Defining Risks of Taxane Neuropathy: Insights from Randomized Clinical Trials

David Kudlowitz and Franco Muggia

Abstract
Sensory neuropathy is a common but difficult to quantify complication encountered during treatment of various cancers with taxane-containing regimens. Docetaxel, paclitaxel, and its nanoparticle albumin-bound formulation have been extensively studied in randomized clinical trials comparing various dose and schedules for the treatment of breast, lung, and ovarian cancers. This review highlights differences in extent of severe neuropathies encountered in such randomized trials and seeks to draw conclusions in terms of known pharmacologic factors that may lead to neuropathy. This basic knowledge provides an essential background for exploring pharmacogenomic differences among patients in relation to their susceptibility of developing severe manifestations. In addition, the differences highlighted may lead to greater insight into drug and basic host factors (such as age, sex, and ethnicity) contributing to axonal injury from taxanes.

Introduction
Taxanes have become key drugs in the treatment of several malignancies as the antitumor activity of paclitaxel and docetaxel was established in the early 1990s. A major problem in the clinical use of these drugs, particularly paclitaxel, has been the development of sensory neuropathy. To better define factors resulting in this neurotoxicity, we have reviewed the extent of taxane neuropathy observed in randomized clinical trials with a particular focus on trials where paclitaxel, its nanoparticle albumin-bound paclitaxel formulation (nab-paclitaxel), and docetaxel are compared.

Historically, the contributions of paclitaxel to the treatment of breast, ovarian, and lung cancers became apparent in the early 1990s. Bristol-Myers Squibb, once acquiring licensing rights from the National Cancer Institute under the original generic name Taxol, proceeded to explore (in ovarian cancer trials) dose schedule and hypersensitivity issues that had plagued its early development in the 1980s (1). Shorter than the established safe 24-hour infusions were explored including a randomized phase II study with a 2 × 2 design comparing every 3 weeks 135 versus 175 mg/m² doses, and 24- versus 3-hour infusions (2, 3). The higher dose was more active in both schedules, whereas the shorter schedule proved safe but had more sensory neuropathy. Soon after, docetaxel underwent clinical development as Taxotere (under sponsorship of Sanofi-Aventis) and became widely used for breast and lung cancers (4). The nanoparticle albumin-bound paclitaxel (nab-paclitaxel or Abraxane) achieved approval for the treatment of breast cancer in 2005. Cabazitaxel (5) subsequently obtained U.S. Food and Drug Administration (FDA) approval for docetaxel-refractory prostate cancer and paclitaxel polyglutamate (6) is undergoing registration trials; both are less informative for the purpose of this review.

The background describes taxane neurotoxicity and its risk factors such as dose schedule, drug pharmacology, potential drug interactions, and preexisting conditions. Clinical trials in breast, lung, and ovarian cancers are then analyzed to highlight dose and schedule risk factors for sensory neuropathy.

Background

Description of taxane neurotoxicity
Distal symmetrical paresthesias, at first transient and then constant (with gradual improvement over months to years without further exposure), are the hallmark of paclitaxel-induced neuropathy. Other manifestations (such as autonomic and motor changes) are occasionally seen upon coadministration of other neurotoxic drugs or by the presence of preexisting conditions (such as long-standing diabetes mellitus). Plantar surfaces at the metatarsal-phalangeal junction are often first affected. A frequent finding is distal fingertip paresthesia. Unlike cisplatin-related neuropathies, taxanes rarely cause loss of distal deep tendon reflexes (7, 8). Asymmetrical findings usually point to other contributory causes like neurogenic damage from discogenic root compression.

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Paclitaxel was initially paired with cisplatin in the first-line treatment of ovarian cancer before Gynecologic Oncology Group GOG158 trial showed the noninferiority of the less neurotoxic carboplatin (9). This resulted in many women experiencing irreversible life-long neurotoxicity. When given by itself or with carboplatin, taxane sensory neuropathy is usually fully reversible unless dosing is not modified before incurring in severe neurotoxicity (10). Retreatment with taxanes is often associated with an accelerated development of this toxicity. In summary, neurons conducting pain and touch sensations in the distal extremities are most vulnerable to taxanes, to other anti-tubulin agents, and to platinums (11). Pharmacogenomic studies are seeking to explain an individual susceptibility to severe taxane neuropathy (12–15). The current analysis focuses on specific taxane clinical data on neuropathy from large randomized clinical trials.

Drug formulations and pharmacology
Paclitaxel, docetaxel, and nab-paclitaxel target identical sequences in β-tubulin leading to stabilization of microtubular dynamics and “bundling.” Major pharmacodynamic differences between these drugs are summarized in Table 1. Cross-resistance patterns (e.g., with doxorubicin and vinca alkaloids) reflect, in part, the greater affinity of paclitaxel for P-glycoprotein (P-gp; ref. 16). Moreover, CrEL is also a substrate for P-gp, this solubilizing vehicle modifies the influx and efflux of paclitaxel, affecting the development/reversibility of neuropathy and of myelosuppression (ref. 17; Fig. 1). However, factors other than P-gp explain the effect of CrEL on paclitaxel PK (18). Differences in pharmacokinetics and intracellular dynamics may account for the variable occurrence of neuropathy and myelosuppression, as well as less common effects (e.g., edema, skin rash, and nail changes). Further information on the drug properties of paclitaxel, docetaxel, and nab-paclitaxel is provided in the Supplementary Text (see Drug Properties).

Methods
Neuropathy, myelosuppression, and outcome reported by selected National Cancer Institute (NCI) U.S. cooperative group trials in breast, ovarian, and lung cancers are reviewed. All trials are full publications except for CALBG 40502 (19). In addition, similar data from trials using response evaluation and toxicity criteria adopted by NCI-supported trials are

Table 1. Distinguishing pharmacologic features of nab-paclitaxel, paclitaxel, and docetaxel

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nab-paclitaxel</th>
<th>Paclitaxel</th>
<th>Docetaxel</th>
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<tbody>
<tr>
<td>Linearity</td>
<td>Linear</td>
<td>Nonlinear</td>
<td>Linear from 75 to 100 mg/m²</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Albumin</td>
<td>CremophorEL and dehydrated ethanol USP (1:1, v/v)</td>
<td>Polysorbate 80 and 13% ethanol per 1.5 mL</td>
</tr>
<tr>
<td>Half-life</td>
<td>21.6 h (17.2 coeff variation for 260 mg/m²)</td>
<td>20.5 h (14.6 coeff of variation, for 175 mg/m²)</td>
<td>Alpha, beta, gamma 4.5, 38.3, and 12.2 h</td>
</tr>
<tr>
<td>Intracellular pharmacodynamic factors</td>
<td>Albumin leading to tumor accumulation via SPARC (67)</td>
<td>Major substrate for P-gp more than docetaxel (16)</td>
<td>Longer intracellular retention time and higher intracellular concentration in target cells (compared with paclitaxel; ref. 68) Substrate for P-gp (69)</td>
</tr>
<tr>
<td>Clinical delivery</td>
<td>10-min low-volume infusion</td>
<td>Infusion rate limited by volume and also need for special tubing (PDR)</td>
<td>Rate of delivery volume less constrained than for paclitaxel CYP3A4 metabolism (72) Improved by ritonavir (CYP3A4 inhibitor and minor P-gp inhibitor; ref. 73)</td>
</tr>
<tr>
<td>Issues in oral bioavailability</td>
<td>Not studied</td>
<td>Low bioavailability 1. P-gp transporters found in high concentration in the gastrointestinal tract 2. Presystemic metabolism by CYP3A4 and CYP2C8 (70) 3. Improved by GF120918 (71)</td>
<td>CYP3A4 metabolism (72) Improved by ritonavir (CYP3A4 inhibitor and minor P-gp inhibitor; ref. 73)</td>
</tr>
<tr>
<td>Intraperitoneal therapy</td>
<td>Not studied</td>
<td>Ideal dosing in phase I study found to be at 60–65 mg/m² weekly in ovarian cancer (74) Phase 2 trial showed that paclitaxel weekly intraperitoneal 60 mg/m² with intraperitoneal carboplatin every 3 wks had effective systemic exposure (75)</td>
<td>Pharmacologic advantage at 100 mg/m² every 3 wks (76) Lower concentrations than intraperitoneal paclitaxel, but better penetration likely without myelocytosis due to CremophorEL (77)</td>
</tr>
</tbody>
</table>
analyzed. Neuroropathy was defined by NCI common toxicity criteria (CTC; ref. 20), supplemented at times by the FACT-Neurotoxicity self-reported assessments (22–24), and instruments aimed at better “quantifying” neuropathy (25). To further characterize neurotoxicity risks, we highlight comparison of the following schedules: (i) of the same taxane (every 3 weeks vs. weekly) in the 3 cancers, (ii) of 2 different taxanes in breast and non–small cell lung cancer (NSCLC) trials, and (iii) of 2 different taxanes in combination with platinum in ovarian and NSCLC. Studies not appearing in Supplementary Tables are cited.

Results

Relative neurotoxic potential from randomized trials with taxanes

Breast cancer trials. Taxanes have a major role in the treatment of early and advanced breast cancers. The Eastern Cooperative Oncology Group (ECOG) led an intergroup study of optimal taxane dose schedules. The study was done in the adjuvant setting after 4 cycles of doxorubicin and cyclophosphamide [Sparano and colleagues (26); Supplementary Table S1]. The study found that paclitaxel 80 mg/m² every 1 week gave patients the best 5-year survival rate when compared with every 3-week paclitaxel 175 mg/m² (89.7% vs. 86.5%; P = 0.01). Increased grades 2 to 4 sensory neuropathy were seen in the weekly regimen, but importantly, grades 3 and 4 sensory neuropathy were similar to docetaxel. These results, which contrast with studies in advanced breast cancer, point to the relatively low neurotoxic potential of 4 cycles of paclitaxel (which is also relevant in advanced lung cancer trials). Subsequently, this sequential therapy was superior in efficacy while yielding similar peripheral neuropathy when compared with concurrent therapy (27).

In 2005, the registration trial for nab-paclitaxel compared nab-paclitaxel 260 mg/m² with paclitaxel 175 mg/m² (each every 3 weeks). Nab-paclitaxel documented better efficacy and less myelosuppression than paclitaxel [Gradishar and colleagues (28); Supplementary Table S2]. Despite improved survival, nab-paclitaxel had significantly more neurotoxicity, possibly reflecting the higher doses administered, more protracted treatment, and unknown (paradoxically protective?) effects of CrEL. Neurotoxicity equilibrated by 28 days, suggesting that nab-paclitaxel neuropathy is more transient than paclitaxel’s. This study was confirmed by Guan in 2007 (29), but subsequent studies have raised additional questions. Dosing schedules of nab-paclitaxel in randomized phase II studies were further addressed by Gradishar and colleagues (refs. 30, 31; Supplementary Table S2) in a study that also included docetaxel 100 mg/m² every 3 weeks leading to the selection of nab-paclitaxel 150 mg/m² every 1 week for the subsequent phase III intergroup trial versus weekly paclitaxel. The results of this comparison were given at the American Society of Clinical Oncology (ASCO) 2012 presentation by Rugo (ref. 19; Supplementary Table S3). This Intergroup study compared nab-paclitaxel 150 mg/m² every 1 week, paclitaxel 90 mg/m² every 1 week, and the microtubule-stabilizing drug ixabepilone (32) 16 mg/m² every 1 week, all with bevacizumab every 2 weeks. There was no difference in overall survival among the three arms, but patients on paclitaxel and bevacizumab had less neurotoxicity and neutropenia than those on nab-paclitaxel and bevacizumab [the ixabepilone arm terminated early when deemed unlikely that a superior progression-free survival (PFS) could occur]. Neurotoxicity (grades 2–4) and neutropenia (grades 3 and 4) were milder with paclitaxel than with nab-paclitaxel. These results are strikingly different than what Gradishar found in 2005 and 2009/2012. How bevacizumab contributed to these results (this trial is awaiting full publication) is uncertain, although bevacizumab has not been shown to alter neurotoxicity when added to most taxane regimens (33–35). Notably, the higher incidence of neuropathy in the E2100 trial attributed to paclitaxel 90 mg/m² weekly combined with bevacizumab at 10 mg/kg every 2 weeks versus paclitaxel alone (23.5% vs. 17.7%, P = 0.05) is likely related to added paclitaxel treatment until progression in the bevacizumab-containing arm. There was a longer PFS of 11.8 months (compared with 5.9 months) and median duration of 7.1 months of paclitaxel treatment (compared with 5.1 months) with this combination compared with paclitaxel alone (36).

Ovarian cancer trials. In Gynecologic Oncology Group (GOG) trials, an every-3-week paclitaxel 135 mg/m² given in 24-hour infusions with cisplatin had become standard following GOG104 (37). Longer paclitaxel infusions (96 hours) had less neuropathy (4%–6% grade 3) versus the 24-hour infusion, but no difference in efficacy (38) when combined with cisplatin. Subsequently (after GOG158

Figure 1. The framework for axonal damage from taxanes with unbound paclitaxel as well as its solubilizing vehicle (Cremophor EL) interacting with neurons, their axons, and Schwann cells. Once intracellular, taxanes bind to axonal microtubules or undergo metabolism and/or export via ABC transporters. Nanoparticle albumin-bound paclitaxel is considered to behave as “unbound” paclitaxel unless facilitated cell entry takes place in neurons via SPARC (secreted protein acidic rich in cysteine; see Table 1). A, axon; N, neuron; S, Schwann cell. Figure adapted from Mielke and colleagues (86), Copyright 2006, with permission from Elsevier.
showed noninferiority of carboplatin + paclitaxel vs. cisplatin + paclitaxel), 175 mg/m² 3-hour paclitaxel infusions every 3 weeks were universally adopted in carboplatin-based regimens with "acceptable" rates of severe neuropathy. The Japan GOG ‘paclitaxel dose-dense’ study (ref. 39; Supplementary Table S4) showed that patients on paclitaxel 80 mg/m² every 1 week with carboplatin every 3 weeks had better overall survival (OS) and PFS than patients receiving 3-hour paclitaxel 180 mg/m² with carboplatin every 3 weeks. Neurotoxicity grades 3 and 4 did not differ between 'dose-dense' and every 3-week arms. However, it is important to note that not only schedule and dose but also number of cycles is a key factor in the development of sensory neuropathy with taxanes (40). Nab-paclitaxel 100 mg/m² every 1 week has only recently been studied (41).

A phase III comparing the every 3-week carboplatin + paclitaxel versus carboplatin + docetaxel (42) conducted by the SCOTROC group (Vasey, Supplementary Table S4) found no difference in efficacy. However, patients who received paclitaxel every 3 weeks had significantly higher rates of grades 2-4 neurotoxicity than those treated with docetaxel. Docetaxel administration incurred higher rates of neutropenia, including febrile neutropenia—data consistent with the adjuvant breast trial of Sparano and colleagues (26).

Another randomized study assessing the strategy of inhibiting P-gp was ineffective but provided some glimpse at P-gp contribution to protecting against taxane central nervous system toxicity (43–47).

NSCLC trials. Both paclitaxel and docetaxel have played a significant role in NSCLC regimens in the past 2 decades. Paclitaxel is generally paired with carboplatin, whereas docetaxel has preferably been combined with cisplatin. Paclitaxel doses per cycle are higher than in breast and gynecologic cancers (Supplementary Table S5 on paclitaxel dose schedules with or without carboplatin). In CALGB 9730 (48), paclitaxel 225 mg/m² every 3 weeks was compared with carboplatin and paclitaxel (same dose and schedule): no differences were found between the single agent and the combination in OS or peripheral neuropathy. An improved response rate and failure-free survival with the combination chemotherapy led to its widespread use. In addition, Belani and colleagues (49) and other sources [including a meta-analysis (50)] have embraced 225 mg/m² every 3 weeks as the optimal dosing for paclitaxel in NSCLCs.

The similar outcomes following platinum-containing doublets (51) led to exploring non–taxane-containing doublets (partly to avoid neuropathy; refs. 52–54). The most recent addition to NSCLC treatment regimens is nab-paclitaxel in combination with carboplatin: FDA approval followed data showing this regimen’s superior outcome in elderly patients with NSCLCs (ref. 55; selected trials in Supplementary Tables S5 and S6 include comparisons of neurotoxicity paclitaxel weekly vs. every 3 weeks). Docetaxel neuropathy has not been as an issue; time on treatment in all these studies is generally shorter than for breast cancer.

Nab-paclitaxel was compared with paclitaxel (ref. 56; Supplementary Tables S6) at the dose schedule from Socinski and colleagues (57): carboplatin was given with either nab-paclitaxel 100 mg/m² every 1 week or paclitaxel 200 mg/m² every 3 week. Results showed similar OS and PFS. The nab-paclitaxel had more objective responses (33% vs. 25%, P = 0.005) with less severe neuropathy and hematologic toxicity. The OS in patients older than 70 years was better (12.7 and 9.8 months, P = 0.008) in the North American patients receiving nab-paclitaxel and carboplatin. The significantly lesser neurotoxicity for nab-paclitaxel weekly in these lung cancer trials must be contrasted with the findings with weekly paclitaxel in Rugo and colleagues (19) breast cancer trials (Supplementary Table S3). This underscores key issues relating to the lower weekly dose of nab-paclitaxel and lesser number of treatments as well as higher doses of paclitaxel in NSCLC trials in contrast to tolerance comparisons in breast cancer trials.

Summary of taxane dose schedule effects in randomized trials

These studies in several disease categories show consistency in documenting grade 2 or greater peripheral neuropathies across taxane schedules (weekly or every 3 weeks) and type of taxane-containing regiments (paclitaxel, nab-paclitaxel, and docetaxel). Differences across disease areas reflect, in part, patient-related susceptibilities and/or investigator coding practices. However, they support conclusions further addressed in the discussion.

Taxane neuropathy in drug combinations

Neuropathy in any particular regimen is dependent on whether taxanes are coupled with other neurotoxic drugs, particularly platinum (Supplementary Table S4). The contribution of cisplatin to neuropathy is significantly greater than carboplatin’s—originally reported by Neijt and colleagues (10) and in intraperitoneal GOG trials (58). In lung cancer, most platinum-doublet neurotoxic events are related to paclitaxel used at ≥200 mg/m² (59). Docetaxel or paclitaxel combinations with nonneurotoxic drugs in patients with breast cancer, leading to grade 2 or greater neuropathy, did not differ between the 2 taxanes (60). On the other hand, neuropathy observed in combinations of taxanes with other mitotic inhibitors often precluded going beyond phase I studies, despite encouraging preclinical and clinical effects (61–65).

Discussion

We have highlighted randomized studies potentially most informative for contributory clinical risk factors in the sensory neuropathy of taxanes. The lack of uniform quantitation of this toxicity, its time of occurrence, and extent of reversibility have been challenging. The current direction, also tied to clinical trials, is to compare genome-wide analysis of patients incurring in severe neuropathy versus others. To aid in planning such future investigations, we have highlighted the diverse clinical settings for taxane use and what can be learned from existing clinical trials.

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Some general factors associated with taxane neuropathy emerge:

1. Both nab-paclitaxel and paclitaxel give rise to more severe sensory neuropathy than docetaxel. The sensory neuropathy of docetaxel is evident mostly when compared with chemotherapy regimens not containing mitotic inhibitors or platinum. Data on nab-paclitaxel schedules are inconsistent and hard to interpret based on greater dose rates and lesser myelosuppression.

2. The impact of CremophorEL on paclitaxel’s neuropathy is unclear. Intermittent (every 3-week) doses of paclitaxel have enhanced myelosuppression presumably from vehicle-related enhanced exposure time above a 0.05 μmol/L paclitaxel threshold that has correlated with pharmacodynamic effects on myeloid cells. Nab-paclitaxel versus paclitaxel comparative studies are clouded by different doses used.

3. How ABC transporters and metabolism lead to differential pharmacodynamics in specific tissues is unknown. The potent marrow and gastrointestinal toxicities of docetaxel have been attributed to better protection against paclitaxel by ABC transporters. Not explained is lesser neurotoxicity of docetaxel, not its therapeutically inferior results from weekly administration relative to paclitaxel. Both nab-paclitaxel and docetaxel, but especially nab-paclitaxel, reportedly exhibit faster reversal of sensory neuropathy than paclitaxel, perhaps pointing to an effect of CremophorEL in prolonging the exposure of paclitaxel on neurons (in lieu of a postulated direct neurotoxic effect of the solvent).

4. Clinical and pharmacodynamic factors that contribute to neuropathy from various taxanes and their formulations require further study. Accelerated toxicities, primarily seen with paclitaxel or nab-paclitaxel, point to predisposing pharmacogenomic factors in some individuals. However, a neglected major impact relates to dose rate, cumulative doses, and the effect of other drugs. Beyond patient or regimen-related susceptibilities, could investigator coding practices, gender-related handling of taxanes, as well as other accompanying drugs play a role? Whereas breast and ovary trials are confined to women, lung trials apply to male-preponderant populations.

Analyzing data from clinical trials may shed light on the possible impact of key demographic factors on neurosensory changes that have yet to be explored: age, gender, and ethnicity; we comment separately on each one of these.

**Age**

Given the potential for complications in elderly individuals manifesting neuropathy, it is surprising that some of the larger trials have not examined the effect of age on the susceptibility of developing sensory neuropathy. A sub-analysis of a previously discussed study conducted by Socinski and colleagues (refs. 55, 56; Supplementary Table S6) focused on outcome in elderly patients with NSCLC. Neuropathy was assessed on the basis of the Functional Assessment of Cancer Therapy or FACT (21) for self-reporting of various symptoms at baseline and at completion of therapy. An analysis of neurotoxicity was provided with 884 patients <70 and 154 patients ≥70. Excess grade 2/3 neuropathies in the older subset was particularly prominent in the paclitaxel 200 mg/m² every 3-week arm (21%/22% vs. 19%/9%, respectively, in the younger population). All patients also received carboplatin. Both percentage of neuropathies and differences by age were less prominent in the weekly nab-paclitaxel arms. Mining data from large clinical breast cancer trials of taxanes for age-related differences would be of interest.

**Gender**

This factor would need to be confined to NSCLC trials, and only indirectly hinted by comparisons across trials (e.g., prostate cancer vs. breast cancer). In fact, prostate cancer trials report a high rate of neuropathies. However, this could be, in part, related to age, and also longer duration of therapy. The above NSCLC trial by Socinski and colleagues (55, 56) would be particularly suitable for an analysis on the impact of gender, given the self-assessment toxicity determinations that have been carried out. Also, women represented about one fourth of the 1,052 patients entered, and comparisons by gender could shed light on potential differences in taxane tolerance.

**Ethnicity**

Examining the impact of ethnicity would be particularly challenging, given the requirement for large patient cohorts representing distinct ethnicities within a single trial. Only indirect comparisons across trials are possible: it is of interest that the Japan GOG study reported neuropathy rates not unlike those obtained in ovarian cancer trials by the GOG (39, 42).

In conclusion, this review of the comparative neurotoxic potential of 2 taxane products in common use reveals clinically relevant major gaps in our knowledge of this class-related toxicity. In addition to pharmacogenomic studies, better quantitation of sensory neuropathy and characterization of tissue-specific (e.g., pharmacodynamics) factors in the handling of individual drugs both in the clinic and in the laboratory are needed to continue enhancing the therapeutic index of these widely used drugs. Large clinical trials are a resource for continuing to address the questions that have been raised.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: D. Kudlowitz, F. Muggia
Development of methodology: D. Kudlowitz, F. Muggia
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Kudlowitz, F. Muggia

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Kudlowitz, F. Muggia

Writing, review, and/or revision of the manuscript: D. Kudlowitz, F. Muggia

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