, temperature alteration and by the rare earth chemical lanthanum [3-7]. In addition, jasmonic acid, a cyclized and modified fatty acid derivative, seems to be very effective in stimulating production of paclitaxel, allowing for a more efficient production process for the drug [8-10].

3. Biologic effects of paclitaxel

Paclitaxel is the prototype of a new class of chemotherapeutic agents [11] in which the assembly of microtubules is promoted and the disassembly inhibited via tubulin stabilization [12], not destabilization. Paclitaxel interacts with a specific site on β-tubulin in a binding pocket formed by α-helices and β-strands to prevent microtubule depolymerization [13,14]; the conformation of taxol in its binding site is optimized as a t-shaped structure, with structural similarity to a portion of the B9 – B10 loop in the α-tubulin subunit [15]. This induces mitotic arrest and apoptosis in proliferating cells through stabilization of the mitotic spindle [16]. The cell's resulting inability to de-construct the mitotic spindle during mitosis leads to cessation of the cell cycle with arrest at the G2/M phase [17,18]. Because the G2 and M phases are the most radiosensitive phases of the cell cycle, paclitaxel is also a potent radiosensitizer.

Besides its effects on tubulin, paclitaxel appears to possess other additional biological effects. Paclitaxel can alter cell signaling through activation of mitogen-activated protein kinases, Raf-1, tyrosine kinases, c-Jun NH_2-terminal kinase and nitric oxide synthase [19-25]. Paclitaxel also triggers apoptosis through caspase-dependent and -independent pathways [26-29] by regulating the expression of apoptosis-related proteins such as Bcl-2, Bad and Bcl-xL [30-33]. Low picomolar concentrations of paclitaxel have been shown to selectively inhibit human endothelial cell proliferation and angiogenesis *in vitro* [34,35].

4. Pharmacodynamics and pharmacokinetics

Paclitaxel is highly bound to plasma protein (88 – 98%) and the steady-state volume of distribution is large [36]. Single-dose intravenous administration of paclitaxel at 135 – 350 mg/m^2 produces a mean plasma concentration of 0.23 – 10 μM, which is significantly higher than concentrations that produce anti-microtubule effects *in vitro* (0.1 μM) [37]. Paclitaxel has a broad tissue distribution along with an average distribution half-life of 0.34 h and an average elimination half-life of 5.8 h [38,39].

The clinical dosing schedules commonly used today are 1-h and 3-h weekly, biweekly or three times weekly. Typically, 175 mg/m^2 for three times weekly and 80 – 100 mg/m^2 for the weekly schedule, and doses up to 100 mg/m^2 usually maintain concentrations in the linear range of the curve [40-43]. Although it has a large volume of distribution, paclitaxel does not cross the blood–brain barrier (BBB) in significant quantities [44].

Hepatic metabolism by the CYP system (isoenzymes CYP2C8 and -3A4) and biliary excretion are responsible for the elimination of paclitaxel into the stool [37]. Therefore, dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction. A number of factors have been shown to affect the pharmacokinetics of paclitaxel and, thus, its potential for toxicity. Body surface area, total bilirubin and patient age were all confirmed to affect paclitaxel elimination in an extended retrospective population analysis, whereas patient gender had a significant and independent effect on both elimination and distribution [45].

Because cytotoxic drugs like paclitaxel are often hydrophobic, toxic solubilizing agents such as Cremophor/ethanol (CrEL) are often used to administer the drug [46-48]. Paclitaxel in its injectable form is supplied in 50% Cremophor and 50% dehydrated ethanol. After dilution to a concentration of 1 mg/ml, it can be administered intravenously over a period of 3 – 24 h. The hydrophobicity of paclitaxel is associated with unfavorable kinetics, high levels of protein binding and volumes of distribution that greatly exceed total body water [46]. The CrEL solvent also causes alterations in the pharmacokinetic profile of paclitaxel. Altogether, these factors have a profoundly negative impact on the therapeutic index because only a small proportion of the administered dose actually reaches the intended site of treatment. The therapeutic index and toxicity profile of any cytotoxic agent are related to the length of time that sensitive tissues are exposed to a biologically relevant concentration of the drug. The pharmacokinetics of paclitaxel,

when the drug is administered systemically, are associated with limited tumor exposure and comparatively high systemic exposure leading to a low therapeutic index. Furthermore, elimination kinetics may necessitate inconvenient dosing schedules to realize optimal efficacy. Thus, alternative delivery strategies have been explored to improve intratumoral concentrations of paclitaxel.

Studies suggest that the nonlinear pharmacokinetics of paclitaxel result from CrEL [42,49]. Micellar entrapment of paclitaxel by CrEL in plasma not only makes it less available for tumor tissue distribution, but also results in a substantial increase in systemic exposure to paclitaxel and reduced systemic clearance, altering the pharmacodynamics of the drug and increasing the risk for systemic toxicities [50]. Notably, CrEL-free formulations (e.g., albumin-bound, polyglumax, polymeric-micellar paclitaxel) tend to require less volume and decreased administration times compared with standard formulations with CrEL. CrEL-free formulations allow for higher paclitaxel doses to be administered without increasing the severity of adverse effects. Overall, CrEL-free formulations induce fewer and less severe adverse effects and allow for improved control of effective plasma levels [51,52]. However, because paclitaxel is a substrate of the efflux transporter, P-glycoprotein, CrEL-free formulations of paclitaxel do not result in any improvement in the drug's ability to cross the BBB when administered systemically.

5. Adverse events and effects of paclitaxel with systemic administration

Adverse effects associated with paclitaxel administration include the hypersensitivity reactions, myelosuppression, bradycardia, hypotension, peripheral neuropathy, myalgias, arthralgias, nausea, diarrhea, mucositis and alopecia. However, the presentation and occurrence of adverse effects varies from patient to patient and is often schedule dependent. Neutropenia, for example, is more frequent with 24-h infusions compared with 3-h infusions, but most frequent with 1-h infusions [53]. Certain adverse effects (e.g., neutropenia) are fairly common, whereas other adverse effects (e.g., bradycardia) tend to be rare. In addition, some adverse effects may not be directly caused by paclitaxel itself. Biologic effects such as acute hypersensitivity and peripheral neuropathies have been described as related to the CrEL vehicle and are under investigation with CrEL-free formulations of paclitaxel.

Clinical studies over the last 20 years have led to changes in the paclitaxel dosing and scheduling regimens, namely reductions in infusion times and increases in dose density. Premedication with steroids and histamine blockers has allowed for shorter infusion times (1 – 3 h) [54]. On the other hand, infusion times < 1 h appear to increase the risk of severe anaphylactic shock [55]. Hematologic toxicities, such as leukopenia, may be controlled with growth factors such as granulocyte stimulating factor, which leaves neurotoxicity as the primary dose-limiting adverse effect [56].

5.1 Hypersensitivity

Paclitaxel was one of the first taxanes used clinically and was administered to more than 10,000 patients by 1995. In initial Phase I studies conducted nearly 20 years ago, administration of paclitaxel was complicated by the appearance of life-threatening type I anaphylactic reactions [57]. These severe hypersensitivity reactions may have been induced by the drug itself or its polyoxyethylated castor oil (CrEL) vehicle, which was required to keep the lipophilic drug in solution during intravenous administration [48,54]. Type I hypersensitivity reactions, including mild hypotension, dyspnea with bronchospasm, urticaria, abdominal and extremity pain, angiedema, and diaphoresis [54,58], suggest that these reactions are mediated by histamine. *In vitro* studies clearly show that CrEL is able to induce complement activation by itself and, therefore, may play an important role in triggering these reactions [59]. It is generally believed that the CrEL vehicle significantly contributes to the hypersenstitivity reactions and that these reactions are related to infusion rate [60]. Nonetheless, hypersensitivity reactions to taxanes formulated without CrEL have been reported, suggesting that the paclitaxel molecule itself may contribute, at least in part, to the development of hypersensitivity reactions [61]. Premedication with corticosteroids and H1 and H2 antagonists can curtail these adverse effects [54]. Therefore, to minimize the risk of hypersensitivity reactions patients should be pretreated with a standard regimen containing a corticosteroid, such as dexamethasone, an H1 and an H2 blocker, prior to any paclitaxel infusions. Even with these pretreatments, minor hypersensitivity reactions occur in 40% of all patients [60,62] with only 3% of patients experiencing life-threatening reactions [54].

5.2 Hematologic toxicity

Overall, bone marrow suppression is the major dose-limiting toxicity of the standard paclitaxel formulation. The principal hematologic toxicity associated with paclitaxel is neutropenia [57], which results in immunocompromise and increases the risk of infectious complications. Early clinical trials demonstrated that leukopenia and neutropenia due to paclitaxel administration is dose dependent and often rapidly reversible. Leukopenia and neutropenia are also significantly affected by the schedule of administration; longer durations of infusion (24 h) are more likely to cause hematologic toxicity than shorter durations (3 h) [53]. At doses of 200 – 250 mg/m^2 on a 24-h infusion schedule, neutropenia is usually severe, with absolute neutrophil count nadirs frequently < 500/µl in both minimally pretreated and non-pretreated patients.

Fortunately, the duration of severe neutropenia is usually brief and treatment delays for unresolved neutropenia are rare. Neutropenia is infrequently cumulative and absolute neutrophil count nadirs are similar with repetitive dosing, suggesting that paclitaxel does not irreversibly damage hematopoeitic stem cells.

The principal determining factor for the severity of neutropenia is the extent of prior myelotoxic therapy. In addition, infusion duration appears to have a greater impact on

myelosuppression than dose [53]. Among patients treated in a Phase III second-line ovarian cancer study with a 3-h infusion of paclitaxel, neutrophil counts declined below 500 cells/mm^3 in 14% of the patients treated with a dose of 135 mg/m^2 compared with 27% at a dose of 175 mg/m^2 [53]. Severe neutropenia (< 500 cells/mm^3) was more frequent with the 24-h than with the 3-h infusion [53]. Neutropenia does not appear to be more frequent or more severe for patients receiving radiation therapy simultaneously.

Recently, researchers have suggested a possible genetic predisposition to the occurrence of paclitaxel-induced neutropenia through the *ABCB1* transporter gene involved in paclitaxel elimination [63]. Patients with genetic variants at both the ABCB1 2677G > T/A and 3435C > T loci seem to develop a more severe degree of neutropenia [63].

Paclitaxel-induced thrombocytopenia and anemia present with less severity than neutropenia. In a Phase III study, bleeding episodes were reported in 10% of patients; however, patients treated with a 3-h infusion did not require platelet transfusions [53]. Anemia, on the other hand, was observed in 78% of patients and was severe (Hb < 8 g/dl) in 16% of cases. No consistent relationship was observed between dose or schedule and the frequency of anemia. The main mechanism involved in the development of paclitaxel-induced anemia appears to be direct toxicity to bone marrow. Renal impairment with a secondary deficiency in production of erythropoietin may also be a cause of anemia. Recent experiments also suggest that paclitaxel-induced anemia is partially due to a novel mechanism of stress-induced erythrocyte death, eryptosis, which is characterized by enhanced cytosolic $Ca^{(2+)}$ levels, increased ceramide formation and exposure of phosphatidylserine at the cell surface [64].

Combination treatments with paclitaxel and other cytotoxic chemotherapeutic agents appear to exacerbate myelosuppression. Treatment with carboplatin and paclitaxel induced grade 3/4 anemia in 34% of patients, with 30% ultimately required blood transfusions [65]. The most frequently reported grade 3/4 hematological toxicities (pancytopenia) occurred when paclitaxel was administered sequentially with doxorubicin and cyclophosphamide [66]. The use of growth factors, such as granulocyte colony stimulating factor [56], and the recent discovery that a reduction of infusion time from 24 to 3 h reduces the incidence of grade 3/4 neutropenia [53] has contributed to safer patient drug schedules and decreased complications from myelosuppression.

5.3 Infections

Although infections may be attributed to immunocompromise from hematological toxicity, certain infections are particularly common in patients receiving paclitaxel. Neutropenic entercolitis has been specifically associated with chemotherapy involving the taxane family of drugs during early stages of drug delivery [67]. Overall, fever occurs in ~ 12% of treatment courses and infectious episodes occur in 30% of all patients. Urinary tract infections and upper respiratory tract infections are the most frequently reported infectious complications. Other afflictions include pneumonia, sepsis and peritonitis. In a Phase III second-line ovarian study, infectious episodes were reported in 20% of patients treated with a dose of 135 mg/m^2 and 26% of patients treated with 175 mg/m^2, both given as 3-h infusions. In patients with advanced HIV disease and AIDS-related Kaposi's sarcoma, a severely immunocompromised patient population, 61% of the patients reported at least one opportunistic infection during paclitaxel treatments.

5.4 Neurotoxicity

Neurotoxic events attributable to the CrEL vehicle include ganglionopathy, axonopathy and demyelination. However, clinical data strongly supports a direct and independent effect of paclitaxel in the development of peripheral neuropathy [68]. Peripheral neuropathy from paclitaxel is a cumulative phenomenon [69-71] and represents the most important non-hematological toxicity associated with paclitaxel administration [56,72], especially in the existing weekly drug administration regimens [73-79].

Peripheral neuropathy is a major dose-limiting toxicity and, unfortunately, is encountered in a majority of patients along the course of their therapy [77]. Paclitaxel's effects on microtubule assembly and disassembly reduces normal axonal transport [80] leading to a length-dependent sensorimotor axonal neuropathy that is a common dose-dependent adverse effect of paclitaxel treatment [81,82]. Clinically, the paclitaxel-induced peripheral neuropathy is characterized by numbness and paresthesias in a glove-and-stocking distribution [70]. Examination usually reveals distal sensory deficits in both large fibers and small sensory fibers.

Cranial neuropathies, motor involvement and autonomic dysfunction have also been reported at high doses, particularly in patients with pre-existing neuropathies [83]. Rare cases of encephalopathy and seizures have occurred at doses > 600 mg/m^2 [84,85]. Even in otherwise asymptomatic patients, electrophysiological data suggests that motor nerve dysfunction occurs with paclitaxel administration [85].

Overall, the neurotoxic effect of paclitaxel is both dose- and time-dependent [86]. Unlike hypersensitivity reactions, peripheral neuropathy has been shown to be severe even with CrEL-free paclitaxel formulations [51]. As treatment options for peripheral neuropathy are rare and recent data supports that paclitaxel itself, and not its vehicle CrEL, is associated with peripheral neuropathy development [87], neurotoxicity of paclitaxel represents the major remaining challenge for further improvements of paclitaxel administration [51,52]. Because peripheral neuropathy often limits the clinical effectiveness of paclitaxel, research on the prevention of neuropathy development in patients being administered the drug is an important area of research.

Treatment options are limited and most treatment options available today are palliative, including dose reduction and cessation of treatment [68]. Tricyclic antidepressants and anticonvulsants are the most widely used treatments for

neuropathic pain, but the beneficial effects are often limited [88]. Administration of glutamine in patients receiving paclitaxel treatment has been shown to reduce symptoms of parasthesias and the development of neuropathy, although results of nerve conduction studies did not show significant improvement in sensory signals [89].

Inhibition of calpains, proteolytic enzymes found in the brain and muscle, by drugs such as CX-295, has been shown to reduce the clinical and pathological effects of paclitaxel in rodent models of paclitaxel-induced neuropathy. The reduction in neurotoxicity with administration of calpain inhibitors does not appear to be related to reduction of paclitaxel's effects on microtubule aggregation or programmed cell death. Therefore, overall potency of the chemotherapeutic regimen should not be affected significantly [90]. Recently, the neuroprotective effect of vitamin E has also been explored as a prophylactic treatment for peripheral neuropathy in patients treated with paclitaxel [91].

The neurotoxic mechanism of paclitaxel varies at the cellular level between different neuronal populations. Dorsal root ganglion dissociated postmitotic neurons were observed to die due to necrosis when exposed to paclitaxel, whereas proliferating human neuroblastoma SH-SY5Y cells and cortical neurons exposed to paclitaxel died due to apoptosis [86]. Genetic studies of patients experiencing neurotoxicity may provide us with a better understanding of the mechanism underlying these adverse effects and lead to improved treatments. Patients who are homozygous wild type for the ABCB1 3435 C > T transition have been shown to be less at risk for developing clinically significant peripheral neuropathy [63]. The differential response of various neuronal populations to paclitaxel underlines the importance of the biochemical and molecular phenotype of the neuronal population in determining cellular behavior, vulnerability to paclitaxel and the presentation of neurotoxic events. Thus, therapies aimed at reducing peripheral neuropathy must take into account the phenotypes of the neuronal populations most at risk.

5.5 Cardiac toxicity

As experience with paclitaxel has increased, it has become evident that the cardiac disturbances associated specifically with paclitaxel treatment consist primarily of asymptomatic bradycardia and/or hypotension [92]. Bradyarrhythmias with or without heart block have been noted in clinical trials from the late 1990s. In one clinical trial, bradycardia occurred in ~ 29% of patients during a 24-h period of continuous cardiac monitoring [93]. Other adverse cardiac effects are usually isolated and have no significant hemodynamic consequences. Second- and third-degree heart block are infrequently observed [94], although there have been reports of Mobitz I (Wenckebach syndrome) and Mobitz II atrioventricular (AV) blocks in the literature [92,94,95], along with more profound AV blocks culminating in third-degree block and requiring placement of a cardiac pacemaker or external cardiac pacing [96].

Fatal myocardial infarctions and atypical chest pains have rarely been reported. Asymptomatic bundle branch block and short runs of spontaneously resolving ventricular tachycardia have been noted in patients treated with paclitaxel alone or in combination with cisplatin [92,95].

When paclitaxel is administered with doxorubicin, the cardiotoxic events that appear arise from the paclitaxel-mediated conversion of doxorubicin to doxorubicinol. Doxorubicinol is an alcohol metabolite that is responsible for irreversible myocardial damage [97]. This likely explains the high risk of congestive heart failure when paclitaxel is used in combination with doxorubicin. Interestingly, low concentrations of paclitaxel appear to stimulate doxorubicinol formation in human heart cytosol, whereas higher concentrations decrease doxorubicinol levels back to control levels [97].

5.6 Myalgias

Myalgias, or muscle pain, can be observed immediately after infusion, during infusion, or 2 – 3 days after treatment with paclitaxel at higher doses, but usually resolve within 5 days. These pains can be easily misinterpreted as chest pain and angina [53,77]. In a Phase III paclitaxel trial comparing paclitaxel doses ranging from 135 to 250 mg/m^2, the occurrence of myaliga was greater with paclitaxel 250 mg/m^2 ($p < 0.05$) [98]. Myopathies, or neuromuscular diseases from myofiber dysfunction, are very rarely noted and have only been seen in patients receiving high doses of paclitaxel (300 – 350 mg/m^2) in combination with cisplatin and G-CSF [56].

6. Alternative delivery strategies for delivery of paclitaxel in cancer

The poor solubility of paclitaxel necessitates the use of CrEL in the commercial formulation of the drug, but, as has already been discussed, acute hypersensitivity reactions, neurotoxicities and alteration in pharmacokinetic profiles are drawbacks of the CrEL system. CrEL-free solutions and local drug delivery strategies incorporating intratumoral or regional drug delivery continue to gain momentum as novel and effective treatment modalities for cancer therapy due to the substantial decrease in systemic toxicity associated with these strategies. Researchers are now exploring the impact that the CrEL system has in the administration of paclitaxel through novel delivery strategies (e.g., nanoparticles, co-solvents, liposomes and micropsheres) that can reduce the amount of or completely eliminate the use of CrEL. Novel formulations include paclitaxel protein-bound particles (nab paclitaxel; ABI-007), docosahexaenoic acid (DHA)-paclitaxel, paclitaxel polyglumex (CT-2103), polymeric micellar paclitaxel, paclitaxel injectable depot, liposome encapsulated paclitaxel and Paclimer™ (Guilford Pharmaceuticals).

6.1 Systemic delivery strategies

Paclitaxel protein-bound particles (PPBP) are a CrEL-free nanoparticle colloidal suspension made by homogenizing

paclitaxel and human serum albumin (3 – 4%) under high pressure [51]. This nanoparticle formulation preferentially accumulates in tumor beds and facilitate the partitioning of PPBP into tumor tissue [51] and, therefore, may be especially effective in solid tumors. Preclinical data shows that PPBP have a concentration in tumor tissue that is 33% higher than concentrations obtained with standard paclitaxel formulations [99]. PPBP have a number of advantages over the traditional paclitaxel CrEL formulation. The use of the gp60 receptors, specific for the binding of albumin, allow for transport of the PPBP across blood vessel endothelial cell walls directly into tumor tissue, leading to enhanced antitumor activity [99]. Because PPBP can be reconstituted in normal saline at concentrations of 2 – 10 mg/ml instead of the 0.3 – 1.2 mg/ml for CrEL paclitaxel, less volume and decreased administration times are also advantages of these nanoparticles.

In addition, due to the absence of CrEL in the PPBP formulation, steroid premedication has been deemed unnecessary based on Phase I, II and III trials. The dose-limiting toxicities encountered in one Phase I trial consisted of sensory neuropathy, stomatitis and superficial keratopathy [51]. Another Phase I trial determined that grade 4 neutropenia and grade 3 peripheral neuropathy were the dose-limiting toxicities [100]. The maximum tolerated dose (MTD) was determined to be 300 mg/m^2 at a 30-min infusion rate every 3 – 4 weeks in the Phase I trial conducted by Ibrahim *et al.* [51], a dose which is ~ 70% higher than the MTD for the standard paclitaxel 3-week regimen. No significant hypersensitivity reactions were reported in any of the trials, Phase I – III, in the groups that were administered PPBP. In a Phase III trial comparing PPBP with standard paclitaxel, grade 4 neutropenia occurred less frequently in the PPBP arm (9% versus 22%, $p < 0.001$), even though the cumulative dose of paclitaxel was substantially higher [101]. Unfortunately, the incidence of grade 3 sensory neuropathy was significantly higher in the PPBP arm than in the standard formulation paclitaxel arm (10 versus 2%, $p < 0.001$) [101].

A Phase III trial conducted by Gradishar *et al.*, which was based on an intent-to-treat analysis, demonstrated improved efficacy of the PPBP ABI-007compared with standard formulations of paclitaxel for the treatment of metastatic breast cancer [101]. PPBP demonstrated significant improvements in response rates compared with the paclitaxel arm for patients receiving first-line therapy (33 versus 19%, $p = 0.001$) and for those patients receiving second-line or greater therapy (27 versus 13%, $p = 0.006$) and patients with prior anthracycline exposure (34 versus 18%, $p = 0.002$). A trend for improved median survival with PPBP compared with standard paclitaxel was observed (65 versus 55.7 weeks, $p = 0.374$).

In addition to binding to proteins such as albumin, paclitaxel can also be bound to fatty acids for therapeutic administration. Several studies have shown that tumors rapidly accumulate fatty acid from blood and require it for growth [102,103]. Based on these findings, Bradley *et al.* conjugated DHA, a natural fatty acid, to paclitaxel and tested its effects against 56 human tumor cell lines that included leukemias, melanomas, lung, colon, central nervous system, ovarian, renal, prostate and breast tumors [104]. Preclinical pharmacokinetic analyses indicated that the drug-conjugate remains inactive as a cytotoxic agent until metabolized by tumor cells to its active form, leading to a 21-fold higher conversion of DHA-paclitaxel to paclitaxel, which was observed in tumor relative to plasma [104]. Because the drug conjugate is less toxic than standard paclitaxel, up to a 4.4-fold higher concentration of DHA-paclitaxel can be delivered to tumor. Similar pharmacokinetic profiles were observed in Phase I clinical trials [105].

The clinical preparation of DHA-paclitaxel uses a vehicle containing 80% less CrEL on a molar basis than standard paclitaxel [104]. This formulation can be reconstituted in dextrose 5% to a maximum concentration of 8 mg/ml and can be administered over 2 h every 3 weeks [105]. However, patients do still need to receive steroid and antihistamine premedications due to the presence of CrEL in the formulation. Phase I trials to determine the MTD of DHA-paclitaxel have demonstrated neutropenia to be the dose-limiting toxicity; grade 3/4 neutropenia occurred in 11 out of 12 patients at doses of 880 mg/m^2 [106]. Interestingly, in a Phase I trial studying DHA-paclitaxel in combination with carboplatin, patients did not develop peripheral neuropathy or musculoskeletal toxicity beyond grade 1 [106].

Another novel formulation being evaluated in Phase III trials is paclitaxel poliglumex, a macromolecule consisting of a biodegradable, water-soluble polymer of a naturally occurring amino acid, glutamic acid, linked to paclitaxel [107]. Because polyglutamic acid is capable of solubilizing highly hydrophobic molecules such as paclitaxel, this formulation does not require CrEL. Much like PPBP, the lack of CrEL allows for shorter infusion times and elimination of antihistamine and steroid premedication. Preclinical data from rodent studies suggest that administration of paclitaxel poliglumex enhances tumor tissue distribution and exposure compared with standard paclitaxel [108]. Poliglumex paclitaxel has been show to be a potent radiosensitizer in animal cancer models [109-111]. Although preclinical data also indicate that paclitaxel poliglumex can evade multi-drug-resistant efflux pumps via pinocytic tumor uptake [108], the formulation, unfortunately, does not appear to have clinical activity in taxane-resistant disease [112]. In a Phase II trial in patients at high risk with advanced NSCLC, poliglumex paclitaxel was well tolerated and had activity at a dose level of 175 mg/m^2 as first-line monotherapy [113]. These trials demonstrated that reversible neutropenia was the predominant toxicity, although the occurrence of mild neurotoxicities and alopecia were minimal [113].

6.2 Regional and local delivery strategies

Several studies have demonstrated the effectiveness of paclitaxel-based local drug delivery systems against lung, ovarian and breast cancer [114-116]. In order to combat the toxic events

resulting from paclitaxel's CrEL solvent, Lu *et al.* used a novel delivery approach in an ovarian cancer rat model [114]. They developed a biodegradable nanoparticle system for delivery of paclitaxel. Intraperitoneal administration of paclitaxel using this delivery system reduced tumor weight and ascites volume while inducing apoptosis of cancerous cells [114]. Subsequent studies have corroborated the effectiveness of paclitaxel nanoparticles and its increased therapeutic benefits over traditional paclitaxel administration with CrEL [117,118].

Ruel-Gariepy *et al.* have recently reported using the BST-Gel™ platform technology (Biosyntech, Inc.), a chitosan-based solution that remains liquid at room temperatures, but turns into a gel as temperature increases to body temperature [119,120], for delivery of paclitaxel [115]. This formulation can be injected directly at the site of tumor resection and the liquid uniformly coats the cavity as it sets into the gel. Laboratory tests against the EMT-6 murine carcinoma in Balb/c mice demonstrate that a single injection of the chitosan formula containing paclitaxel produced results similar to four intravenous injections of paclitaxel. In addition, the chitosan-based system showed significantly less toxicity when compared with systemic paclitaxel administration [115].

Intraperitoneal therapy with paclitaxel in the form of injection, microspheres and nanoparticles, instead of intravenous administration, has been proposed as a more site-specific and regional therapy for ovarian cancer [114,121,122]. In a recent randomized Phase III clinical trial involving women with previously untreated stage III ovarian cancer, intravenous paclitaxel followed by intravenous cisplatin was compared with treatment of intravenous paclitaxel followed by intraperitoneal cisplatin and intraperitoneal paclitaxel [121]. Administration of treatment occurred every 3 weeks for 6 cycles. The intravenous therapy group received an intravenous paclitaxel infusion at 135 mg/m^2 over a 24-h period on day 1, followed by intravenous cisplatin 75 mg/m^2 on day 2; whereas the intraperitoneal group received intravenous paclitaxel at 135 mg/m^2 over a 24-h period on day 1 followed by intraperitoneal cisplatin at 100 mg/m^2 on day 2 and intraperitoneal paclitaxel at 60 mg/m^2 on day 8 [121].

World Health Organization grade 3 and 4 toxicities were significantly more common in the intraperitoneal therapy group than in the intravenous therapy group; only 42% of the patients in the intraperitoneal therapy group completed all six cycles. Patients in the intraperitoneal group also reported a lower quality of life before cycle four and 3 – 6 weeks after treatment [121]. However, the median duration of progression-free survival in the intraperitoneal therapy group was prolonged by 5.5 months ($p = 0.05$), and overall survival was extended by 15.9 months ($p = 0.03$) [121]. This study demonstrated that intraperitoneal administration of paclitaxel and cisplatin significantly improved disease progression and overall survival compared with intravenous administration.

Another clinical trial recently tested the efficacy of intralesional Oncogel® (MACROMED, Inc.), a novel thermo-responsive gel (Regel™) composed of a new PLGA-PEG-PLGA triblock coplolymer and PEG-100, and loaded with paclitaxel [123]. In this trial, Oncogel was used to treat 14 patients with histologically confirmed, recurring and progressive skin tumors after breast cancer. Patients received injections into multiple sites of the tumors at dosages that were 10% of the MTDs, based on animal experiments. Although the starting dose was only 0.06 mg/cm^3, later dosages were continuously doubled until grade 2 local skin toxicity or grade 2 systemic toxicity was noted. The results from this study were promising, with one complete remission, seven cases of stable disease and only one case of tumor progression. Importantly, there were no reported results of drug-related toxicity [123].

Although systemically administered paclitaxel has been shown to be clinically effective against NSCLC, the effect is modest. A recent review found that the cumulative response rate in nine separate studies of NSCLC was only 26% [124]. To improve the efficacy of paclitaxel for treatment of NSCLC, Harper *et al.* developed the PACLIMER™ delivery system (MGI Pharmaceuticals), which consists of 10% paclitaxel (w/w) encapsulated in a proprietary polilactofate polymer in the form of microspheres. This delivery system was capable of sustained drug release for up to 90 days. In murine models of NSCLC, they demonstrated that the efficacy of intraperitoneal PACLIMER was superior to intraperitoneal paclitaxel administration [116]. They also demonstrated that tumor control in mice was improved with intraperitoneal PACLIMER compared with direct intratumoral injection of paclitaxel [116].

7. Local delivery of paclitaxel for brain tumors

Patients with malignant brain tumors face a dismal prognosis despite recent advances in imaging and surgical and radiation techniques. The treatment of malignant brain tumors with chemotherapy is severely limited by the BBB, which prevents the access of many drugs to the CNS. The strategy of polymer-based drug delivery for the treatment of brain tumors has recently been explored for paclitaxel in the laboratory. However, the development of implantable controlled-release biodegradable polymers (e.g., Gliadel®, MGI Pharmaceuticals) to release paclitaxel and other chemotherapeutic agents has created a novel, safe and effective strategy for treatment of malignant gliomas [125-130]. Local drug delivery with controlled-release polymers allows for continuous release and direct access to the CNS across the BBB, thereby enhancing local concentrations of drug while minimizing systemic toxicity [131,132].

Though paclitaxel is effectively cytotoxic to glioma cells *in vitro* [133], paclitaxel, when administered systemically, is unable to penetrate the BBB [134] and, therefore, has not been clinically effective [135]. Thus, local delivery of paclitaxel is an attractive strategy for treatment of brain tumors as it has the potential to deliver this highly effective agent directly to the site of the brain tumor, while minimizing the restrictions of

the BBB and the toxicity of systemic administration. In one study, paclitaxel was incorporated into a biodegradable polyanhydride matrix and implanted intracranially into rodents bearing brain tumors. These drug-loaded polymers increased the median survival of these rats up to threefold compared with control animals [130]. A subsequent study tested the toxicity and efficacy of biodegradable polilactofate microspheres loaded with paclitaxel (PACLIMER delivery system) in the 9L gliosarcoma model and demonstrated that paclitaxel in a microsphere formulation was also capable of prolonging survival in a rodent glioma model [136]. The safety of intracranial PACLIMER was further demonstrated in a canine model, in preparation for future clinical studies [127]. Intraparenchymal administration of PACLIMER microspheres did not result in any significant myelosuppression, which was commonly seen with systemic paclitaxel delivery. In addition, animals treated with 2 and 20 mg/kg PACLIMER showed no signs of systemic or neurologic toxicity, respectively [127].

Convection-enhanced drug delivery (CED), is another novel strategy that has been developed for intratumoral drug administration for brain tumors. CED strategies use a pump connected to an intratumoral catheter for continuous drug infusion. CED relies upon convection, instead of simple drug diffusion, to improve intracerebral drug distribution. Recent studies using CED with paclitaxel have demonstrated promising antitumor responses [137]. Unfortunately, treatment-associated complications arose due to leakage of paclitaxel into the subarachnoid space [137]. Overall, the advancements made in local delivery of paclitaxel to brain tumors could potentially be used, in the future, as new delivery strategies of paclitaxel for malignancies outside of the CNS.

8. Conclusion

Paclitaxel remains an attractive drug for the treatment of a variety of malignancies. Older treatment regimens are hampered by high rates of toxicities such as myelosuppression and peripheral neuropathy. To improve the safety profile of paclitaxel, a number of advances have been made in dosing schedules and delivery strategies. Local or intratumoral delivery methods may ultimately lead to both safer and more effective formulations of paclitaxel.

9. Expert opinion

Paclitaxel is a drug with a unique mechanism of action which possesses significant cytotoxicity against a variety of malignancies, making it an attractive drug for cancer therapy. However, the adverse toxicities associated with paclitaxel administration have previously limited its clinical effectiveness. Predictable hematologic toxicities occur at high doses and with certain dosing regimens. Other adverse effects include myalgias, cardiac arrhythmias, hypersensitivity reactions and opportunistic infections. Especially troubling are the neurotoxic effects, which often result in painful and debilitating peripheral neuropathies, because these effects appear to be cumulative in nature and are often dose-limiting.

Older formulations of paclitaxel, which relied on CrEL for solubilization and delivery of paclitaxel via intravenous routes, were hampered by both the inherent toxicities associated with paclitaxel and the toxicities associated with the CrEL delivery agent. Newer formulations of paclitaxel have circumvented many of the problems associated with CrEL formulations. These newer formulations use paclitaxel bound in a novel fashion to proteins, polypeptides or fatty acids to assist in solubilization. Elimination of CrEL improves the safety profile of these paclitaxel formulations tremendously. Interestingly, some of these formulations also appear to produce paclitaxel accumulation specifically within tumoral tissues, and not within normal tissues. Several clinical trials have already demonstrated the superior safety profile and potential efficacy of these formulations compared with standard paclitaxel formulations and, therefore, have led to a rebirth of paclitaxel as a chemotherapeutic agent.

The safety of paclitaxel-based treatments for cancer will be improved even further by local or regional delivery strategies that reduce systemic drug exposure, and thus systemic toxicity. Ideally, these delivery strategies will also improve local and intratumoral paclitaxel concentrations and the overall exposure time of susceptible tumor to cytotoxic drug concentrations. It has been shown recently that polymer-based paclitaxel drug delivery systems achieve these goals in brain tumor models. Others have also investigated use of different techniques, such as CED of paclitaxel, for the treatment of malignant brain tumors. Treatment of brain tumors with paclitaxel is particularly challenging because standard paclitaxel-based treatment regimens do not provide sufficient CNS drug concentrations due to limitations imposed by the BBB. Future studies will hopefully build on these local delivery strategies and expand their applications to include other non-CNS malignancies.

The development of novel, safer and more effective delivery strategies for paclitaxel will ultimately rely on close collaborations between clinicians, biomedical engineers, chemists and drug delivery specialists. The ideal drug delivery vehicle should be able to selectively deliver a number of different drugs in discrete quantities at specific time intervals so that one can take advantage of combinatorial drug strategies and complex dosing schedules to improve tumor response rates while minimizing systemic toxicity. In theory, this technology could be used to first deliver prophylactic agents to reduce toxicities such as myelosuppression and neurotoxicity, followed by continuous or intermittent infusion of paclitaxel and other chemotherapeutic agents, to maintain therapeutic cytotoxic tumor drug concentrations over extended periods of time. The authors' laboratory has collaborated recently with Robert Langer's and Michael Cima's laboratories at MIT to develop microchip-based delivery systems that may someday be able to accomplish these goals [138-142]. Future advancements in other fields, such as nanotechnology, will also lead to safer and more effective delivery strategies for paclitaxel.

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