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Review

Peripheral neuropathy: A persisting challenge in paclitaxel-based regimes

Stephan Mielke[a,*], *Alex Sparreboom*[b,c], *Klaus Mross*[d]

[a]*Department of Hematology and Oncology, University of Freiburg Medical Center, Freiburg i. Br., Germany*
[b]*Clinical Pharmacology Research Core, National Cancer Institute, Bethesda, MD, USA*
[c]*Department of Medical Oncology, Erasmus MC – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[d]*Tumor Biology Center of Freiburg at the Albert-Ludwigs University, Freiburg i. Br., Germany*

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ABSTRACT

Cumulative peripheral neuropathy (PNP) still remains a limitation to optimal treatment with paclitaxel (PAC), especially in more dose–dense schedules. This primary sensory PNP may affect the majority of patients after administration of certain cumulative dosages of PAC, while the exact mechanisms of PAC-induced PNP are not known. While a number of preclinical models revealed its vehicle Cremophor EL (CrEL) to be mainly responsible for ganglionopathy, axonopathy and demyelination, clinical data also supports a strong and independent effect of PAC itself, which is most likely based on disturbances in the microtubules in perikaryons, axons and glia cells. Indeed, clinical trials of CrEL-free formulations of PAC still report grade III neurotoxicity as dose-limiting. As treatment options of PAC-induced PNP are rare the use of specific scoring systems for screening purposes is strongly encouraged. In this report we review and discuss the pathogenesis, incidence, risk factors, diagnosis, pharmacodynamics and treatment options for PAC-induced PNP.

1. Introduction

After the initial discovery of paclitaxel (PAC) as a novel and promising antineoplastic agent deriving from the bark of the Pacific yew *Taxus brevifolia* in 1971 [1], its initial clinical application in phase I studies almost 20 years ago was severely complicated by the appearance of life-threatening type I anaphylactic reactions [2]. These severe hypersensitivity reactions (sHSR) could have been induced by PAC itself or its polyoxyethylated castor oil vehicle, Cremophor EL (CrEL) required to keep lipophilic PAC in solution when administering it intravenously [3,4]. A combination of corticosteroids, and H1 and H2 antihistaminics as premedication diminished these reactions significantly but could never avoid them completely [3]. In vitro studies clearly show that CrEL is able to induce complement activation and thus might be an important factor in triggering these sHSR [5]. Meanwhile, new CrEL-free drug formulations of PAC are under investigation, which so far appear not to induce sHSR [6,7]. The second challenge that needed to be overcome has been hematological toxicity primarily appearing in the form of severe neutropenia [2]. The clinical usage of growth factors (G-CSF) [8] and the important discovery that a reduction of infusion time from 24 to 3 h re-

* *Corresponding author.* Present address: Stem Cell Allogeneic Transplant Section, Hematology Branch, DIR/NHLBI, National Institutes of Health (NIH), Building 10, CRC Room 3-5288, 10 Center Drive MSC 1202 Bethesda, MD 20892-1202, USA. Tel.: +1 301 402 3294; fax: +1 301 496 8396.
E-mail address: mielkes@nhlbi.nih.gov (S. Mielke).
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duced the incidence of grade III/IV neutropenia [9] contributed greatly to patient safety in today's schedules. Neurotoxicity, mainly seen as cumulative sensory peripheral neuropathy (PNP) [10–14] represents the most important non-hematological toxicity [8,15] associated with PAC administration, especially in the currently applied regimes with the drug given once a week [16–21]. Due to its cumulative effects, PNP is usually seen in a majority of patients in the course of their therapy [19]. As treatment options are rare and recent data supports that PAC itself and not its vehicle CrEL is associated with PNP development [22], PNP is representing the remaining challenge for further improvement of PAC administration, which also includes the novel CrEL-free drug formulations of PAC [6,7]. Here, we review pathogenesis, incidence, risk factors, diagnosis and prognosis of PAC-induced PNP as well as pharmacodynamic aspects and treatment options. Furthermore, we discuss different scoring systems currently available for the close monitoring of PNP development in order to maintain patient safety and quality-of-life (QoL).

2. Pathogenesis

PAC promotes the polymerization of tubulin leading primarily to mitotic cell arrest [23,24]. However, normal function of microtubules is required for a number of vital cellular interphase processes, including motility, maintenance of shape, intracellular transport and signal transduction [25–27]. Ultrastructural studies have highlighted the critical role of microtubules for the neuronal growth cone which is essential for dendrite growth and cell movement [28]. PAC has been shown in animal models and in vitro to inhibit neurite growth [29,30] and to cause damage to neurons and peripheral glia (Schwann cells) leading to demyelination, nerve cell degeneration and impairment of regenerative abilities [29–37]. Employing a rat model to study comparative neurotoxic effects of PAC and docetaxel treatment it has been shown that both drugs mainly damage large myelinated fibers of peripheral nerves [38]. One of the very limited numbers of published studies involving human nerve biopsies after treatment with PAC has revealed fiber loss, axonal atrophy and secondary demyelination in a symptomatic patient after long-term treatment with PAC, supporting mainly ganglionopathy rather than axonopathy or demyelination as the most likely process associated with PAC-induced PNP [39].

A potential cofactor for this damage is CrEL, whose neurotoxic properties are most likely based on residual unsaturated fatty acids and ethylene oxide, possibly induced by the peroxidation products affecting neurons and Schwann cells [4]. In both animal models [40] and clinical studies of cyclosporine [41], the clinical preparation of which also contains CrEL, have revealed the neurotoxic potential of CrEL, while our pharmacodynamic study in PAC-treated patients lacked to find an association between PNP development and CrEL [22].

Taken together, the exact pathogenesis of PAC- and/or CrEL-induced PNP remains unknown and data obtained from animal models have to be interpreted cautiously. In this context, it is surprising that radioactive labeled PAC could not be detected in the peripheral nerve, the dorsal root ganglion or the spinal cord of treated rats [42]. The likely mechanisms leading to PNP are shown in Fig. 1 summarizing the experience from in vitro experiments, animal models and human studies.

3. Incidence and risk factors

The incidence of reported significant neuropathy may vary between different regimes [15]. Factors affecting the development of neuropathy could include application of PAC as a sin-

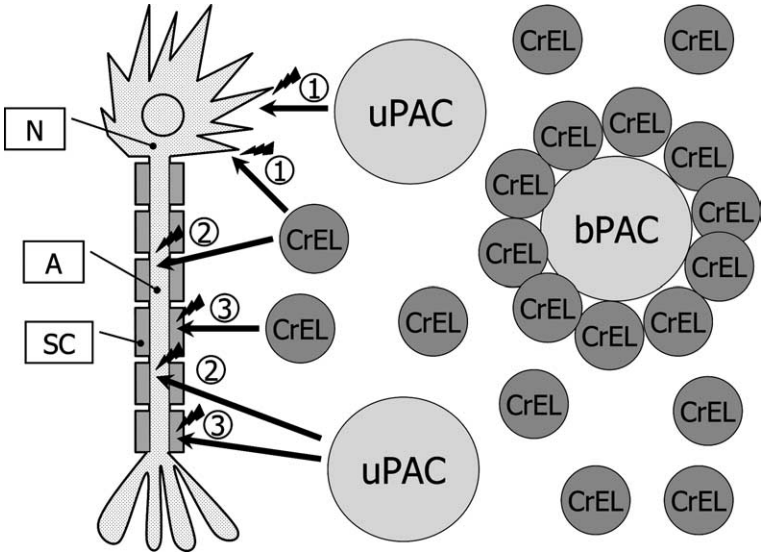

Fig. 1 – Model of Paclitaxel-induced peripheral neuropathy (PNP). Based on data provided by in vitro experiments, animal models and clinical studies both paclitaxel (PAC) and the vehicle Cremophore EL (CrEL) are likely associated with three possible mechanisms leading to PNP: (1) ganglionopathy; (2) axonopathy; (3) demyelination. PAC is formulated by CrEL as bound PAC (bPAC). Unbound PAC (uPAC) represents the active drug component, which might affect neurons (N), axons (A) and Schwann cells (SC) in the interplay with CrEL.

gle agent or in combination with other chemotherapeutics, single and cumulative dose levels, schedules and individual features of the subjects studied (e.g., age, pretreatment, comorbidities). Due to the diversity of existing PAC-based regimes we will focus in this paragraph on the weekly schedule, that is widely applied and on the treatment of metastatic breast and advanced lung cancer. Based on the common toxicity criteria of the National Cancer Institute (NCI-CTC) incidence of grade III neuropathy has been reported in 10% of women with metastatic breast cancer treated in a phase II study with weekly PAC doses not exceeding 100 mg/m^2 [18]. Comparable results were obtained in two further phase II studies in women with metastatic breast cancer and weekly PAC treatments of 80 mg/m^2 [43] and 100 mg/m^2 [20], where 9% and 11% developed grade III neuropathy respectively. This data coincides also with a 8% incidence of grade III neuropathy in patients with non-small cell lung cancer (NSCLC) treated in a phase I trial with escalating doses of 100–200 mg/m^2 PAC for six times in a 8-week cycle [16]. However, the delivery of weekly 150 mg/m^2 in a phase II study using the same schedule resulted in 24% incidence of grade III sensory and 8% motor neuropathy [17]. In contrast to these results, two other phase II studies observed only a 0–3% incidence of grade III neuropathy in patients with NSCLC treated with weekly 80 mg/m^2 PAC three times in a 4-week cycle [21,44]. In our multicenter phase III trial of weekly 1 and 3 h infusions of PAC in patients with advanced cancer of different origin (mainly breast and lung) where neurotoxicity was the primary endpoint, we observed a high rate of clinically significant PNP in both infusion groups [19]. In this study, only about 25% of assessable patients remained free of PNP after 12 weeks of therapy. This was most likely due to the application of a weekly PNP scoring system to monitor patients closely considering the strong cumulative character of PNP development [19]. Thus, reported incidences may vary in dependence of delivered dose-density, therapy duration and applied screening systems.

The risk of developing a PNP appears to be increased for patients with coexisting alcoholic or diabetic disease resulting in a more rapid onset of clinically significant PNP [10,15]. In a phase III trial of weekly PAC in advanced lung cancer patients, an older age and hyperglycemia were found to be associated with greater neurotoxicity. A previous therapy with vincamycin has been identified as an independent risk factor for later PNP development in a pharmacodynamic substudy [22], although this could not be confirmed in our larger clinical study [19].

4. Clinical manifestations and diagnosis

PAC given as a single agent or in combination with cisplatin predominantly induces a cumulative sensory neuropathy [10–15,19]. Primary symptoms may include numbness/paraesthesia, tingling and burning in a symmetric stocking-and-glove distribution [15]. Usually, the lower extremities are affected first, but a simultaneous onset in the upper and lower extremities has also been reported [15,45]. Motor neuropathy is much less frequent then sensory symptoms and includes a mild distal weakness, especially of the toe extensor muscles [11,15]. Orthostatic hypotension, cardiac arrhythmia and paralytic ileus have been reported especially in the early clinical trials as possible signs of autonomic neuropathy [15,46].

Diagnosis is usually made based on a clinical examination and electrophysiological measurements [10,11,47,48], whilst nerve biopsies provide a further diagnostic tool [39]. Even if there might be a strong diagnostic value of such biopsies, usually obtained from the sural nerve, the methods seem to be inappropriate as compared to other less invasive and thus better tolerated examinations. An alternative and potential future approach may include the examination of intraepidermal fibers in skin biopsies that have already been described as a diagnostic tool in diabetic neuropathies [49]. However, their exact value for the detection of chemotherapy-induced PNP has to be addressed in further studies. Magnetic resonance imaging of the spinal cord dorsal columns as a non-invasive approach to detect ganglionopathies will require further validation before entering the clinical routine [50]. Additional neurophysiologic evaluations such as measurements of distal latencies, conduction velocities and amplitudes are improving the sensitivity of PNP evaluation and may even facilitate the identification of patients with an increased risk of PNP development earlier and prior to the onset of clinically significant PNP [10]. Recently, a decrease of more than 50% in sural sensory action potentials as compared to baseline was reported by Argyriou and colleagues as an independent neurophysiologic parameter predicting PNP development in patients treated with a combination of PAC and/or cisplatin [51]. In another study Cavaletti described the careful evaluation of deep tendon reflexes and vibration perception (even particularly effective if evaluated by the tuning fork test in a semi-quantitative manner) as an early predictor for the outcome of PNP in patients treated with a combination of PAC and cisplatin [48]. In this study, the decrease of serum nerve growth factor (NGF) levels correlated with the severity of PNP but failed to be of predictive value [48]. It has to be pointed out that electrophysiological measurements, even if of predictive value as stated by Argyriou [51], are unlikely to be available in the general oncological practice. Cavaletti reported earlier a comprehensive evaluation of different oncological grading scales (NCI-CTC [52]; ECOG [53]; Ajani et al. [54]) in comparison with the total neuropathy score (TNS) [55] and found good correlation between these scores even if the application of the TNS allowed a more complex evaluation of PNP including electrophysiological measurements [47]. With view to feasibility, a minimal requirement for such a PNP screening system would be the evaluation of the vibration sense by the tuning-fork test, deep tendon reflexes and sensory symptoms [10] even if sensory symptoms seem to have primarily diagnostic rather than predictive value.

Thus, we favor an easy-to-perform scoring system for PAC-induced PNP based on patient symptoms and on a clinical examination prior to every administration of chemotherapy. This clinical examination should also include the evaluation of strength for the detection of motor neuropathy even if being usually less frequent than sensory neuropathy [12]. In Table 1, we provide a scoring system that we have employed in our phase III multicenter trial with neurotoxicity as the primary endpoint that fulfills these criteria [19].

Table 1 – Peripheral neuropathy (PNP) score as previously published [19] and modified after Berger et al. [10] and Chaudhry et al. [11]

Score	0	1	2	3
Sensory symptoms	None	Numbness/paraesthesia in the feet	Numbness/paraesthesia in feet and fingers	Functionally disabling numbness /paraesthesia
Vibratory sense (tuning fork test)	8/8	<6/8	<4/8	None
Strength	Normal	Weak toe extension	Weak toe extension and weak finger abduction	General/diffuse weakness
Tendon reflexes	Normal	Single reflexes reduced	Single reflexes absent	All reflexes absent

The total PNP score is calculated as the sum of scores obtained for sensory symptoms, vibratory sense, strength and tendon reflexes (0–3 each, 0–12 total). Graduation of PNP score: 1–3: mild PNP, 4–6: moderate PNP, >6: severe PNP.

5. Pharmacodynamics

In the more dose–dense PAC schedules (e.g., weekly) clinically significant PNP appeared after administration of cumulative doses of around 1500 mg/m^2 [56]. Dependent on the applied screening tool, cumulative neuropathy can be detected much earlier in treatment [19]. Furthermore, infusion duration and the level of applied doses have important effects on PAC pharmacokinetic parameters as well [9,56–60]. Eisenhauer et al. [9] showed that a reduction of infusion time from 24 to 3 h reduces the frequency of severe neutropenia significantly, possibly as a result of diminishing the area under the curve (AUC) of PAC. In another randomized multicenter trial we demonstrated that the shortening of the infusion duration from 3 to 1 h also resulted in a decreased AUC for both unbound PAC (uPAC) and total (tPAC) but the AUC of Cremophor EL (CrEL) increased [57]. As both PAC and CrEL were suspected to be responsible for PNP development it was difficult to predict which infusion schedule (1 or 3 h) would be the more preferable regarding neurotoxicity. Furthermore, starting with doses of 100 mg/m^2 plasma concentrations of PAC may exceed the linear range of dose–exposure relationship, which in itself is most likely related to CrEL [57,58,61,62].

Systematic attempts to describe relationships between individual pharmacokinetic parameters associated with the administration of PAC and the development of PNP often failed to provide specific trends [60,63,64]. One reason for this failure might be that neurotoxicity was not the primary endpoint in these studies, and thus was probably scored less accurately. For both neutropenia [60,65,66] and therapeutic efficacy [67], threshold models have been found to be valuable to describe the association between PAC pharmacokinetic parameters and outcome. In such models, pharmacodynamic information (e.g., myelosupression) is linked to a pharmacokinetic parameter, which describes the duration when plasma PAC concentrations are greater than a certain threshold level (e.g., 0.05 μmol/l). In a recent analysis, we demonstrated that certain threshold parameters, in particular concentrations of PAC above 0.05 μmol/l ($T_{>0.05}$) for 10.6 h or more, were independently associated with an increased risk of PNP development in the course of therapy [22]. Another interesting finding from the analysis was that pharmacokinetic parameters of CrEL were not associated with PNP development [22], which seemingly contradicts findings reported from animal models and clinical studies on cyclosporine, as previously discussed [40,41]. The finding that measures of exposure to PAC rather than CrEL might be closely linked with PNP is further supported by recent studies on CrEL-free PAC formulations. In these studies, an association between systemic exposure to PAC and grade III neurotoxicity was found in spite of the small number of studies subjects with PNP development [6,7]. Interestingly, no cases of severe PNP have been described for docosahexaenoic acid-paclitaxel (DHA-PAC), a fatty-acid conjugated prodrug of PAC containing CrEL that is associated with prolonged exposure to very low concentrations of PAC ($T_{>0.01}$ = 6–7 days) [68]. Collectively, the weight of data suggest that with regards to PNP development following PAC treatment, both the 1 and 3 h infusions are equally safe, with no significant difference in PNP frequency being observed between the infusion durations in a weekly regimen [19]. This finding is consistent with the notion that the threshold parameter $T_{>0.05}$ is not significantly different for 1 or 3 h infusions [57] and further suggests that CrEL seems to be less important for PNP development [22].

6. Prognosis, treatment options and prophylaxis

Mild sensory neuropathies appear often to be reversible within few months whilst more severe forms may persist significantly longer [15]. Tricyclic antidepressants and anticonvulsants are nowadays widely used in the treatment of neuropathic pain [69]. However, clinical studies focusing on the symptomatic treatment of chemotherapy-induced PNP are rare. In a placebo-controlled trial the tricyclic antidepressant nortryptiline showed only a very modest effect on the relief of paraesthesia in the treatment of symptoms associated with cisplatin-induced neuropathy [70]. In a single case study the antidepressant venlafaxine, a reuptake-inhibitor of norepinephrine and serotonin, was reported to induce a dramatic recovery of symptoms in a patient suffering from severe PAC-induced PNP [71]. Gabapentin, an anticonvulsant related to the neurotransmitter gamma aminobutyric acid with antihyperalgesic activity, with promising efficacy in different neuropathic pain syndromes [72,73], might also relieve symptoms associated with PAC-induced PNP. Of course, this hypothesis has to be addressed in further clinical studies.

As treatment options are obviously limited, prophylaxis plays an important role. Screening systems including clinical

and/or electrophysiological evaluations have already proven their predictive value and may help avoid more severe and impairing PNP following PAC treatment by dose reductions, especially in the palliative situation [48,51]. In our multicenter phase III trial all patients with a PNP score exceeding three (Table 1) received a 25% dose reduction of PAC for all further courses of treatment and patients with a PNP score exceeding six were excluded from the trial [19]. However, dose reductions are potentially associated with the risk of losing therapeutic efficacy and thus have to be performed with caution especially if there is curative intent to treatment. Therefore, investigation of neuroprotective agents could be critical for future therapy improvement. Unfortunately, amifostine, a neuroprotective agent that appeared to be promising in vitro [74] failed to show significant benefits in clinical studies so far [75,76]. Recently, neuroprotective effects of a vitamin E prophylaxis in patients treated with PAC and/or cisplatin have been reported from a randomized clinical trial [77].

7. Conclusions and future perspectives

Despite all improvements that have been achieved for the treatment with paclitaxel (PAC) during the last two decades PNP persists as a challenge especially in the currently applied more dose–dense regimes. The exact pathogenesis of PAC-induced PNP remains still unclear [15]. Pharmacodynamic investigations including Cremophor EL (CrEL), unbound PAC (uPAC) and total PAC (tPAC) support a strong effect of PAC itself [22]. Like therapeutic efficacy [67] side-effects such as neutropenia [60,65,66] and cumulative neurotoxicity [22] appear to be best explained by pharmacodynamic threshold models including parameter estimates like time of concentrations above 0.05 μmol/l ($T_{>0.05}$) and 0.01 μmol/l ($T_{>0.01}$) of PAC. In this context novel drug preparations like docosahexaenoic acid-paclitaxel (DHA-PAC) could be of significant advantage so far they do not exceed threshold expositions to PAC as required to develop significant PNP, but maintain full antitumor activity by their preferential uptake into tumor cells [68]. The exact effects of CrEL-free drug formulations on PNP development have to be addressed in individual studies. A recently published study employing a rodent model revealed NK105, a PAC-incorporating micellar nanoparticle formulation to be significantly less neurotoxic as compared to the standard formulation of PAC [78]. This interesting finding might be a result of an altered drug distribution, which is presumably based on a reduced drug leakage from normal blood vessels, and a minimized drug capture by the reticuloendothelial system as supposed by the authors [78]. PAC is eliminated by a cytochrome P-450-mediated pathway [79,80] and by P-glycoprotein-mediated hepatobiliary and intestinal secretion [81]. Expression variability in the corresponding proteins could influence drug clearance and thereby antineoplastic and side-effects as well. However, an exact association between the pharmacokinetics of PAC and polymorphisms of these proteins has not yet been described, but future dosing could be tailored to individuals considering that different isoforms are involved the elimination process of PAC.

As treatment options of PNP are rare, close monitoring of all patients treated with PAC is strongly encouraged to avoid more severe forms of PNP. Prevention may also play an important role in future schedules, thus, the development of novel neuroprotecting agents might be critical.

Conflict of interest statement

None declared.

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