Novel formulations of taxanes: a review. Old wine in a new bottle?

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Received 13 August 2005; revised 5 November 2005; accepted 7 November 2005

Over the past two decades, the taxanes have played a significant role in the treatment of various malignancies. However, the poor solubility of these compounds necessitates the inclusion of surfactant vehicles in their commercial formulations. Cremophor EL and polysorbate 80 have long comprised the standard solvent system for paclitaxel and docetaxel, respectively. A number of pharmacologic and biologic effects related to both of these drug formulations have been described, including clinically relevant acute hypersensitivity reactions and peripheral neuropathy. In addition, these solvents affect the disposition of intravenously administered solubilized drugs and leach plasticizers from polyvinylchloride infusion sets. A number of strategies to develop formulations of surfactant-free taxanes have been developed. They include albumin nanoparticles, polyglutamates, taxane analogs and prodrugs, emulsions, and liposomes. An overview of these novel formulations of taxanes, their mechanisms of action, pharmacokinetics, dose and administration, adverse effects, and clinical efficacy will be discussed.

Key words: novel formulations, taxanes, vehicles

introduction

Of the several new chemotherapeutic agents introduced recently, the taxanes have had a profound impact in a wide variety of malignancies. Paclitaxel and docetaxel are approved for clinical use by the Food and Drug Administration (FDA) board for the treatment of breast cancer, ovarian cancer, non-small-cell lung cancer (NSCLC) and prostate cancer. The taxanes are a unique class of hydrophobic antineoplastic agents that exhibit cytotoxic activity by binding to tubulin and promoting inappropriately stable, non-functional microtubule formation [1]. Interference with microtubule function leads to disrupted mitosis and cell death. The toxicity profiles for these agents are somewhat different; paclitaxel has been most widely associated with peripheral neuropathies and myalgias/arthralgias, whereas docetaxel most commonly results in cumulative fluid retention that may be dose-limiting in some cases.

Paclitaxel was first discovered in the early 1960s as part of a National Cancer Institute screening study to identify natural compounds with antineoplastic activity. Paclitaxel was identified as the crude extract from the bark of the North American pacific yew tree, Taxus brevifolia, in the early 1970s and found to exert significant cytotoxic effects in preclinical studies against many tumors [2]. However, clinical development was slowed until the early 1980s owing to the scarce supply of the pacific yew tree bark and its poor solubility.

Docetaxel is a semisynthetic compound produced from 10-deacetylbaccatin-III, which is found in the needles of the European yew tree, Taxus baccata [3]. Although slightly more water soluble than paclitaxel, docetaxel also requires a complex solvent system for its commercial formulation. The semisynthetic production process of docetaxel circumvented the availability problems that first plagued the development of paclitaxel. A semisynthetic process has now been developed for paclitaxel production as well [4].

Despite overcoming the initial difficulties surrounding a limited drug supply, problems related to solubility of both agents remain challenging. After much investigation, Cremophor EL® (CrEL), a polyoxyethylated castor oil vehicle, and dehydrated ethanol USP (1:1, v/v) was identified as the most viable option for the solvent system employed in the commercial formulation of paclitaxel. CrEL has been widely used as the vehicle for a number of hydrophobic pharmacologic agents, including propofol, diazepam and cyclosporine [5]. Notably, the concentration of CrEL in the therapeutic dose of parenteral paclitaxel is relatively high compared with other agents using this solvent [4]. In contrast, docetaxel is solubilized in another polyoxyethylated surfactant, polysorbate 80 (Tween 80), for clinical use. Both solvents are both biologically and pharmacologically active. A number of biologic effects related to both of these drug formulation vehicles have been described,
including acute hypersensitivity reactions and peripheral neuropathies. In addition, several reports have linked these solvents to alterations in the pharmacokinetic profiles of both paclitaxel and docetaxel [5].

drawbacks of current taxane formulations

toxicities of vehicles

In the early development of paclitaxel, a high incidence of acute hypersensitivity reactions characterized by respiratory distress, hypotension, angioedema, generalized urticaria and rash were observed [6, 7]. It is generally felt that CrEL contributes significantly to the hypersensitivity reactions, as the vehicle has induced similar release reactions in dogs [8, 9]. These reactions appear to be associated with an increased rate of infusion [10]. Researchers initially investigated alternative excipients such as polyethylene glycol for paclitaxel solubilization; however, this compound appeared to decrease the antitumor activity of paclitaxel in murine models. Thus, CrEL has remained the standard solvent [7]. Despite premedications with corticosteroids and histamine antagonists, minor reactions (e.g. flushing and rash) still occur in approximately 40% of all patients, and nearly 3% of patients experience potentially life-threatening reactions [5, 11]. Prolonging the infusion does not eliminate the risk of hypersensitivity reactions [6]. In addition, the cumulative toxicities of dexamethasone used as a premedication may contribute to treatment-related morbidity. Docetaxel has been known to cause infusion-related reactions in the absence of premedication; however, these reactions have occurred at a decreased frequency when compared with paclitaxel and can be effectively managed by premedication with corticosteroids and histamine receptor antagonists [9].

Agents formulated in CrEL have been known to cause peripheral neurotoxicity. Whether CrEL is the sole causative agent remains unknown. Electrophysiologic studies in patients who developed neurotoxicity after paclitaxel treatment have shown evidence of both axonal degeneration and demyelination [12]. Administration of intravenous cyclosporine, which contains CrEL in its formulation, results in development of peripheral neuropathies in 25% of patients [13]. The oral formulation, on the other hand, never induces this adverse effect, which is consistent with the observations that CrEL is not absorbed through the gastrointestinal tract. Furthermore, CrEL plasma concentrations achieved after administration of therapeutic doses of both paclitaxel and intravenous cyclosporine have been noted to cause axonal swelling, vesicular degeneration and demyelination in rat dorsal root ganglion neurons exposed to the formulation vehicle [14]. Recent evidence suggests that the ethoxylated derivatives of castor oil account for much of the neuronal damage observed [15]. Polysorbate 80 is also capable of producing vesicular degeneration. Although sensory neuropathies have been associated with docetaxel administration, the incidence is much lower than that seen with paclitaxel administration. However, the polysorbate 80-containing epipodophyllotoxin etoposide is not a known neurotoxin, suggesting that the mechanism of taxane-induced neuropathy may be multifactorial, at least in part contributed by the vehicle formulation [5].

influence of vehicles on the pharmacokinetics of taxanes

CrEL and polysorbate 80 have also been demonstrated to alter the disposition of intravenously administered paclitaxel and docetaxel. The pseudo-non-linear plasma pharmacokinetics of paclitaxel in patients has long been established; however, the cause of this phenomenon is less well understood. Pharmacokinetic studies conducted in mouse models first described that the non-linear pharmacokinetics of paclitaxel result exclusively from CrEL [16]. Human studies have since reported similar findings [17]. At the higher doses administered most often on a thrice weekly schedule and shorter infusion rates (3 h versus 24 h), the plasma concentration of paclitaxel appears to exceed the metabolic capacity of its elimination pathways. The overall resulting effect is a substantial increase in systemic exposure to paclitaxel with a concomitantly reduced systemic clearance, leading to altered pharmacodynamic characteristics of the solubilized drug. This is a result of the micellar entrapment of paclitaxel by CrEL in plasma, and these micelles subsequently act as the principal carriers of paclitaxel in systemic circulation. It has been shown that the percentage of total paclitaxel trapped in micelles increases disproportionately with the administration of higher doses of CrEL, thereby making it less available for tumor tissue distribution, metabolism and biliary excretion [18]. Diminished clearance and prolonged exposure to high concentrations of the chemotherapeutic agent place patients at risk for severe systemic toxicities. Winer and colleagues demonstrated that dose escalation of standard formulation paclitaxel resulted in increased toxicity, but with no improvement in efficacy [19]. Moreover, weekly paclitaxel administration has improved response rates in patients with metastatic breast cancer and rates of pathologic complete remission in those receiving treatment in the neo-adjuvant setting [20–22]. Notably, CrEL micelles may entrap other hydrophobic drugs (e.g. doxorubicin) or inhibit drug uptake in the plasma (e.g. cisplatin), and place patients at risk for increased adverse effects and diminished efficacy when these agents are used in combination with paclitaxel [5, 23]. An additional problem linked to the CrEL solvent is the leaking of plasticizers from polyvinylchloride (PVC) bags and infusion sets used routinely in clinical practice. Consequently, paclitaxel must be prepared and administered in either glass bottles or non-PVC infusion systems with in-line filtration.

It has long been thought that polysorbate 80 is rapidly degraded in plasma and does not interfere with kinetics of docetaxel [24], but recent evidence suggests that this vehicle may indeed influence binding of docetaxel in plasma in a concentration-dependent manner [25]. Furthermore, Baker and colleagues reported a similar pharmacokinetic profile when docetaxel was administered weekly compared with 3-weekly [26]. In this study, the weekly regimen was administered over 30 min while the 3-weekly regimen was given over 1 h, resulting in similar polysorbate 80 concentrations at the end of the docetaxel infusion in either arm. This practice was deemed consistent with current modes of docetaxel administration.
the impact of vehicles on efficacy

Some in vitro models have demonstrated that CrEL and polysorbate 80 may enhance cytotoxic activity by modulating P-glycoprotein and inhibiting multidrug resistance gene expression [27–29]. However, in vivo studies have failed to replicate this finding with either surfactant. This lack of efficacy in vivo is likely due to the low volume of distribution of CrEL and rapid degradation of polysorbate 80 in plasma. Historically, overexpression of multidrug transporter P-glycoprotein by intestinal enterocytes has limited the oral absorption of the taxanes. Oral administration of both paclitaxel and docetaxel has been attempted with P-glycoprotein inhibitors, but there are limited human clinical data supporting this alternative for administration [30–32]. In addition, several reports have suggested that these drug formulation vehicles may have antitumor activity on their own [33, 34]. The intrinsic cytotoxic activity of CrEL is thought to result from free radical formation by polyunsaturated fatty acids in its formulation. Conversely, some investigators have demonstrated that CrEL may antagonize the cytotoxicity of paclitaxel through cell cycle arrest when administered at therapeutic concentrations [35]. The exact contribution of polysorbate 80 to antitumor effects has not been clarified; however, several reports suggest that it may be linked to the release of oleic acid, a fatty acid known to interfere with malignant cell proliferation, and inhibition of angiogenesis [36, 37].

Owing to the complexity of the effects of CrEL and polysorbate 80 on taxane administration and antitumor activity, changing the solvent system and replicating clinical data previously published is a daunting task. Still, there is good evidence that these formulation vehicles are responsible for a number of severe adverse effects and clinically relevant drug–drug interactions. The drawbacks of the taxane formulation vehicles have spurred interest in the development of surfactant-free taxane formulations, while continuing to maximize the proven activity of the taxanes against many solid tumors. Several strategies are in progress to develop alternative formulations of paclitaxel and docetaxel, including the use of albumin nanoparticles, prodrugs, polyglutamates, analogs, emulsions and liposome, to avoid vehicle-related adverse effects, overcome resistance attributed to P-glycoprotein and the multi-drug resistance (MDR) gene, and increase response rates beyond those achieved with standard taxanes [38] (Tables 1 and 2). In addition, some of the new compounds may enable better drug delivery to tumor sites. This article will review these novel formulations of taxanes in their mechanisms of action, pharmacokinetics, dose and administration, adverse effects, and clinical efficacy (Tables 3 and 4).

paclitaxel protein-bound particles

formulation

Paclitaxel protein-bound particles (nab paclitaxel; ABI-007; Abraxane™) is a novel formulation of paclitaxel that does not employ the CrEL solvent system. This novel formulation is prepared by high-pressure homogenization of paclitaxel in the presence of human serum albumin at a concentration of 3–4%, similar to that of albumin concentration in the blood, resulting in a nanoparticle colloidal suspension [39]. The resultant nanoparticle has a mean particle diameter of 130–150 nm, approximately one-hundredth the size of a single red blood cell, thus eliminating the need for any solvent. In addition, nanoparticle drug carriers have been known to preferentially accumulate in tumor beds and facilitate the partitioning of nab paclitaxel into tumor tissue [39]. nab paclitaxel is the first biologic chemotherapeutic compound to exploit the gp60 receptor (albondin)-mediated pathway in endothelial cell walls of tumor microvessels to achieve enhanced intratumoral concentrations. The gp60 receptors are specific for albumin and, once activated, allow for transport of albumin complexes across blood vessel wall barriers into underlying tumor tissue [40]. nab paclitaxel can be reconstituted in normal saline at concentrations of 2–10 mg/ml, compared with 0.3–1.2 mg/ml for paclitaxel [39]. Thus, infusion of nab paclitaxel requires less volume and administration time compared with standard formulation paclitaxel. Furthermore, the absence of CrEL eliminates the need for steroid premedication and alleviates the danger of leaching plasticizers from infusion bags or tubing.

Table 1. Alternative formulations of taxanes in clinical development

<table>
<thead>
<tr>
<th>Delivery strategy</th>
<th>Agent</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles</td>
<td>Paclitaxel protein-bound particles (Abraxane™)</td>
<td>FDA-approved</td>
</tr>
<tr>
<td>Prodrugs</td>
<td>DHA–paclitaxel (Taxoprexin®)</td>
<td>Clinical (phase III)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel polyglumex (Xyotax™)</td>
<td>Clinical (phase II)</td>
</tr>
<tr>
<td>Analogos</td>
<td>BMS-184476</td>
<td>Clinical (phase I)</td>
</tr>
<tr>
<td></td>
<td>D1-927 (oral)</td>
<td>Clinical (phase I)</td>
</tr>
<tr>
<td></td>
<td>BMS-275183 (oral)</td>
<td>Clinical (phase I)</td>
</tr>
<tr>
<td></td>
<td>Orlataxel (oral/intravenous)</td>
<td>Clinical (phase II)</td>
</tr>
<tr>
<td></td>
<td>RPR 109881A</td>
<td>Clinical (phase II)</td>
</tr>
<tr>
<td>Co-solvents</td>
<td>Polymetric-micellar paclitaxel (Genexol®-PM)</td>
<td>Clinical (phase I)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel injectable depot (OncoGel®)</td>
<td>Clinical (phase II)</td>
</tr>
<tr>
<td>Liposomes</td>
<td>Liposome-encapsulated paclitaxel</td>
<td>Clinical (phase I)</td>
</tr>
<tr>
<td>Emulsions</td>
<td>TOCOSOL/S-8184</td>
<td>Clinical (phase II)</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Plalimer</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; DHA, docosahexaenoic acid–paclitaxel.
**preclinical data**
In five animal models, Desai and colleagues consistently demonstrated enhanced efficacy and reduced toxicity of nab paclitaxel when compared with paclitaxel at the maximum tolerated doses (MTDs) of each agent [41]. These investigators examined the plasma pharmacokinetics and tumor tissue/red blood cell partitioning of radiolabeled paclitaxel from nab paclitaxel and paclitaxel in a human breast tumor cell line implanted in athymic mice. nab paclitaxel partitioned rapidly into red blood cells after intravenous administration and exhibited enhanced biodistribution and prolonged half-life. It appears that nab paclitaxel has a concentration in tumor tissue that is 33% higher than that of standard paclitaxel [42].

**phase I trials**
Several phase I trials have been performed to examine the toxicity profile, MTD and pharmacokinetics of nab paclitaxel. In a clinical study performed by Ibrahim et al., nab paclitaxel was administered over 30 min at doses ranging from 135 to 375 mg/m² every 21 days in 19 patients [39]. The majority of the enrolled patients had a histologic diagnosis of breast cancer. The dose-limiting toxicities were sensory neuropathy, stomatitis and superficial keratopathy. Of the 96 treatment cycles administered, only seven (7.3%) resulted in absolute neutrophil count nadir <500/mm³; six of these events occurred at the dose level above the determined MTD. The authors determined the MTD to be 300 mg/m² administered every 3 weeks. No hypersensitivity reactions were reported despite the lack of steroid or antihistamine premedication.

A phase I clinical study evaluating the safety, MTD and antitumor activity of weekly administration of nab paclitaxel in non-hematological malignancies was recently presented [43]. In this study, patients were stratified according to their level of pretreatment. Doses ranged from 80 to 200 mg/m²/week and were administered over 30 min without premedications for 3 of 4 weeks. Dose-limiting toxicities were grade 4 neutropenia for heavily pretreated patients and grade 3 peripheral neuropathy for those that had received less prior therapy. The authors determined the MTD to be 100 mg/m²/week in heavily pretreated patients and 150 mg/m²/week for the lightly pretreated group. Other phase I studies in various tumor types have evaluated intraarterial administration of nab paclitaxel at doses ranging from 120 to 300 mg/m² every 3–4 weeks have reported considerable cytotoxic activity as well as acceptable toxicity [44, 45].

**phase II trials**
Ibrahim et al. have reported the results of two multicenter phase II studies of single-agent nab paclitaxel in the treatment of metastatic breast cancer (MBC) [46]. Patients received either nab paclitaxel at 175 mg/m² (n = 43) or 300 mg/m² (n = 63), administered intravenously over 30 min every 3 weeks. In the group of patients receiving the lower dose, 21 (51%) patients experienced an objective response, with complete response in

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**Table 2. Drug characteristics of novel taxane formulations**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formulation vehicle</th>
<th>% Parent</th>
<th>Administration time</th>
<th>Premedications required?</th>
<th>P–glycoprotein substrate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Cremophor EL®</td>
<td>100%</td>
<td>i.v. over 1, 3 or 24 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Polysorbate 80</td>
<td>100%</td>
<td>i.v. over 1 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paclitaxel-protein-bound</td>
<td>–</td>
<td>10%</td>
<td>i.v. over 30 min</td>
<td>No</td>
<td>No data available</td>
</tr>
<tr>
<td>particles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHA–paclitaxel</td>
<td>Cremophor EL®</td>
<td>73%</td>
<td>i.v. over 2 h</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paclitaxel polyglumex</td>
<td>–</td>
<td>37%</td>
<td>i.v. over 10 min</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>BMS-184476</td>
<td>Cremophor EL®</td>
<td>–</td>
<td>i.v. over 1 h</td>
<td>Further evaluation warranted</td>
<td>Moderate</td>
</tr>
<tr>
<td>DJ-927</td>
<td>–</td>
<td>–</td>
<td>Oral (single dose)</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>BMS-275183</td>
<td>–</td>
<td>–</td>
<td>Oral (single dose)</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>Ortataxel</td>
<td>–</td>
<td>–</td>
<td>Oral daily for 5 days</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>RPR 109881A</td>
<td>Polysorbate 80</td>
<td>–</td>
<td>i.v., ranging from 1–24 h</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Polymeric-micellar paclitaxel</td>
<td>Polymeric micelles</td>
<td>25%</td>
<td>i.v. over 3 h</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Paclitaxel injectable depot</td>
<td>ReGel® delivery system</td>
<td>100%</td>
<td>Intratumoral delivery</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Liposomal-encapsulated paclitaxel</td>
<td>–</td>
<td>Data unavailable</td>
<td>i.v. over 45 min</td>
<td>Further evaluation warranted</td>
<td>Yes</td>
</tr>
<tr>
<td>Paclitaxel vitamin E emulsion</td>
<td>–</td>
<td>100%</td>
<td>i.v. over 15 min</td>
<td>No</td>
<td>Formulation contains P–glycoprotein inhibitor</td>
</tr>
<tr>
<td>Microsphere encapsulation of paclitaxel</td>
<td>PACLIMER delivery system</td>
<td>10% or 40%</td>
<td>Intratumoral delivery</td>
<td>No</td>
<td>–</td>
</tr>
</tbody>
</table>

*All data for P–glycoprotein substrates obtain from preclinical models.
i.v., intravenous; DHA, docosahexaenoic acid.
three (7%) patients. Grade 4 neutropenia was observed in
5% of patients, while no grade 3/4 peripheral neuropathy was
reported. At the 300 mg/m² dose level, 36 patients (61%) of
patients experienced an objective response, of which three
patients had received prior taxane therapy. The response rate
in previously untreated patients was 76%. Grade 4 neutropenia
occurred in 23% and grade 3/4 peripheral neuropathy
was reported in 10% of patients in the higher-dose group.
No hypersensitivity reactions were reported in either group.
These results lead to the development of a phase III
international study comparing nab paclitaxel to standard
paclitaxel in MBC.

Table 3. Summary of phase I clinical studies of novel taxane formulations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose escalation</th>
<th>Dose-limiting toxicity</th>
<th>Maximum tolerated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim et al. [39]</td>
<td>135–375 mg/m²</td>
<td>Neuropathy, stomatitis, superficial keratopathy</td>
<td>300 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Nyman et al. [43]</td>
<td>80–200 mg/m²</td>
<td>Neutropenia, peripheral neuropathy</td>
<td>100–150 mg/m² weekly</td>
</tr>
<tr>
<td>Wolff et al. [49]</td>
<td>200–1100 mg/m²</td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Harries et al. [52]</td>
<td>660–800 mg/m² in combination with carboplatin AUC 5</td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Verrill et al. [67]</td>
<td>11–266 mg/m²</td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Shipley et al. [68]</td>
<td>235–270 mg/m²</td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Kudelka et al. [70]</td>
<td>175–250 mg/m² in combination with cisplatin 75 mg/m²</td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Bolton and Nemunaitis [69]</td>
<td>175–250 mg/m² in combination with carboplatin AUC 5</td>
<td>Neutropenia</td>
<td>225 mg/m² every 3 weeks in combination with carboplatin AUC 6</td>
</tr>
<tr>
<td>Hidalgo et al. [81]</td>
<td>20–80 mg/m²</td>
<td>Neutropenia, diarrhea, mucositis</td>
<td>60 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Plummer et al. [82]</td>
<td>7–50 mg/m²</td>
<td>Neutropenia, diarrhea</td>
<td>50 mg/m² every 2 weeks, repeat every 3 weeks</td>
</tr>
<tr>
<td>Sun et al. [83]</td>
<td>40–60 mg/m² in combination with cisplatin 75 mg/m²</td>
<td>Neutropenia</td>
<td>60 mg/m² every 3 weeks in combination with cisplatin 75 mg/m²</td>
</tr>
<tr>
<td>Bilenker et al. [84]</td>
<td>40–60 mg/m² in combination with carboplatin AUC 5–6</td>
<td>Neutropenia</td>
<td>50 mg/m² every 3 weeks in combination with carboplatin AUC 6</td>
</tr>
<tr>
<td>Syed et al. [88]</td>
<td>1.5–40 mg/m²</td>
<td>Thrombocytopenia, neuropathy, diarrhea, mucositis</td>
<td>27 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Broker et al. [89]</td>
<td>5–320 mg/m²</td>
<td>Peripheral neuropathy</td>
<td>200 mg/m² weekly</td>
</tr>
<tr>
<td>Tomkin et al. [98]</td>
<td>10–70.1 mg/m²</td>
<td>Febrile neutropenia</td>
<td>Not specified</td>
</tr>
<tr>
<td>Laurence et al. [97]</td>
<td>20–60 mg/m²</td>
<td>None reported</td>
<td>75 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Gelmone et al. [100]</td>
<td>7.5–52.5 mg/m²</td>
<td>Diarrhea, granulocytopenia</td>
<td>45 mg/m² on days 1 and 8 every 3 weeks</td>
</tr>
<tr>
<td>Kurata et al. [101]</td>
<td>15–75 mg/m²</td>
<td>Neutropenia, fatigue</td>
<td>75 mg/m² every 3 weeks as 1-h infusion (60 mg/m² recommended for phase II study)</td>
</tr>
<tr>
<td>Sessa et al. [103]</td>
<td>15–105 mg/m²</td>
<td>Febrile neutropenia</td>
<td>90 mg/m² every 3 weeks (given as 1-h infusion)</td>
</tr>
<tr>
<td>Kim et al. [112]</td>
<td>135–390 mg/m²</td>
<td>Neuropathy, myalgia, neutropenia</td>
<td>390 mg/m² every 3 weeks (300 mg/m² recommended for phase II study)</td>
</tr>
<tr>
<td>Treat et al. [115]</td>
<td>90–300 mg/m²</td>
<td>Mucositis, neutropenia</td>
<td>175 mg/m² every 3 weeks</td>
</tr>
<tr>
<td>Spigel et al. [119]</td>
<td>125–225 mg/m²</td>
<td>Neutropenia</td>
<td>Not yet determined</td>
</tr>
</tbody>
</table>

DHA, docosahexaenoic acid; AUC, area under the curve.
Table 4. Summary of phase II clinical studies of novel taxane formulations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Disease state</th>
<th>Administration schedule</th>
<th>No. patients</th>
<th>Overall response rate</th>
<th>Grade 3–4 toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim et al. [46]</td>
<td>Paclitaxel protein-bound particles</td>
<td>MBC</td>
<td>Every 3 weeks</td>
<td>106</td>
<td>61% (300 mg/m²) 51% (175 mg/m²)</td>
</tr>
<tr>
<td>Blum et al. [128]</td>
<td>Paclitaxel protein-bound particles</td>
<td>Taxane-refractory MBC</td>
<td>Weekly</td>
<td>106</td>
<td>15%</td>
</tr>
<tr>
<td>Schacter et al. [53]</td>
<td>DHA–paclitaxel</td>
<td>Advanced NSCLC</td>
<td>Every 3 weeks</td>
<td>44</td>
<td>47.7% (900 mg/m²) 30% (1100 mg/m²)</td>
</tr>
<tr>
<td>Modiano et al. [57]</td>
<td>DHA–paclitaxel</td>
<td>Malignant melanoma</td>
<td>Every 3 weeks</td>
<td>34</td>
<td>7.6%</td>
</tr>
<tr>
<td>Sabbatini et al. [61]</td>
<td>Paclitaxel polyglumex</td>
<td>Recurrent epithelial ovarian, Fallopian tube or primary peritoneal</td>
<td>Every 3 weeks</td>
<td>99</td>
<td>10%</td>
</tr>
<tr>
<td>Bodkin et al. [73]</td>
<td>Paclitaxel polyglumex</td>
<td>Advanced NSCLC (≥70 years of age or PS ≥2)</td>
<td>Every 3 weeks</td>
<td>28</td>
<td>7%</td>
</tr>
</tbody>
</table>

MBC, metastatic breast cancer; NSCLC, non-small-cell lung cancer; PS, performance status.

Based upon the results of a phase I study evaluating weekly administration, Blum and colleagues initiated a phase II clinical study of weekly administration of nab paclitaxel in taxane-refractory MBC [47]. In this trial, patients ($n = 106$) received nab paclitaxel at a dose of 100 mg/m² weekly over 30 min on days 1, 8 and 15 on a 28-day cycle. Patients did not receive premedications or prophylactic growth factor support. The median age of the patient cohort was 54 years (range 34–76) and 65% had more than three sites of metastatic disease. Prior to enrollment, patients received a median of two (range two to eight) chemotherapy regimens and 89% had tumor growth while on taxane therapy. All patients were evaluable for response and toxicity. While 91% were treated at full dose with no reductions from 100 mg/m²/week throughout the study, 16 patients [15%; 95% confidence interval (CI) 8.3% to 21.9%] achieved an objective response. One patient developed grade 4 neutropenia and no patients experienced grade 3 sensory neuropathy.

phase III trials

Gradishar and colleagues recently reported the results of a phase III, randomized clinical trial comparing the efficacy and safety of nab paclitaxel with paclitaxel in 460 patients with MBC [48]. The primary objective of this study was to demonstrate non-inferiority of nab paclitaxel when compared with paclitaxel. Eligible patients [age ≥18 years, measurable MBC, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, no prior taxane therapy] were randomized to receive either nab paclitaxel at a dose of 260 mg/m² ($n = 229$), administered intravenously over 30 min, or paclitaxel 175 mg/m² ($n = 225$), administered intravenously over 3 h. Both agents were administered every 3 weeks. Tumor responses were assessed after two cycles of treatment and confirmed after the completion of six cycles. All data underwent independent radiologic review. A total of 454 patients received at least one treatment and were included in the data analysis. Patients in both groups received 98% of the planned chemotherapy doses. The mean delivered dose of paclitaxel received by patients in the nab paclitaxel arm was 49% higher compared with the standard formulation paclitaxel arm (mean ± standard deviation, 85.13 ± 3.118 versus 57.02 ± 3.008 mg/m² per week, respectively). Based upon an intention-to-treat analysis, nab paclitaxel 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 similar trend was observed for the elderly subset (>65 years) and patients with poor prognostic factors (i.e. non-visceral dominant lesions). Median time to progression was significantly longer with nab paclitaxel than with standard paclitaxel in all patients (23 versus 16.9 weeks, respectively; $P = 0.006$). The median time for overall survival was 103 weeks for nab paclitaxel and 101 weeks for standard paclitaxel at the time of analyses; a trend for improved median survival with nab paclitaxel was observed with all patients (64 versus 55.7 weeks, respectively; $P = 0.374$). There was not a statistically significant difference between the two treatment groups for those receiving first-line therapy; however, for those receiving second-line therapy or greater, the difference did reach statistically significance (56.4 versus 46.7 weeks; $P = 0.024$).

Toxicity data were collected and compared through six cycles of chemotherapy. Despite higher cumulative doses of paclitaxel, grade 4 neutropenia occurred less frequently in the nab paclitaxel arm (9% versus 22%; $P < 0.001$). Grade 3/4 thrombocytopenia, anemia, and febrile neutropenia occurred in <2% of patients in both groups. No deaths related to infection were reported. The incidence of grade 3 sensory neuropathy was 10% in the nab paclitaxel arm and 2% in patients receiving standard formulation paclitaxel ($P < 0.001$). Subgroup analyses reported similar toxicities observed in patients receiving front-line therapy compared with those receiving salvage treatment [48].

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**DHA–paclitaxel**

**formulation**

Docosahexaenoic acid–paclitaxel (DHA–paclitaxel; Taxoprexin®) is a novel compound formed by covalently linking the natural fatty acid docosahexaenoic acid (DHA) to paclitaxel. This conjugate was designed to function as a prodrug and accumulate preferentially in tumor tissue [49]. DHA is classified as a nutritional additive by the United States FDA, found in human milk, and is added to infant formula in Europe. The clinical preparation of DHA–paclitaxel is formulated in a vehicle containing 80% less CrEL and ethanol on a molar basis than standard formulation paclitaxel [50]. This agent can be reconstituted in dextrose 5% to a maximum concentration of 8 mg/ml and administered intravenously over 2 h every 21 days [49]. Owing to the presence of CrEL, steroid and antihistamine premedications, as well as non-PVC tubing and in-line filtration systems, are required for drug administration.

**preclinical data**

Bradley et al. demonstrated enhanced antitumoral activity when mice bearing the Madison 109 (M109) s.c. lung tumor received equimolar doses of DHA–paclitaxel compared with those receiving standard formulation paclitaxel [50]. The mean tumoral area under the curve (AUC) of paclitaxel was six-fold higher after intravenous administration of DHA–paclitaxel than that from standard paclitaxel. The drug conjugate appeared to remain inactive as a cytotoxic agent until metabolized by tumor cells to its active form. Notably, the performed pharmacokinetic analysis indicated a 21-fold higher conversion of DHA–paclitaxel to paclitaxel in tumor relative to plasma. The drug conjugate is less toxic than paclitaxel, allowing 4.4-fold higher concentrations to be delivered. In the M109 mouse models, DHA–paclitaxel caused sustained complete regressions at a dose of 120 mg/kg, whereas an equitoxic dose of paclitaxel 20 mg/kg did not induce tumor regression in any of the tested models. In addition, the prolonged tumoral half-life of DHA–paclitaxel (240 h versus 16 h standard paclitaxel) may contribute to its improved antitumor activity. In preclinical pharmacokinetic studies, DHA–paclitaxel exhibited a relatively small volume of distribution [50]. In *vitro*, DHA–paclitaxel was found to be extensively bound to plasma (99.6%) in a dose-independent manner [51]. Despite the small volume of distribution and relatively high plasma binding, DHA–paclitaxel resulted in greater tumor delivery of paclitaxel than that of the standard formulation [50]. The preliminary evidence of cytotoxic activity, favorable toxicity profile and pharmacokinetic behavior prompted investigation of the novel conjugate in a phase I study.

**phase I trials**

In order to characterize the primary toxicities, MTD and pharmacokinetic profile, Wolff and colleagues conducted a phase I study of DHA–paclitaxel in patients with advanced refractory solid tumors [49]. Twenty-four patients received DHA–paclitaxel at doses ranging from 200 to 1100 mg/m², administered intravenously over 2 h every 21 days. Dose level one (200 mg/m²) was equivalent to 146 mg/m² of paclitaxel on an equimolar basis. All patients received steroid and antihistamine premedications. Patients received a median two cycles (range one to eight). The authors determined the MTD to be 1100 mg/m², the dose level at which neutropenia was the principal toxicity (grade 3/4 neutropenia observed in 100% of patients). Neutropenia appeared to be dose related, but not cumulative, and no cycles of therapy were delayed due to persistent myelosuppression. Non-hematological toxicity was infrequent and mild. No patients developed alopecia, peripheral neuropathy greater than grade 1 or musculoskeletal toxicity greater than grade 1. Two patients developed grade 1 acute hypersensitivity reactions on the first cycle, and five others developed mild facial flushing on subsequent cycles of treatment. At the MTD, DHA–paclitaxel demonstrates a dramatically different pharmacokinetic profile compared with standard paclitaxel, similar to that observed in preclinical models. Additionally, a phase I clinical trial evaluating weekly administration of single-agent DHA–paclitaxel is underway in patients with refractory malignant solid tumors. The starting dose of DHA–paclitaxel in this study was 200 mg/m².

Harries and colleagues, to determine the MTD of DHA–paclitaxel and carboplatin when administered in combination, conducted a phase I study in 15 patients with advanced refractory solid tumors [52]. Patients were treated with either carboplatin AUC 5 and DHA–paclitaxel 660 mg/m² or carboplatin AUC 5 and DHA–paclitaxel 880 mg/m². Both agents were administered on day 1 out of a 21-day cycle. Enrolled patients were heavily pretreated; 11 patients (79%) had received at least one prior chemotherapy regimen. In the group receiving DHA–paclitaxel 880 mg/m², 75% (nine of 12 patients) required dose reduction, while 42% were required to delay treatment on cycle 2 due to persistent myelosuppression. Like the single-agent phase I trial, neutropenia was the dose-limiting toxicity; grade 3/4 neutropenia occurred in 11 of 12 patients at the higher dose level. Minimal alopecia and peripheral neuropathy was observed in both cohorts. The authors recommended DHA–paclitaxel at a dose of 660 mg/m² and carboplatin AUC 5 given every 3 weeks as the regimen for further study.

**phase II trials**

A number of phase II clinical trials have been conducted to determine the efficacy and tolerability of DHA–paclitaxel in patients with NSCLC, prostate cancer, breast cancer, pancreatic cancer, malignant melanoma, gastric cancer or esophageal cancer [53–58]. Schacter et al. conducted a multicenter clinical study to determine the efficacy and safety of DHA–paclitaxel as front-line therapy for the treatment of advanced or metastatic NSCLC [53]. DHA–paclitaxel was administered intravenously over 2 h every 21 days at one of two doses, 900 mg/m² (*n* = 31) or 1100 mg/m² (*n* = 13). Patients were premedicated with steroids and antihistamines. Owing to excess toxicity, including one toxic death, the starting dose was reduced to 900 mg/m² for the remainder of the trial. Grade 3 or 4 neutropenia was the main toxicity, occurring in 34 (77%) patients, and appears to be dose related. No grade 3 or 4 neuropathy, nausea or vomiting, or stomatitis was observed. Alopecia was rare. Forty patients were evaluable for response. In the group of patients treated at 900 mg/m², partial response and stable disease were observed in two
of 30 patients (6.7%) and 13 of 30 patients (43%), respectively, and at the higher dose of 1100 mg/m², zero of 10 patients and patients and three of 10 (30%) achieved partial response and stable disease, respectively. Median survival was 9.8 months in the lower dose group compared with 5.3 months at the higher dose level. A second phase II study examining DHA–paclitaxel in combination with carboplatin is ongoing.

The efficacy and safety of DHA–paclitaxel in previously untreated malignant melanoma was examined by Modiano and colleagues in a phase II clinical study [57]. In an interim report, the authors describe the efficacy and tolerability of DHA–paclitaxel administered intravenously at a dose of 1100 mg/m² over 2 h every 21 days in 34 patients. Neutropenia was the primary toxicity, with 17 (50%) patients experiencing grade 4 and two related deaths. Sensory neuropathies and stomatitis were generally mild, while alopecia rarely occurred. Notably, a mild skin rash (grade ≤2) was observed in 27% of the cohort. Secondary to toxicity, the authors recommended a dose of 900 mg/m² for future investigation. Of the 26 evaluable patients, two (7.6%) demonstrated partial response, whereas 12 (46%) had disease stabilization. Overall, median survival was 10.2 months, which is comparable to that previously shown with either single-agent dacarbazine or temozolomide. These results have prompted initiation of a phase III study comparing single-agent dacarbazine with DHA–paclitaxel in this setting.

Similar to the previously described phase II trials, DHA–paclitaxel has been evaluated in patients with previously untreated hormone-refractory prostate cancer, pancreatic cancer and gastric cancer, as well as second-line MBC [54–56, 58]. In each of these trials, DHA–paclitaxel was administered intravenously every 21 days at a dose of 1100 mg/m². Dose reduction to 900 mg/m² was permitted. In each of these studies, reversible neutropenia was the main toxicity. Owing to this toxicity and the observance of related deaths, the authors of each of these trials recommended a dose of 900 mg/m² for further study. Alopecia, stomatitis and sensory neuropathies were observed notably less than that expected for either paclitaxel or docetaxel. A skin rash most often characterized by pigmentation changes was observed, but was not dose limiting. In each of these tumor types, DHA–paclitaxel demonstrated promising cytotoxic activity.

**phase III trials**

A phase III trial comparing DHA–paclitaxel with single-agent dacarbazine for first-line treatment of metastatic malignant melanoma is currently enrolling patients. The primary objective of this study is to compare overall survival between the two treatment groups. Secondary outcomes include response rate, response duration, time to progression, time to treatment failure and toxicities.

**paclitaxel polyglumex formulation**

Paclitaxel polyglumex (CT-2103; Xytotax™) is another novel conjugate postulated to enhance solubility of hydrophobic drugs, increase tumor permeability and retention of paclitaxel, minimize normal tissue exposure to free drug and evade MDR efflux pumps via pinocytic tumoral uptake [59]. Paclitaxel polyglumex is a macromolecule consisting of a biodegradable, water-soluble polymer of glutamic acid, a naturally occurring amino acid, linked to paclitaxel [60]. Its molecular weight is ~80 000 Da and it contains 37% paclitaxel by weight [61]. Unlike standard formulation paclitaxel, the clinical preparation of paclitaxel polyglumex does not contain the toxic vehicle CrEL owing to the ability of polyglutamic acid to render highly hydrophobic molecules soluble. This results in shorter infusion times and eliminating the need for antihistamine and steroid premedications. This agent can be safely administered over 10 min through a peripheral vein every 21 days.

**preclinical data**

Preclinical models support the theorized benefits of paclitaxel polyglumex. In mice exposed to melanoma tumors, administration of paclitaxel polyglumex appears to be more toxic to tumor tissue distribution and exposure compared with standard paclitaxel alone [59]. Another preclinical study in rodents bearing either breast or ovarian carcinoma demonstrated rodents disease-free after a single intravenous injection of conjugated paclitaxel at a doses equivalent to paclitaxel that ranged from 40 to 160 mg/kg [62]. Similar results have also been noted in paclitaxel-resistant tumors [63]. Additionally, this agent seems to exhibit synergistic activity with irradiation and improved tumor radiocurability in animal models [64–66].

**phase I trials**

Two single-agent, phase I trials are being conducted in patients with either NSCLC or advanced solid malignancies to determine the safety and pharmacokinetic profile in humans [67, 68]. Pharmacokinetic analyses in each of these trials demonstrated a linear relationship between paclitaxel polyglumex dose and AUC. Paclitaxel polyglumex displayed biphasic elimination with a significantly longer elimination half-life of >130 h [68]. Its volume of distribution at steady state (Vss) was relatively low as well (mean 4 ± 2.5 l), suggesting strictly plasma volume distribution. The AUC of unconjugated paclitaxel represented between 2% and 6% of the total plasma content of paclitaxel polyglumex [67, 68]. This compound does not appear to accumulate in patients when administered every 3 weeks [68]. In each of these trials, the predominant toxicity has been neutropenia. Only mild neurotoxicities occurred and alopecia was minimal. When administered every 21 days, responses were observed in heavily pretreated patients with a variety of solid tumors, including those with NSCLC. In the ongoing single agent study in NSCLC, the formal MTD has not yet been defined [68].

Paclitaxel polyglumex has also been evaluated in phase I studies in combination with platinum chemothepapeutic agents in tumor types refractory to conventional therapy [69, 70]. At doses up to 250 mg/m² paclitaxel polyglumex in combination with cisplatin 75 mg/m², Kudelka and colleagues reported reversible neutropenia as the predominant toxicity [70]. Cytotoxic activity was observed across a number of solid malignancies. In combination with carboplatin in MTD, Bolton et al. evaluated paclitaxel polyglumex at doses ranging from 175 up to 250 mg/m² [69]. Results similar to those seen with...
cisplatin combination therapy were observed. The primary toxicities were neutropenia and thrombocytopenia, consistent with the known toxicity profile of carboplatin. In this trial, disease response and stabilization were noted across many refractory solid tumors, including NSCLC with good performance status (0/1) and platinum-refractory ovarian carcinoma. The authors determined an MTD of 225 mg/m² conjugated paclitaxel in combination with carboplatin AUC 6.

Paclitaxel polyglumex is being evaluated in combination with radiotherapy with or without chemotherapy for the treatment of esophageal or gastric carcinoma and locally advanced, non-resectable NSCLC. Additional studies exploring the role of paclitaxel polyglumex and carboplatin combination therapy for first-line treatment of epithelial ovarian or primary peritoneal carcinoma as well as weekly administration are ongoing.

**phase II trials**

Based upon the preclinical activity of paclitaxel polyglumex against a taxane-resistant ovarian cancer cell line and the antitumor activity demonstrated in the phase I studies, Sabbatini and colleagues initiated a multicenter phase II clinical study in patients with epithelial ovarian, primary peritoneal or Fallopian tube cancer [61]. In this trial, paclitaxel polyglumex was administered intravenously over 10 min at a dose of 175 mg/m² every 3 weeks without routine premedications. In this study, 99 patients, both platinum-sensitive (n = 42) and platinum-resistant or refractory (n = 57) were enrolled and received at least one cycle of chemotherapy. All patients had received at least one prior regimen, and a majority (61%) had received three or more prior regimens. The principal toxicities were neutropenia and neurotoxicity. Reversible grade 3/4 neutropenia occurred in 15 (15%) and nine (9%) patients, respectively. No cases of febrile neutropenia were reported. Grade 3 neuropathy was observed in 15 patients, seven of which reported neuropathies at study entry and 12 had received five or more cycles of paclitaxel polyglumex. Eight patients (8%) were removed from study secondary to neuropathies. The incidence of clinically relevant neuropathies was higher than predicted, but a majority had received prior platinum/taxane-based chemotherapy; thus, further study is needed to characterize this polyglumex designed to demonstrate superiority in overall survival did not differ significantly between the two treatment arms (7.9 versus 8 months; hazard ratio 0.97; n = 400) [77]. However, alopecia, arthralgias/myalgias, and cardiac events were significantly less frequent in the paclitaxel polyglumex treatment arm (P < 0.05). In addition, the median time to development of neuropathy was significantly longer for the paclitaxel polyglumex-treated patients (100 versus 54 days; P < 0.001). STELLAR 4 is a randomized, open-label trial comparing paclitaxel polyglumex 175 mg/m², administered every 3 weeks, with either single-agent gemcitabine or vinorelbine in a patient population similar to that of STELLAR 3. This compound is also being evaluated as...
second-line monotherapy in the STELLAR 2 trial at a dose of 210 mg/m² (performance status 0–1) or 175 mg/m² (performance status 2) every 3 weeks compared with single-agent docetaxel. Enrollment in each of these trials has been completed.

**taxane analogs**

As another means to bypass the toxicity of conventional taxanes and maintain or improve clinical antitumor activity, investigators have sought the development of taxane analogs. Many researchers are seeking the development of a compound with good oral bioavailability, having at least comparable efficacy to the parenteral taxanes currently available, and the absence of unmanageable side-effects.

**BMS-184476**

BMS-184476 is a novel taxane analog, characterized by substitution of a 7-methylthiomethyl ether group for the 7-hydroxyl group present on paclitaxel [78]. The 7-methylthiomethyl ether substitution increases the solubility of the drug and allows for formulation with 80% less CrEL per milligram of drug, thus potentially eliminating the need for routine premedications [79].

It has demonstrated properties that suggest an advantage over standard taxanes in preclinical and early clinical models [79, 80]. In various *in vitro* and *in vivo* tumor models, BMS-184476 has shown improved potency over either paclitaxel or docetaxel and has the ability to overcome paclitaxel resistance in some models [79]. Particularity encouraging is its antitumor activity in taxane-resistant human tumor cell lines with MDR due to P-glycoprotein overexpression or mutated tubulin [79]. BMS-184476 also enhances the effects of radiation in human lung cancer cells both *in vitro* and *in vivo* [80].

Two phase I studies of BMS-184476 as a single agent with 3-weekly and weekly administration have been published. Hidalgo and colleagues have reported the results of their study in which BMS-184476 was administered intravenously over 1 h every 3 weeks at doses ranging from 20 to 80 mg/m² in 34 patients with advanced solid tumors. An MTD of 60 mg/m² was established based on a toxicity profile of febrile neutropenia, diarrhea and mucositis [81]. Plummer et al. [82] initially treated 53 patients with BMS-184476 weekly every three out of four weeks, but this schedule was later modified to a regimen of weekly administration for two consecutive weeks every 21 days. At a MTD of 50 mg/m², dose-limiting neutropenia was the main toxicity and diarrhea emerged as a prominent non-hematological toxicity. The authors recommended a phase II dose of 50 mg/m² for weekly administration. The incidence of hypersensitivity reactions in each of these studies was minimal and did not require use of prophylactic medications.

Several phase I trials have evaluated BMS-184476 in combination with various chemotherapeutic agents. Sun and colleagues have published the results of their phase I trial evaluating BMS-184476 as a 1-h infusion followed by cisplatin every 21 days [83]. Twenty-seven patients with advanced solid malignancies were treated with BMS-184476 at doses ranging from 40 to 60 mg/m² in combination with cisplatin 75 mg/m². At the MTD of BMS-184476 60 mg/m² and cisplatin 75 mg/m², neutropenia and diarrhea were dose-limiting but manageable with appropriate supportive care measures. Unlike the single-agent trials, an initial observation of hypersensitivity reactions prompted use of routine premedications. Based on their findings, the authors recommended doses of BMS-184476 60 mg/m² and cisplatin 75 mg/m² with standard premedications for further study. Similarly, a combination study of BMS-184476 50 mg/m² and carboplatin AUC 6, administered every 3 weeks, reported dose-limiting toxicities of neutropenia and diarrhea [84]. Weekly and 3-weekly administration of BMS-184476 prior to bolus doxorubicin were associated with dose-limiting neutropenia. The high degree of hematological toxicity observed in the 3-weekly regimen was attributed to pharmacologic interaction and prompted a decision to administer the agents in a weekly manner (BMS-184476 35 mg/m²/week and doxorubicin 50 mg/m²³). Pharmacokinetic analysis did not reveal enhanced formation of doxorubicin’s cardiotoxic metabolite when given in combination [85]. In conclusion, the results of these early trials indicate that both single-agent and combination therapy with BMS-184476 appear to be worth testing in future trials.

**DJ-927**

DJ-927 is a new oral taxane analog designed to overcome drug resistance and improve clinical efficacy. Preclinically, this compound has shown marked efficacy *in vitro* and *in vivo* in various tumor cell lines. DJ-927 displayed higher intracellular concentrations in P-glycoprotein-expressing tumors and enhanced potency compared with both paclitaxel and docetaxel [86]. In mice, dogs and monkeys, the pharmacokinetic profile of DJ-927 was compared with standard taxanes [87]. The authors reported that DJ-927 has many similar pharmacokinetic characteristics compared with commercially available taxanes, including route of elimination, degree of plasma protein binding and wide distribution to all tissue except the brain. In contrast, DJ-927 is well absorbed and displays a long biologic half-life when administered orally. Its oral bioavailability eliminates the need for toxic vehicles and attendant hypersensitivity reactions. A phase I study to determine its MTD and characterize its toxicity profile is ongoing [88]. In this study, patients with advanced malignancies receive DJ-927 as a single oral 3-weekly dose at doses ranging from 1.5 to 40 mg/m². Above the MTD of 27 mg/m², neutropenia was dose-related and dose-limiting. Minor reponses were observed in one patient with breast cancer and another with bladder carcinoma; disease stabilization was seen in 15 (35%) patients. Pharmacokinetic analysis indicates dose-proportional absorption and long elimination half-life (180 h).

**BMS-275183**

BMS-275183, a C-3′-t-butyl-3′-N-t-butyloxycarbonyl analog, is yet another orally bioavailable (24% in humans) and efficacious novel taxane currently in phase I clinical trials [89, 90]. *In vitro*, BMS-275183 demonstrated similar potency to paclitaxel. Interestingly, in an MDR-overexpressing tumor cell line, a rather modest loss of potency was seen compared with...
standard paclitaxel [91]. Similar findings were exhibited in vivo. Administration schedule effects have been investigated and, in rat models, it appears that intermittent use of BMS-275183 is optimal. Treatment schedules are being evaluated in initial clinical trials.

It has been found in phase I testing to have notable activity in patients with heavily pretreated NSCLC when administered weekly [89]. The main dose-limiting toxicity was cumulative peripheral neuropathy; major hematologic toxicity was infrequent. Based on these observations, Rose and Wild initiated preclinical testing of BMS-275183 and the anti-epidermal growth factor receptor (EGFR) inhibitor, cetuximab, in mice bearing EGFR-expressing human tumor xenografts [92]. The combination appears to exhibit synergistic activity warranting clinical evaluation.

**orataxel**

Like its class counterparts, orataxel (BAY 59-8862; IDN 5109) was synthesized to overcome resistance in cell lines expressing the MDR phenotype. Compared with paclitaxel, orataxel displayed an improved toxicity profile as well as enlarged spectrum of antitumor activity in a large array of human tumor xenografts after intravenous administration [93, 94]. These results prompted researchers to investigate its toxicity and cytototoxicity activity after oral administration [95, 96]. Preclinically, orataxel demonstrates an oral bioavailability of approximately 50%, owing to the inability of P-glycoprotein to recognize it as a substrate. Notably, compared with the intravenous formulation of paclitaxel and intravenous orataxel, oral orataxel exhibited similar anti-tumor potency in multiple models [95, 96].

Initial phase I clinical studies have been conducted [97, 98]. Tonkin and colleagues [98] initiated a multicenter, open-label, uncontrolled trial to evaluate oral orataxel administered daily for 5 days every 3 weeks. Oral bioavailability of the compound ranged from 19% to 31% and the compounds half-life extended to nearly 70 h. Febrile neutropenia was the dose-limiting toxicity; nausea and vomiting was the most common non-hematological adverse event. Laurence et al. [97] have investigated weekly administration of the intravenous formulation in patients with advanced solid tumors. Both hematological and non-hematological toxicity were mild and authors determined the MTD for 3-weekly administration to be 75 mg/m² [97]. Based upon the phase I findings, a phase II study evaluating its antitumor efficacy and safety as a single agent in patients with taxane-resistant NSCLC is ongoing [99]. Interim findings in 65 patients revealed partial responses in four (1.5%) patients; no patient with brain metastases achieved response. Orataxel was well-tolerated as a 3-weekly intravenous infusion; mild anemia was the most frequent hematological toxicity, while fatigue was the most common non-hematological adverse event.

**RPR 109881A**

RPR 109881A is a novel semisynthetic taxane compound similar in origin and mechanism to docetaxel. The activity of RPR 109881A has been assessed, both in vitro and in vivo, in various murine and human tumor cell lines compared with conventional docetaxel. RPR 109881A has demonstrated a broad spectrum of activity both in docetaxel-sensitive and -resistant murine tumor cell lines [100, 101]. Of note, RPR 109881A is also active against tumor models overexpressing the MDR-1 gene [102]. In addition, it was found to cross the blood–brain barrier, probably a consequence of its decreased recognition by P-glycoprotein [101]. Preclinical evaluation of the optimal treatment schedule of RPR 109881A revealed that split-dosing schedule allowed the highest total dosage to be administered [100]. RPR 109881A is supplied as a single-dose vial containing polysorbate 80 solvent for administration.

A number of early clinical trials in heavily pretreated patients with solid malignancies were initiated in Europe, the USA, Canada and Japan in the mid-1990s [100, 101, 103–106]. Each of these trials sought to assess the toxicity profile and tolerability of different durations of infusion, ranging from 1 to 6 h, up to a 24-h continuous infusion. The reported toxicity patterns have been reproducible across all studies, with the neutropenia and diarrhea reported as the main dose-limiting toxicities. To date, infusion duration and toxicity do not seem to be correlated. Owing to polysorbate 80 in its formulation, prophylactic premedications were administered to prevent hypersensitivity reactions. Furthermore, the pharmacokinetic profile of RPR 109881A has been consistently described and does not appear to be schedule-related [107]. In contrast to docetaxel, RPR 109881A reaches detectable levels in the cerebrospinal fluid shortly after administration. This unique characteristic may substantially enhance therapeutic benefits for patients with brain metastases; however, further clinical investigation in this area must be completed. Phase II evaluation in patients previously treated with taxoids for MBC is ongoing [108].

**co-polymers**

**polymeric-micellar paclitaxel**

Polymeric-micellar paclitaxel (Genexol-PM) is another novel taxane formulation utilizing paclitaxel and a biodegradable block copolymer [109]. Polymeric micelles serve as an alternative vehicle to CrEL for hydrophobic paclitaxel. In vitro, this compound demonstrated comparable cytotoxicity compared with commercially available paclitaxel against many human cancers, including ovarian, breast, NSCLC and colon cancer cell lines [109–111]. Moreover, this compound was found to have three-times higher MTD and the biodistribution of paclitaxel after its administration in various tissues, including liver, spleen, kidney and lung, was nearly two to three times that expected with standard formulation. The antitumor efficacy of polymeric-micellar paclitaxel in vivo has exceeded that of paclitaxel in a variety of tumor cell lines [109–111]. In initial phase I testing, 21 patients with refractory solid tumors received Genexol-PM intravenously over 3 h every 3 weeks without premedications. The main dose-limiting toxicities at the determined MTD of 390 mg/m² were neuropathy, myalgia and neutropenia [112]. Its CrEL-free formulation permits administration of higher paclitaxel doses than the conventional paclitaxel without associated increase in toxicities. Phase II
studies with Genexol-PM are currently underway for patients with advanced breast and NSCLCs.

**liposomal-encapsulated paclitaxel**

The advancement of liposomal drug-delivery systems has recently expanded from encapsulation of doxorubicin to paclitaxel to attenuate its systemic toxicities. In preclinical evaluation, liposomal-encapsulated paclitaxel (LEP) demonstrated its ability to modulated MDR in human ovarian cancer cell lines and demonstrated comparable antitumor activity in mice models [113, 114]. Additionally, its elimination half-life was twice as long as conventional paclitaxel, while drug distribution of LEP was significantly enhanced as well [114].

Based upon its success preclinically, a number of phase I clinical trials have been initiated [115–118]. In the trial conducted by Trat and colleagues [115], LEP was administered over 45 min intravenously every 3 weeks to 26 patients. At the MTD of 175 mg/m², mucositis and neutropenia were the dose-limiting adverse effects. No clinically significant neuropathies, myalgias or alopecia was observed. To combat liposome infusion reactions, the investigators required the routine administration antihistamines and steroids prior to treatment. The reported toxicity profile was similar in each of the studies; however, hypersensitivity reactions were not consistently reported. Further evaluation of the need for routine premedications is warranted.

**paclitaxel vitamin E emulsion**

Paclitaxel vitamin E emulsion [paclitaxel injectable emulsion (PIE); TOCOSOL; S-8184] is a CrEL-free, vitamin E-based paclitaxel emulsion incorporating a P-glycoprotein inhibitor and a small particle size designed to minimize toxicity [119]. In preclinical evaluation, its MTD was three-times that of standard paclitaxel. The ability to administer higher doses of paclitaxel conferred an antitumor activity advantage in animal models. Phase I testing was completed in a wide array of tumor types, Phase II evaluations, PIE was well-tolerated and demonstrated its ability to modulated MDR in human ovarian cancer cell lines and demonstrated comparable antitumor activity in mice models [113, 114]. Additionally, its elimination half-life was twice as long as conventional paclitaxel, while drug distribution of LEP was significantly enhanced as well [114].

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**microspheres**

In an effort to enhance local-regional therapy for patients with CNS malignancies, unresctable NSCLC or advanced prostate cancer, microsphere encapsulation of paclitaxel has been developed to bypass physiologic barriers (PAACLIMER delivery system) [124–126]. Local delivery of a controlled-release paclitaxel may allow sustained exposure and for increased tumoral drug concentrations. Whether these preclinical effects will translate to clinical therapeutic benefits is not yet known.

**conclusions**

In conclusion, there are a number of novel taxane formulations, from albumin nanoparticles to produgs and analogs to microsphere encapsulation, currently undergoing development. Coming back to the question we posed in the title of this review, do these agents represent anything more than old wine in a new bottle? With currently available data, we have to say, 'not really'. However, some of the agents discussed above have certain advantages: shorter administration time, lower incidence of hypersensitization reactions, myelosuppression and alopecia.

Some of them are not substrates for P-glycoprotein, the clinical impact of which is unknown presently (Table 2). Whether these agents would improve survival when compared with established taxanes is largely unknown. Paclitaxel protein-bound particles (nab paclitaxel; ABI-007; Abraxane™) has received FDA-approval for the treatment of MBC after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy [127]. The novel formulations of taxanes do hold some promise in cancer therapy and may provide modest improvement in outcomes.

**references**


