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Review

Axonal degeneration in chemotherapy-induced peripheral neurotoxicity: clinical and experimental evidence

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ABSTRACT

Multiple pathological mechanisms are involved in the development of chemotherapy-induced peripheral neurotoxicity (CIPN). Recent work has provided insights into the molecular mechanisms underlying chemotherapy-induced axonal degeneration. This review integrates evidence from preclinical and clinical work on the onset, progression and outcome of axonal degeneration in CIPN. We review likely triggers of axonal degeneration in CIPN and highlight evidence of molecular pathways involved in axonal degeneration and their relevance to CIPN, including SARM1-mediated axon degeneration pathway. We identify potential clinical markers of axonal dysfunction to provide early identification of toxicity as well as present potential treatment strategies to intervene in axonal degeneration pathways. A greater understanding of axonal degeneration processes in CIPN will provide important information regarding the development and progression of axonal dysfunction more broadly and will hopefully assist in the development of successful interventions for CIPN and other neurodegenerative disorders.

INTRODUCTION

Axonal degeneration is a common pathophysiological event, and axonal loss is linked to disability in neurological disorders across both central and peripheral nervous systems. There are a diverse range of triggers which can precipitate axonal degeneration, leading to a systematic cascade of molecular mechanisms resulting in axonal destruction.[1] Axonal degeneration is a key feature in peripheral neuropathy, and fragmentation of sensory peripheral axons produces significant symptoms including loss of sensation, tingling or pain, resulting in functional disability and increased falls risk. Chemotherapy-induced peripheral neurotoxicity (CIPN) is a toxicity of cancer treatment, and a prominent cause of sensory-predominant peripheral axonopathy.[2]

Multiple classes of cancer therapy produce CIPN including microtubule-targeting agents, proteasome inhibitors, immunomodulators and platinum-based agents.[3] Likewise, multiple pathological mechanisms are involved in CIPN including microtubule disruption, interrupted axonal transport and mitochondrial toxicity.[4] However, despite the diversity of mechanisms, there is an evidence that a final common down-stream pathway in CIPN is axonal degeneration.[5] This review will integrate evidence from preclinical and clinical work on the onset, progression and outcome of axonal degeneration in CIPN. We will highlight potential clinical markers of axonal dysfunction to provide early identification of toxicity as well as present potential treatment strategies to intervene in axonal degeneration pathways. Ultimately, understanding and targeting axonal degeneration will be key to developing successful interventions for CIPN and also across neurodegenerative disorders more broadly.

CLINICAL OVERVIEW OF CIPN

CIPN develops with multiple commonly used classes of cancer treatment including cytotoxic chemotherapies such as antitubulins, platinum agents, as well as proteasome inhibitors, immunomodulators, immune checkpoint inhibitors and antibody-drug conjugates.[3] Across all these treatment types, CIPN symptoms reduce treatment tolerability, necessitating dose reduction or premature therapy cessation. In addition to adverse effects during treatment administration, CIPN may produce long-lasting effects in cancer survivors with impact on function and quality of life.[6]

The characteristic CIPN symptom profile includes symmetrical tingling and numbness in the hands and feet, with severe neuropathic pain reported in a minority of patients. Clinical signs include reduction in light touch and vibration sense, which can lead to functional problems with fine motor tasks, balance and mobility.[2] In severe cases, sensory ataxia may develop. While sensory nerve dysfunction is prominent, autonomic and motor nerves may be damaged by some chemotherapy types. CIPN development is likely associated with a range of clinical risk factors, including higher cumulative dose, older age, combined chemotherapy with two neurotoxic agents, that is, cisplatin plus paclitaxel and comorbidities.[2] However, there is significant interindividual variation and multiple genetic risk factors are likely important but remain ill defined.[3]

While broadly, CIPN is symptomatically similar when associated with different agents, there are also differences in clinical presentation and phenotype that are agent-specific. Platinum agent oxaliplatin is associated with prominent acute neurotoxicity which produces cold-triggered paraesthesia and muscle cramps acutely following infusion,[7] a profile that does not occur with other platinum agents such

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328323).

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Received 18 September 2022
Accepted 15 February 2023
Published Online First 4 April 2023

Check for updates

To cite: Park SB, Cetinkaya-Fisgin A, Argyriou AA, *et al*. *J Neurol Neurosurg Psychiatry* 2023;**94**:962–972.

as cisplatin. However, both cause a neuronopathy (ie, primary damage of the soma of the sensory neurons of dorsal root ganglia, DRG), resulting in secondary axonal damage and a chronic sensory neuropathy. Taxanes are also associated with a different acute toxicity profile, with an early pain syndrome consisting of myalgias and arthralgias occurring 1–4 days following infusion.[8] Both taxanes and epothilones also produce a chronic sensory predominant neuropathy, although motor neuropathy can develop at higher doses.[8] Distal sensory and motor neuropathy can occur with vinca alkaloids or thalidomide treatment.[9] Proteasome inhibitors such as bortezomib are associated with prominent sensory neuropathy often with neuropathic pain and a higher risk for autonomic neuropathy,[10] although severe autonomic dysfunction is more typical of vincristine.[11] Although targeted, antibody-drug conjugates can also cause off-target effects, with agents such as brentuximab vedotin producing significant neuropathy, probably again through an antitubulin mechanism.[11] More recent immunomodulating drugs, including immune checkpoint inhibitors, can also induce severe neuropathy, but in these cases the features are those of an acute demyelinating damage, and for this reason they will not be discussed further in this review.

Key to understanding these different phenotypic profiles is improved knowledge regarding underlying pathophysiological mechanisms, including axonal degeneration.

OVERVIEW OF AXONAL DEGENERATION IN CIPN

Axonal degeneration is an active process, producing controlled self-destruction of axons.[1] Chemotherapy-induced axonal degeneration can be initiated by a number of triggers, including disturbed calcium signalling, mitochondrial function disturbance, axonal transport interruption or activation of specific molecular cascades.[5] Below, we provide an overview of CIPN-relevant pathophysiological mechanisms which trigger axonal degeneration and subsequent axonal degeneration pathways.

Triggers of axonal degeneration pathways in CIPN

Ultimately axonal degeneration pathways can be triggered by a wide variety of events. Different anticancer drugs exert different mechanisms of cytotoxicity against cancer cells and, therefore, multiple neurotoxicity mechanisms are likely (a summary of axonal damage events is provided in figure 1). Chemotherapy-induced axonal degeneration is induced by different potential mechanisms that trigger axonal damage specifically related to some properties of each drug class: altered axonal transport, altered mitochondrial functioning, altered ion channels and Ca^{2+} homoeostasis, neuroinflammation and DNA damage.[5 12]

Several chemotherapy classes disrupt microtubule functioning, thus blocking cancer cells in metaphase and leading to cell death: *taxanes* (eg, paclitaxel, docetaxel, cabazitaxel), *epothilones* (eg, ixabepilone), *eribulin* and *vinca alkaloids*. Moreover, it is likely that the neurotoxicity of *vedotins* is due to their strong antitubulin activity, allowing even small amounts of free (ie, non-antibody conjugated) drug to become neurotoxic.[13] Taxanes and epothilones hyperstabilise microtubules, preventing microtubule depolymerisation.[8] Vinca alkaloids (eg, vincristine, vinblastine) and vedotins instead promote microtubule depolymerisation,[13] while eribulin interferes with microtubule dynamics by binding predominantly to a small number of high affinity sites at the plus ends of existing microtubules.[14] The interference of typical antitubulin agents and proteasome inhibitors with microtubule dynamics may negatively affect both anterograde and retrograde axonal transport.[15] In line with this, several in vitro studies

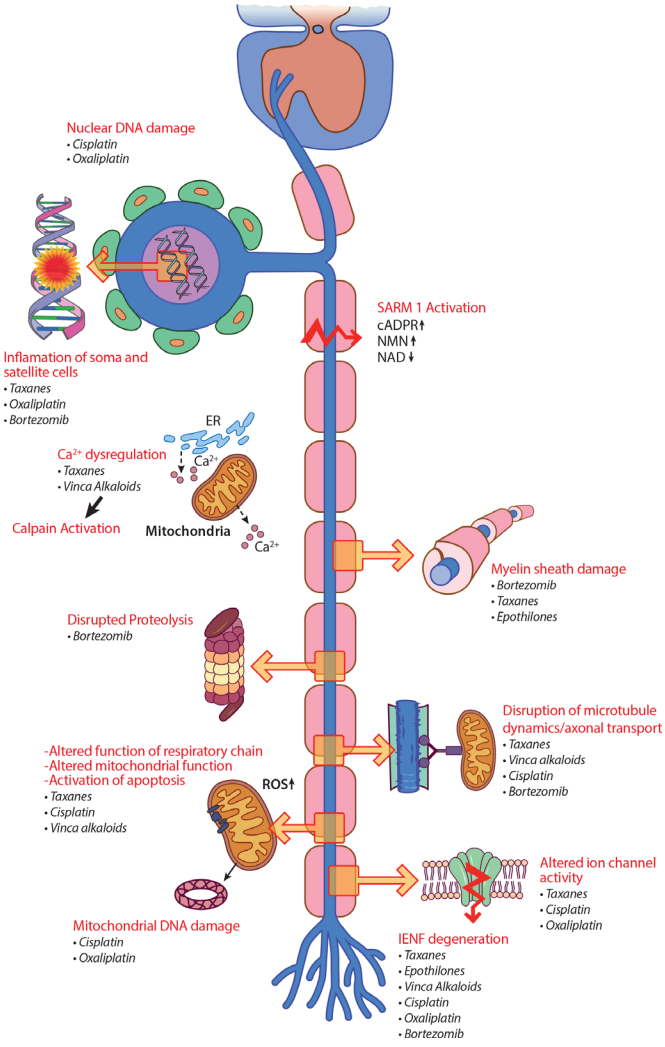

Figure 1 Schematic of CIPN pathophysiological processes depiction of underlying biomolecular mechanisms relevant to CIPN, illustrating that different chemotherapy agents affect multiple components of axons, DRG neurons and satellite cells. cADPR, cyclic adenosine diphosphoribose; CIPN, chemotherapy-induced peripheral neurotoxicity; DRG, dorsal root ganglia; ER, endoplasmic reticulum; IENF, intraepidermal nerve fibre; NAD, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; ROS, reactive oxygen species; SARM1, sterile-α and Toll/interleukin 1 receptor motif containing protein 1.

demonstrated that eribulin, vincristine, paclitaxel and ixabepilone inhibit anterograde and retrograde transport.[5] Similarly, in vitro data showed that bortezomib is also able to enhance tubulin polymerisation[16] and disrupt axonal transport,[17] while the non-neurotoxic proteasome inhibitor carfilzomib has no effect on microtubules at antineoplastic concentrations.[18] Further, bortezomib has been linked to delta 2 tubulin accumulation, altering microtubule stability and dynamics with consequent axonopathy and altered mitochondria motility.[19] Notably, neurographic in vivo molecular imaging demonstrated axonal transport alterations following platinum chemotherapy.[20] However, further investigations are warranted to determine if it is an early or late event due to another primary mechanism of damage (eg, mitotoxicity as reported below).

Mitochondrial dysfunction might be another common event in the neurotoxic pathogenetic cascade related to anticancer drugs. Relying on morphological observations, altered mitochondrial

features, such as swelling, vacuolisation, enlargement and loss of cristae structure have been demonstrated.[5] Vinca alkaloids and taxanes have been linked to changes in mitochondrial fission/fusion machinery and bortezomib has been shown to cause alterations in mitochondrial calcium homoeostasis and mitochondrial respiratory chain failure.[5] Platinum drugs negatively affect mitochondria by inducing mitochondrial DNA damage and hampering its replication and transcription, related to a lack of surveillance by DNA repair systems.[21]

Alterations of Ca^{2+} homoeostasis, in general, may trigger axonal damage via activation of Ca^{2+}-sensitive calpain, phospholipases and nitric oxide synthase that result in neuronal damage.[15] However, imbalance of Ca^{2+} is also linked to Ca^{2+} mobilisation due to mitochondrial damage.[5] The acute neurotoxicity of oxaliplatin may also be related to imbalance of ion homoeostasis with alterations of voltage-operated ion channels preceding axonal damage, as demonstrated via several in vitro and in vivo approaches; notably, this imbalance (mostly related to sodium and potassium channels) may also alter Ca^{2+} homoeostasis.[21]

Preclinical studies have also addressed the potential role of neuroinflammation as a key feature of axonal damage in CIPN.[12] Neuroinflammation, glial activation and cytokine modulation have been linked to CIPN in experimental models. In addition to glial cell activation, immune signalling may be altered in spinal cord, DRG and peripheral nerve and linked to subsequent degeneration. Neuroinflammation may also modulate symptoms expression, for example, neuropathic pain expression.[12]

Platinum drugs (eg, cisplatin, carboplatin, oxaliplatin) rely on forming interstrand DNA adducts that lead to cell cycle arrest in cancer cells. Moreover, platinum drugs exert a second mechanism of cytotoxicity: acquated platinum is able to bind crucial cytoplasmic nucleophiles (glutathione, methionine, metallothioneins and cysteine enriched-proteins), which represent the antioxidant reserves of the cell; therefore, their depletion due to platinum compounds leads to lipid and protein peroxidation. Both increased oxidative stress and DNA damage can lead to neuronal cell damage and secondary axonal degeneration.[7]

Although there are common pathophysiological mechanisms between different chemotherapy agents, some agents produce more direct axonal toxicity while others produce primary damage to neuronal cell bodies. Predominance of direct axonal toxicity has been demonstrated with compartmentalised tissue culture experiments for paclitaxel[22] and vincristine-induced CIPN.[23 24] However, in similar experiments, bortezomib-induced axon degeneration required exposure of the cell body to bortezomib, suggesting that neuronal toxicity occurs in addition to axonal degeneration with bortezomib treatment.[24] Neuronal toxicity is proposed as a primary mechanism of oxaliplatin and cisplatin, which both produce dorsal root ganglion apoptosis[25] but secondary axonal degeneration also may occur.

Axonal degeneration pathways implicated in CIPN

Despite the various potential triggers of axonal degeneration, there is an emerging evidence of common axonal degeneration pathways across multiple types of nerve injury or toxicity. In recent years, there have been many developments in understanding molecular pathways underlying axonal degeneration, comprehensively reviewed in references 1 5 26–28, with an overview of aspects relevant to CIPN presented below (figure 2).

In the setting of peripheral nerve trauma or injury, damaged axons are removed via a mechanism termed Wallerian degeneration, where affected axons develop a dying-back pattern of

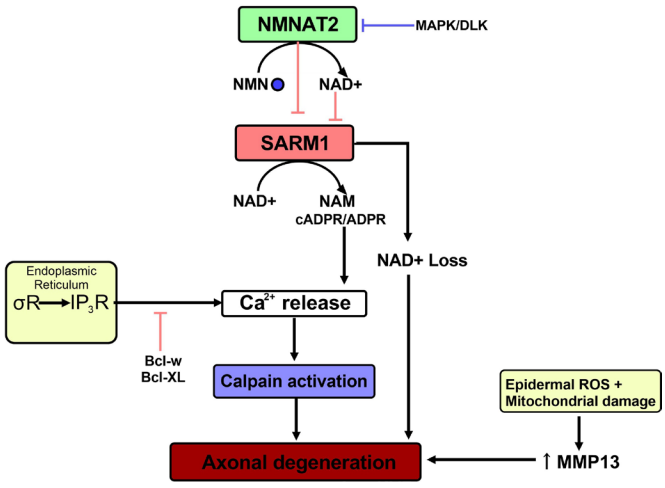

Figure 2 Axonal degeneration pathways involved in CIPN schematic of highlighted axonal degeneration pathways in CIPN. NMNAT2 (nicotinamide mononucleotide adenylyltransferase 2) synthesises NAD^+ (nicotinamide adenine dinucleotide) from NMN (nicotinamide mononucleotide) and ATP. MAPK/DLK (MAP3 K dual leucine zipper kinase) pathways are linked to NMNAT2 turnover. SARM1 (sterile-α and Toll/interleukin 1 receptor motif containing protein 1) is an NADase and converts NAD^+ into NAM (nicotinamide) and ADPR (ADP ribose) or cADPR (cyclic ADPR). Blue circle denotes ATP. NMNAT2 and NAD^+ inhibit SARM1 activation. Once activated, SARM1 triggers NAD+loss and ADPR/cADPR release leading to axonal degeneration, with Ca^{2+} activated calpain proteases. BCL-2 class proteins including Bcl-w and Bcl-XL inhibit proapoptotic cascades involving calcium release from endoplasmic reticulum receptors including inositol 1,4,5-triphosphate receptor (IP_3R). Sigma-1-receptors (σR) modulate IP_3R and BCL-2 pathways. Epidermal mitochondrial damage and reactive oxygen species (ROS) production lead to matrix metalloproteinase 13 (MMP-13) upregulation, linked to subsequent degeneration. CIPN, chemotherapy-induced peripheral neurotoxicity.

damage arising from the injury site.[1] Wallerian degeneration was first well described in 1850 as consequence of mechanical damage and follows a stereotypic pattern of events at the site of damage, including axon fragmentation, mitochondrial swelling and disassembly of the cytoskeleton.[1] A critical turning point paving the way to understanding the biomolecular mechanisms underlying axonal damage, was the observation of a peculiar strain of mice—later named as *Wallerian degeneration slow* (Wld^S) mice—whose axons were able to survive ten times longer than wild-type animals, following axonal transection.[29] In addition to protection following mechanical injury, Wld^S mice proved resistant to axonal degeneration following vincristine[30] and paclitaxel treatment.[31]

Ultimately, subsequent studies allowed identification of Wld^S gene product as a protein consisting of an enzyme involved in nicotinamide adenine dinucleotide (NAD^+) cofactor synthesis: nicotinamide mononucleotide adenyltransferase 1 (NMNAT1) and a component of ubiquitin ligase.[1] Significant research efforts identified a related protein named NMNAT2, pivotal for axonal growth and survival.[32] Both NMNAT1 and NMNAT2 synthesise NAD^+ from the precursor nicotinamide mononucleotide (NMN). However, cytosolic NMNAT2 has a short half-life (less than 40 min in cell lines)[33] meaning that any interruption of NMNAT2 supply (such as due to axon trauma or altered axonal transport), rapidly triggers the process of active axonal degeneration.[1 26] In Wld^S mice, the protein NMNAT1 is axonally located and can replace NMNAT2, effectively blocking degeneration

and stabilising NAD^+ levels after injury.[26] Similarly, axons overexpressing NMNAT1 were protected from vincristine-induced axonal degeneration.[34]

The importance of NAD^+ synthesis pathways in axonal degeneration was underscored by the identification of another fundamental axonal protein, the sterile-α and Toll/interleukin 1 motif containing protein 1 (SARM1).[35] SARM1 has intrinsic NADase activity and is activated in a molecular cascade leading to axonal degeneration.[35] Activation of SARM1 establishes axonal degeneration after nerve injury following a variety of triggers, including neurotoxic chemotherapy.[36 37] The enzymatic activity of SARM1 is tightly controlled due to its catalytic domain keeping it an inactive state, the presence of NAD^+ further stabilises this inactive state.[38] SARM1 is activated by increases in the NMN/NAD^+ ratio, acting as a sensor of altered NAD^+ metabolism.[39] NMNAT2 inhibits SARM1 activation via enzymatic conversion of NMN to produce NAD^+ (reviewed in reference 40). Without functional SARM1, loss of NMNAT2 does not produce an axonal degeneration phenotype and axons are protected from degeneration.[41]

Once activated, SARM1 catalyses NAD^+ degradation into nicotinamide, ADP ribose (ADPR) and its cyclic form (cADPR).[35] Both ADPR and cADPR are powerful calcium mobilisers[42] and alterations in intraneuronal calcium homoeostasis are likely relevant to SARM1-mediated degeneration. Activation of SARM1 ultimately leads to a toxic increase in intraneuronal calcium levels, resulting in activation of calpains and other molecular cascades producing degeneration.[43]

In addition to SARM1-mediated degeneration, axonal degeneration related to calcium dysregulation and calpain activation have been linked to molecular cascades involving the anti-apoptosis protein Bcl-w.[44] BCL-2 class proteins including Bcl-w have prosurvival functions, inhibiting activation of proapoptotic protein cascades.[45] These cascades result in abnormal calcium signalling mediated via calcium release from endoplasmic reticulum governed by receptors including inositol 1,4,5-triphosphate receptor (IP_3R) and eventual activation of Ca^{2+}-triggered calpain proteases producing degeneration. Paclitaxel alters axonal trafficking of Bcl-w, leading to IP_3R-mediated release of intracellular Ca^{2+} and subsequent calpain cascades leading to axonal degeneration.[44] The related protective protein Bcl-XL prevented bortezomib-induced neuronal damage but only delayed axonal damage, suggesting distinct pathways for neuronal and axonal degeneration.[24] Similarly, the sigma-1 receptor is associated with the endoplasmic reticulum and mitochondrial interface, signalling cell survival via BCL-2 cascades and IP_3R pathways[46] and has been implicated in paclitaxel-induced axonal degeneration.[4]

Epidermal damage may precipitate axonal degeneration, with zebrafish studies demonstrating upregulation of matrix metalloproteinase 13 (MMP-13) in skin following paclitaxel treatment.[47] MMP-13 inhibition significantly reduced axonal degeneration following paclitaxel.[47] Epidermal mitochondrial damage and reactive oxygen species production drove MMP-13 upregulation, which was linked to subsequent degeneration of small unmyelinated axons.[48]

Other cascades such as the MAPK dual leucine zipper kinase pathway have been implicated in vincristine-induced axonal degeneration[24] and are linked to NMNAT2 protein turnover.[49] In addition to direct axonal effects, bortezomib-induced axonal degeneration was found to be transcriptionally regulated and potentially linked to caspase-mediated degeneration pathways.[24] Of note, these pathways are not exclusive[27] and interactions between multiple molecular pathways with different neurotoxic agents likely occur. In total, unravelling the molecular mechanisms of axonal degeneration and understanding critical pathways to control this process will likely accelerate identification of potential targets to prevent CIPN. Below, we discuss preclinical and clinical evidence of axonal degeneration in CIPN.

PRECLINICAL EVIDENCE OF AXONAL DEGENERATION IN CIPN

CIPN preclinical models: prerequisites for analysis of axonal degeneration

Preclinical models are crucial in understanding CIPN pathogenesis, enabling pathogenic hypotheses to be tested experimentally. However, when exploiting a bench-side approach to investigate CIPN pathogenesis, the model selected and the outcome measures applied to detect axonal damage are crucial, as extensively described previously.[50] In particular, regarding in vivo models, a specific demonstration that nervous system damage had ensued is mandatory, relying on objective tools such as histopathological analyses or solid surrogate functional biomarkers such as nerve conduction studies (NCS). There is evidence of differences in CIPN manifestation and severity between different CIPN animal models and a lack of standardisation of animal strain, sex, age and drug dosing/schedule.[50] Accordingly, it is important that verification of nervous system damage is used to confirm CIPN development, rather than relying solely on behavioural observations such as nocifensive behaviour.

The key morphological hallmarks of axonopathy in preclinical models include degeneration or loss of large myelinated fibres, which is matched by NCS typical axonal pattern: a predominant decrease of action potential amplitude, with eventual decreased conduction velocity, as a secondary effect of abundant large fibre loss rather than primary demyelination.[50–52] This pattern has been identified across multiple preclinical models of CIPN with different agents. Figure 3 shows representative images of axonal damage in different rodent models of CIPN. Notably, platinum drugs exert their neurotoxic action first at the level of the soma (ie, neuronopathy) and only subsequently the axonal damage

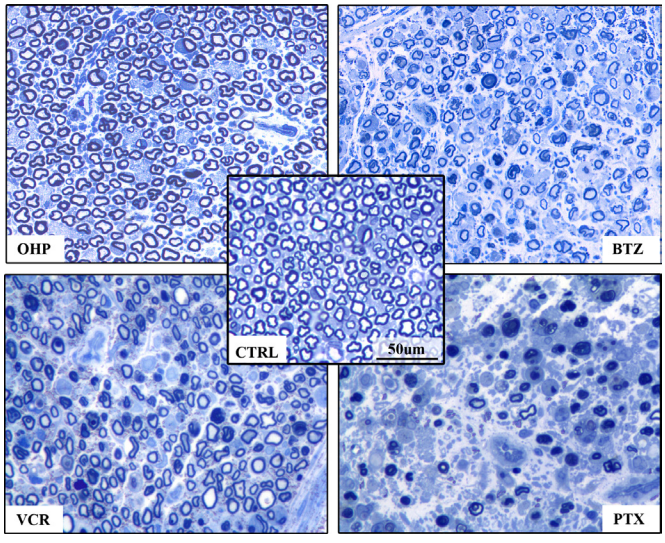

Figure 3 Representative images of axonal damage in different rodent models of CIPN Light micrographs showing the features of experimental CIPN in rats treated with oxaliplatin (OHP), bortezomib (BTZ), vincristine (VCR) and paclitaxel (PTX), in comparison with control, untreated animals (CTRL). Despite all drugs induce axonopathy with very similar features, remarkably different severity of large myelinated fibre loss is evident (bar=50 mm). CIPN, chemotherapy-induced peripheral neurotoxicity.

becomes evident and usually only mild axonopathy is demonstrated; other drug classes, instead, show a higher severity of axonal damage, acting directly and primarily on axons.[12]

Apart from relying on assessment of peripheral nerves using NCS or nerve morphometry, intraepidermal nerve fibre density (IENFD) can be used to demonstrate CIPN-related axonal damage also in small fibres.[53] Notably, once axonal damage is well characterised in the model, this is the ideal ground for proof-of-concept studies aiming at identifying CIPN biomarkers which are crucial to find early surrogate marker(s) of axonal damage. An example of this approach is the analysis of neurofilament light chain (NfL) serum levels in animal models of CIPN in which they increase and parallel the severity of axonopathy.[51 52] NfL is a primary component of neurofilament, a key structural protein of the axonal cytoskeleton, which is released during axonal injury through multiple mechanisms. Examination of NfL in animal models has led to the emergence of clinical studies examining serum NfL levels in conjunction with neurotoxic chemotherapy treatment as a potential biomarker of CIPN (detailed below).

SARM-linked axonal degeneration in CIPN models

In the last few years, the SARM1 pathway has been investigated across different preclinical CIPN models, providing promising evidence of its key role in chemotherapy-induced axonal damage (table 1). In models of paclitaxel-induced CIPN, genetic deletion of SARM1 in mice showed a gene-dosage-dependent neuroprotection profile with the values of sensory action potential amplitudes in paclitaxel-treated heterozygous mice differing between those of wild-type and *Sarm1* knockout mice.[54] Further, the role of SARM1 in paclitaxel axonopathy was linked to cADPR production leading to a toxic Ca^{2+} intraneuronal increase.[55]

Similarly, SARM1 knockout mice showed resistance to vincristine-related neurotoxicity as shown via morphological and neurophysiological endpoints.[56] Interestingly, while SARM1 was required for both vincristine-induced and bortezomib-induced axonal degeneration, there was evidence of different upstream pathways, with involvement of the MAPK pathway with vincristine and caspase dependent processes with bortezomib,[24] demonstrating the principle of a common final pathway with different upstream triggers. Further, there may also be multiple mechanisms involved in neuropathy development, including those targeting neuronal cell bodies as well as distal axons. In cell culture models, bortezomib administration damaged both axon and cell body compartments.[24] While cultured neurons from SARM1 knockout mice demonstrated resistance to bortezomib-induced axonal damage, cell bodies were still affected, indicating that there may be distinct axonal and neuronal degenerative pathways involved in bortezomib-induced neuropathy.[24]

There is also preliminary data related to other drugs that should be further explored: in a model of oxaliplatin acute toxicity syndrome following a single oxaliplatin administration,[57] SARM1 knockout mice did not demonstrate allodynia. However, this observation needs to be strengthened via a chronic—not acute model—to weigh the role of SARM1 on oxaliplatin-related axonal damage. However, both cell culture and mouse models of cisplatin-induced CIPN have demonstrated the role of SARM1 and calpain activation in resulting degeneration.[58]

In total, preclinical evidence all together supports the view that SARM1 might be a promising druggable pathway in CIPN, particularly after exposure to taxanes, vincristine or proteosome inhibitors, with less evidence for platinum-based chemotherapy.

CLINICAL EVIDENCE OF AXONAL DEGENERATION IN CIPN

There is substantial clinical evidence of the central role of axonal degeneration as a pathological process in CIPN. Direct histopathological evidence of axonal degeneration is provided by nerve or skin biopsies from patients with CIPN, while clinical neurophysiological techniques provide indirect functional evidence of axonal loss and dysfunction.

Histopathological evidence of axonal degeneration from the clinical setting

Overall, nerve biopsies have provided evidence of significant axonal degeneration in large sensory fibres of patients with CIPN (table 2). However, nerve biopsies are currently very rarely performed in patients with CIPN, unless they show very uncommon features. Accordingly, biopsy-based evidence is taken from a limited number of patients. Further, it is difficult to rule out confounding factors which limit the ability to establish specific casual relationships between chemotherapy and neuropathology.

Loss of large myelinated sensory fibres is evident in nerve biopsies from patients with CIPN including those treated with platinum agents (cisplatin), taxanes (docetaxel, paclitaxel), vinca alkaloids (vincristine), proteasome inhibitors (bortezomib), thalidomide and immune-conjugates (brentuximab vedotin) (see table 2). Further, histopathological evidence of Wallerian-like axonal degeneration has been observed in nerve biopsies of patients treated with a range of chemotherapies including vincristine,[59 60] thalidomide,[61] cisplatin,[62] paclitaxel[63] and brentuximab vedotin.[64] Biopsies taken early during vincristine treatment demonstrate evidence of active axonal degeneration including Wallerian-like degeneration, axonal swelling and myelin ovoids but no reduction in the number of fibres,[60] suggesting that degeneration precedes axonal loss.

However, with some chemotherapies, particularly platinum agents, there is also pathological evidence of neuronal degeneration. In postmortem tissue, cisplatin-treated patients demonstrated reduced volume of DRG soma and evidence of necrosis, in addition to large fibre axonal loss.[65] Accordingly, neuropathy and axonopathy can coexist and complementary strategies may be required to prevent nerve damage in situ.

While large myelinated fibre loss is predominant in CIPN, loss of unmyelinated smaller sensory fibres also occurs with some agents, including vincristine[59] and paclitaxel.[63] However, minimal to no loss of unmyelinated fibres was evident following cisplatin[62] or thalidomide treatment.[66] However, loss of small fibres is not easy to be demonstrated in nerve biopsies unless formal morphometric analysis is performed, and unmyelinated fibre loss can be evidenced only at the ultrastructural level, while reduction in IENFD in skin biopsies is a sensitive and reliable method.[67]

However, compared with evidence for large fibre loss from nerve biopsies, evidence for small fibre degeneration remains more mixed (reviewed in reference 68). Evidence of reduced IENFD has been found in skin biopsies obtained from patients treated with docetaxel,[69] paclitaxel[70] and oxaliplatin.[69] However, larger, prospective samples of oxaliplatin-treated patients have not found reductions in IENFD across treatment.[71] Similarly, in a group of 33 bortezomib, taxane or platinum treated patients followed up longitudinally, there was no reduction in IENFD across treatment and no relationship between IENFD and CIPN severity could be shown.[72] However, in some skin biopsies with normal IENFD, there was morphological evidence consistent with axonal degeneration, with fibre fragmentation and axonal

Table 1 Preclinical evidence for SARM1 pathway involvement in axonal degeneration in CIPN

Chemotherapy Regimen	Model type	Model details	Evidence of axonal degeneration	Type and effect of SARM1 inhibition	Reference
Paclitaxel 25 mg/kg IV t.i.w CD: 75 mg/kg	In vivo Mice	C57BL/6J SARM1 KO	Significant decrease in IENFD density and SNAP amplitude	IENFD preservation with genetic inhibition of SARM1	Turkiew *et al*, 2017
Paclitaxel 50 mg/kg IV CD: 100 mg/kg	In vivo Mice	C57BL/6J SARM1 KO	65% reduction in tail nerve SNAP amplitude	Genetic deletion of SARM1 preserves SNAP amplitude	Bosanac *et al*, 2021
Paclitaxel 50 mg/kg IV CD: 100 mg/kg	In vivo Mice	C57BL/6J	Reduction in SNAP amplitude, thermal hyperalgesia, reduced IENFD	SARM1 pharmacological inhibition provides partial protection from axonal degeneration	Bosanac *et al*, 2021
Paclitaxel 30 nM, 24 hours	In vitro DRG cultures	E14 S&D rat embryonic	Axonal degeneration in DRG cultures	SARM inhibition by shRNA transduction blocks cADPR production and axonal degeneration	Li *et al*, 2021
Vincristine 1.5 mg/kg IP b.i.w CD:12 mg/kg	In vivo Mice	C57BL/6 SARM1 KO	Reduction in IENFD, distal myelinated axons, SNAP amplitude; development of hyperalgesia	Genetic deletion of SARM1 preserves SNAP amplitude+prevents loss of IENFD, axons and hyperalgesia	Geisler *et al*, 2016
Vincristine 40 nM, 24 hours	In vitro DRG cultures	WT and SARM1 KO ED12.5 mice	Axon fragmentation in DRG cultures	Lack of axon fragmentation in SARM -/- axons	Gerdts *et al,* 2013
Vincristine 40 nM, 48 hours	In vitro DRG culture	E13.5 WT or SARM1 enzymatically disabled (E642A) mice	Axonal degeneration quantified in DRG cultures	Enzymatically active SARM1mediated axon loss, protection in enzymatically disabled SARM1 cultures	Essuman *et al,* 2017
Vincristine 40 nM, 72 hours	In vitro DRG cultures	E13.5 CD-1 and SARM1 KO mice	WT DRG axons completely fragmented after 12–36 hours	Genetic deletion of SARM1 prevented axonal degeneration in primary cultures	Geisler *et al*, 2019
Vincristine 20 nM, 72 hours	In vitro cell cultures	SCG (SARM1 Haploinsufficient; Homozygous); SARM1 ASO-treated DRGs	80% of axon degeneration in 72 hours post Vincristine	Axons remained intact (54 hours in SARM1 haploinsufficient SGC; 72 hours in SARM1 homozygous SCG; 96 hours in ASO-treated DRGs)	Gould *et al*, 2021
Bortezomib 0.8 mg/kg IV b.i.w CD: 6.4 mg/kg	In vivo Mice	C57BL/6J SARM1 KO	Significant decrease in IENFD	SARM1 KO preserves IENFD	Geisler *et al*, 2019
Bortezomib 100 nM, 72 hours	In vitro DRG cultures	E13.5 CD-1 and SARM1 KO mice	WT DRG axons degenerated after 24–36 hours	Genetic deletion of SARM1 prevented axonal degeneration in primary cultures	Geisler *et al*, 2019
Bortezomib 0.1–15 nM 24 or 72 hours, 3 days	In vitro cell culture	Human-induced pluripotent stem cell derived motor and sensory neurons	Reduced neurite length, decrease in neurite diameter, axonal swellings	Degeneration blocked by NAD^+ but no effect of SARM1 inhibitor	Snavely *et al,* 2022
Oxaliplatin 6 mg/kg IP CD: 6 mg/kg	In vivo Mice	C57BL/6 SARM1 KO	Increased mechanical and cold hypersensitivity	SARM1 KO blocks development of mechanical and thermal allodynia	Gould *et al*, 2021
Cisplatin 4 mg/kg IV weekly CD: 16 mg/kg	In vivo Mice	SARM1 KO; C57BL/6	Decreased SNAP amplitude, IENFD, thermal hyperalgesia, formation of DNA-platinum adducts, increased calpain activation	Genetic deletion of SARM1 protected SNAP amplitude and IENFD; prevented thermal hyperalgesia, DNA-platinum adducts and calpain activation	Cetinkaya-Fisgin *et al*, 2020
Paclitaxel 40 µm, Docetaxel 0.1 µm, Oxaliplatin 500 µm, Cisplatin 50 µm, vincristine 50 µm	Zebrafish	WT and SARM1 KO	Damage to distal Schwann cells in wild-type specimens but not in SARM1 KO mutants	Genetic deletion of SARM1 increases Schwann-cell resistance to toxicity by diverse chemotherapeutic agents after axonal injury	Tian *et al*, 2020

A complete reference list for table 1 is located in online supplemental information.

ASO, antisense oligonucleotide; b.i.w, twice a week; cADPR, Cyclic adenosinediphosphate ribose; CD, cumulative dose; CIPN, chemotherapy-induced peripheral neurotoxicity; DRG, dorsal root ganglia; IENFD, Intra Epidermal Nerve Fibre Density; IP, intraperitoneal; IV, intravenous; KO, Knockout; SARM1, sterile-α and Toll/interleukin 1receptor (TIR) motif containing protein 1; SGC, superior cervical ganglion; SNAP, sensory nerve action potential; t.iw, three times a week; WT, wild type.

swellings.[72] This may suggest that small fibre degeneration occurs prior to or in the absence of reduction in fibre density. In line with this, in 22 bortezomib-treated patients, IENFD was not reduced but subepidermal density was decreased with increased density in upper dermis, suggesting sprouting.[73] Further, axonal swellings, which have been demonstrated to precede degeneration, were evident in epidermal fibres.[74] Similarly, skin biopsies in 10 ixabepilone-treated patients demonstrated prominent

Table 2 Evidence of axonal degeneration from nerve biopsies in patients with CIPN

Treatment type	Axonal loss	Regeneration	Other features	Reference
Cisplatin	Loss of large myelinated fibres; axon and myelin degeneration	Patchy/no regeneration	Some mononuclear /macrophage infiltration of Schwann cells	Roelofs *et al* 1984, Pages *et al* 1986, Gastaut and Pellissier 1985, Krarup-Hansen *et al* 1993; 2007
Paclitaxel	Loss of large myelinated fibres; loss of unmyelinated fibres on electron microscopy	No regeneration/occasional regeneration	No microtubule accumulation; Schwann cells containing myelin degradation products; axonal atrophy	Wiernik *et al* 1987, Van Den Bent *et al* 1997; Sahenk *et al* 1994
Docetaxel	Loss of large myelinated fibres	No regeneration/active regeneration (small myelinated fibre clusters)	Axonal atrophy; membranous profiles in axons; Schwann cell subunits devoid of axons	New *et al* 1996*, Fazio *et al* 1999
Bortezomib	Decreased myelinated fibre density; axonal degeneration with secondary demyelination	Thinly myelinated fibres and segmental regeneration	Increased Delta 2 tubulin levels; perivascular epineurial inflammation, perineurial thickening neo vascularisation; swollen endoneurium; no immunodeposition	Pero *et al* 2021; Santilli and Martinez-Thompson 2021; Thawani *et al* 2015
Vincristine	Loss of both large and small fibres, evidence of active Wallerian degeneration; no fibre loss in early treatment	Some regeneration; numerous regenerating fibres with shortened internodes	Swollen myelin sheaths and ovoids; proximal and distal nerves equally affected; some segmental demyelination	Bradley *et al* 1970; Gottschalk *et al* 1968; McLeod and Penny, 1969; Moress *et al* 1967
Thalidomide	Loss of large fibres, preservation of small fibres; ongoing Wallerian degeneration	Evidence of regeneration in three of six patients; a few regenerative clusters	Myelin ovoids, lack of inflammation	Fullerton and O'Sullivan, 1968; Chaudhry *et al* 2002
Brentuximab vedotin	Mild loss of myelinated fibres or decreased myelinated fibres of all sizes; ongoing Wallerian degeneration	Sporadic small clusters of regenerating fibres	No inflammatory infiltrates, no CD-30 expression; electron microscopy alterations to cytoskeleton and microtubule orientation, disorganisation of neurofilaments	Corbin *et al* 2017; Mariotto *et al* 2015

All presented nerve biopsy findings are from sural nerve unless otherwise specified.
A complete reference list for table 2 is located in online supplemental information.
*New *et al* 1996—superficial peroneal nerve biopsy.
CIPN, chemotherapy-induced peripheral neurotoxicity.

alternations in morphology with denervated Schwann cells and reduced axons with fragmentation of microtubules and neurofilaments, and axonal axoplasm compartmentalisation and degradation.[75]

Neurophysiological evidence of axonal degeneration from the clinical setting

Clinical neurophysiological techniques provide evidence of axonal loss, with the neurophysiological signature of axonal degeneration evidenced by reduction in compound action potential amplitude. Axonal neuropathies are characterised by reduced compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) in the context of normal or slightly reduced conduction velocity.

There is substantial electrophysiological evidence for axonal degeneration in CIPN, with widespread evidence of reduced sensory and in some cases motor amplitudes across the spectrum of CIPN (reviewed in.[9 68] Broadly, the main neurophysiological characteristics of CIPN are distal, dying back pattern reduction in sensory amplitudes consistent with axonopathy or diffuse sensory amplitude decrease associated with neuronopathy,[68] with presentation depending on the neurotoxic agent.

Dying-back pattern, progressive reduction in CMAP and SNAP amplitudes is evident with vincristine treatment with predominant sensorimotor loss in the distal nerve segment.[76] Similarly, bortezomib-induced sensory neuropathy has been characterised as length-dependent, with predominant lower limb reduction in sensory amplitudes[77] and distal axonopathy as the most common neurophysiological presentation.[78] Neurophysiological studies in patients treated with brentuximab vedotin identified a sensory predominant axonal neuropathy with some motor involvement.[64] Upper and lower limb reduction in sensory amplitudes were noted, but there was evidence of a sural sparing pattern of axonal loss.

Axonal loss is predominant in distal sensory nerves following taxane treatment but motor axon loss can occur at higher doses and particularly evident in the peroneal nerve.[79] While there is evidence of distal, length-dependent axonopathy in paclitaxel-treated patients,[80] some studies have reported a length-independent pattern consistent with neuronopathy.[79] This may suggest that multiple pathomechanisms are relevant in producing neuropathy in paclitaxel-treated patients. Thalidomide produces a sensory or sensorimotor neuropathy.[81] Some studies have suggested the possibility of neuronal involvement[81] but others have supported a presentation consistent with axonopathy with reduced lower limb sensory amplitudes and preserved upper limb amplitudes.[82]

Conversely, in platinum-based chemotherapies, sensory neuronopathy-like axonal loss is evident with oxaliplatin producing progressive reduction in sensory amplitudes.[83] Similarly in cisplatin-treated patients, evidence of involvement of central projections of the DRG has been found with prolonged somatosensory evoked potential conduction time, suggesting neuronopathy.[65 84]

Other neurophysiological studies have been undertaken in CIPN, and also demonstrated evidence of axonal degeneration. Longitudinal changes in sensory axonal excitability occurred in chronic oxaliplatin neuropathy prior to reduction in SNAP amplitude.[85] This excitability profile was similar to excitability changes associated with Wallerian axonal degeneration in preclinical models of nerve injury.[86] Excitability changes were not evident in motor axons and were correlated with sensory

Table 3 Clinical neurofilament light chain biomarker studies in CIPN

Cohort	Age	CIPN status	Timepoints	NfL findings	NfL cut-off	Reference
Paclitaxel (n=190) ovarian cancer	66.5 (57.0, 72.0) years	43% NCI-CTCAE, grade 2 or higher	Baseline, each cycle (from 2 to 6)	Baseline median 23.6–27.2 pg/mL; Cycle 1 59.9–121.1 pg/mL	>150 pg/mL after 1first cycle had increased risk of CIPN	Mortensen *et al*, 2022
Paclitaxel (n=48) gyneacological cancer	54 (45–63) years	96% with CIPN, grade 2 or 3 in 65%	Pre surgery, baseline, post 2, 4, 6 cycles and 6 months post	Presurgery 18.2–20.3; baseline: 65.3–98.9; 2 cycles: 103.9–225.8 pg/mL	>124 pg/mL after 2 cycle predict grade 3 CIPN	Kim *et al*, 2022
Paclitaxel (n=59) breast cancer	53.1±11.5 years	44% TNSc grades 2–3	Baseline, week 2, week 3, end of treatment	Baseline 15.3±13.3 pg/mL	>85 pg/mL at week 3 to predict CIPN	Karteri *et al*, 2022; Velasco *et al*, 2022
Paclitaxel (n=21) breast cancer	55.7±11.7 years	Mean NCI-CTCAE at end of treatment 1.1±0.6	Baseline, every 2 weeks, end of study	Baseline 38.8 pg/mL; end 280.6 pg/mL	N/A	Benashley *et al*, 2022
Paclitaxel (n=31) breast or ovarian cancer	50 (27–61); 64 (29–69) years	Mean TNSr at end of treatment 5±4	Baseline, 28 weeks later (post-treatment)	Post-treatment 60.3±50.4 pg/mL	ΔNfL 36 pg/mL >50% probability of CIPN	Huehnchen *et al*, 2022
Oxaliplatin (n=34) colorectal cancer	58.7 (9.1) years	70% grade 2 or 3 NCI-CTCAE	Baseline, 3 months, 6 months	Median 12.7 pg/mL (baseline); 22.3 pg/mL (3 months); 115.0 pg/mL (6 months)	195 pg/mL at 6 months predicts Grade 3 NCI-CTCAE	Kim *et al*, 2020

CIPN, chemotherapy-induced peripheral neurotoxicity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NfL, neurofilament light chain; TNSc, Total Neuropathy Score clinical version; TNSr, Total Neuropathy Score reduced version.

CIPN severity. Interestingly, this pattern of excitability change was not evident in paclitaxel-treated patients. Instead, early reductions in sensory amplitude and increased threshold for activation were evident,[87] reflecting a different mechanism of degeneration. Excitability studies in bortezomib-treated patients suggested early axonal depolarisation in both sensory and motor axons.[88] Taken together, these findings highlight the agent-specific profile of neuropathy development and mechanisms of axonal dysfunction.

Emerging biomarker evidence of axonal degeneration

Identification of sensitive blood-based biomarkers of axonal degeneration enable quantification of degeneration prior to symptom expression. There are a variety of potential biomarkers which may provide real-time insight into axonal degeneration including proteins released by damaged axons or neurotrophic factors linked to axonal survival.[89]

Increasing evidence suggests that NfL protein levels are elevated in cerebrospinal fluid and peripheral blood across a range of neurological disorders, potentially acting as a quantitative marker of neuroaxonal degeneration. Because it is a marker of neuroaxonal damage, NfL has been identified as an indicator of disease across multiple neurological disorders and is not specific to peripheral or chemotherapy-induced nerve damage. However, comparison of NfL levels with sural nerve biopsies has revealed elevated NfL in patients with evidence of active axonal degeneration,[90] highlighting the potential role of NfL as a biomarker in CIPN.

Accordingly, there is now evidence from several studies that elevated NfL is associated with CIPN (table 3). The majority of studies have assessed paclitaxel-treated patients (cumulative n=349) and all have demonstrated increased NfL following treatment.[91–95] In 31 paclitaxel-treated patients with breast or ovarian cancer, elevations in NfL were correlated with clinically graded and patient-reported CIPN, with greater NfL associated with more severe CIPN.[91] NfL remained elevated at 28 weeks post-treatment but returned to baseline after 40 weeks. In a separate longitudinal prospective study, 59 weekly paclitaxel-treated patients with breast cancer were assessed at multiple timepoints.[93] NfL levels increased over the course of paclitaxel treatment, and elevations were statistically significant by week 2 in patients who eventually developed more severe (grades 2–3) CIPN. However, NfL was not significantly elevated until end of treatment in patients with minimal neuropathy (grades 0–1). Similarly, clinically graded neuropathy was correlated with NfL level but older age was also an important predictor. Despite its relative moderate sample size, this study provided the first evidence supporting the significance of NfL as a promising early biomarker predicting the final CIPN severity after chemotherapy completion before mid-treatment.[93] A secondary analysis of the latter study showed that NfL levels proportionally increase during chemotherapy administration and significantly correlate with NCS sensory abnormalities.[96] Subsequently, elevated NfL from the initial paclitaxel treatment cycle was found to be predictive of CIPN outcomes in 190 ovarian cancer patients.[94]

A single study has examined NfL in 34 oxaliplatin treated patients,[97] with elevated NfL occurring following 3 and 6 months of treatment. In contrast to findings in paclitaxel-treated patients, NfL levels at 3 months of treatment could not predict those with severe CIPN at the end of treatment. Further, the extent of NfL increase at 3 months was lower than reported in paclitaxel studies. However, at the end of treatment, patient-reported CIPN and sural SNAP amplitudes were correlated with NfL levels and NfL levels were higher in patients with more severe CIPN. Another neurofilament component, neurofilament heavy chain was also increased in paclitaxel-treated patients[91] but not in an earlier study of patients with breast cancer, although it was unclear if all patients were treated with neurotoxic chemotherapy in the cohort.[98] In contrast, the cytoskeletal filament expressed in Schwann cells, glial fibrillar acidic protein was not increased following chemotherapy treatment in paclitaxel-treated[91] or oxaliplatin-treated patients.[97]

A number of early studies have identified reduced nerve growth factor (NGF), a neurotrophic factor necessary for axonal recovery, in CIPN (reviewed in[89]). However, a more recent study identified increased NGF in patients with painful CIPN and greater CIPN severity.[72] Another neurotrophic factor, brain-derived neurotrophic factor (BDNF) had initially been suggested to be reduced in patients with CIPN but other studies have found elevated BDNF in patients with bortezomib-induced neuropathy.[89] Accordingly, there remains a lack of clear results defining

the utility of neurotropic factors as biomarkers of axonal damage in CIPN.

Discriminating early patients at high risk to eventually manifest axonopathy and clinically significant neurotoxicity with NfL and other blood biomarkers longitudinal assays as a surrogate marker of neuroaxonal damage during chemotherapy is very important for future neuroprotection trials and as such, independent replication of these findings is warranted in larger homogeneous and well-characterised cohorts. Nonetheless, it is also important to consider the current cost and limited availability of NfL assay techniques, which currently limit the utility of applying monitoring in every day clinical practice.

TREATMENT HORIZONS

The recent advances in our understanding of the pathogenic processes of CIPN at the molecular level have provided the basis for preclinical research attempting to test novel therapies aimed at prevention of CIPN. Indeed, current evidence shows that axonal degeneration, triggered by loss of the axonal survival factor NMNAT2 and activation of SARM1, might be a significant contributor to CIPN pathogenesis. This is particularly evident after exposure to chemotherapeutic compounds impairing microtubule dynamics.[4] In addition, evidence from preclinical studies using paclitaxel points towards two additional downstream axon degenerative pathways to induce calpain activation and eventually mediate axon fragmentation; one relating to the Bclw-dependent IP3R1 cascade[44] and the other to MMP-13.[47]

As such, treatment strategies targeting these pathways might represent novel therapeutic targets that likely provide clinically meaningful CIPN prevention. Accordingly, SARM1 gene therapy to treat CIPN-associated axonal degeneration has been experimentally tested in vitro and found that degeneration was reduced in DRG neurons expressing dominant negative SARM1 using AAV8-Syn-SARM1-CDN-EGFP (AAV-SARM1-CDN), compared with controls; thus, building the hypothesis that therapy with AAV-SARM1-CDN may protect axons during chemotherapy.[99] Further, application of *Sarm1*-targeting antisense oligonucleotides delayed degeneration following vincristine treatment in vitro, highlighting potential therapeutic strategies involving SARM1-lowering agents.[100]

Drugs which act as SARM1 inhibitors have been identified, providing the promise of pharmacological treatment of axonal degeneration. Small molecule inhibitors have been developed that target a range of sites.[101] Of note, covalent inhibitors targeting cysteine 311 in the armadillo repeat domain of SARM1 prevent vincristine-mediated degeneration in cell culture models.[102] Dehydronitrosonisodipine also blocked SARM1 activation via modification of cysteine 311, inhibiting cADPR production and axonal degeneration after vincristine treatment.[103] Similarly, the adduct forming SARM1 inhibitor NB-3 supressed plasma NfL release, and prevented loss of intradepidermal nerve fibre loss and the development of mechanical allodynia in vincristine treated mice.[104] Moreover, it was also demonstrated in vivo that targeting NADase domain with small molecule SARM1 inhibitors might also be able to spare loss of intraepidermal nerve fibres and partially protect axons from the toxic insult of taxane-based chemotherapy.[54] It was also evident in vitro that DSRM-3716 which is a potent, reversible and selective inhibitor of SARM1 NAD^+ hydrolase, demonstrated protection against axonal degeneration in mouse DRG neurons and iPSC-derived human motor neurons by decreasing cADPR levels; placing this compound, as such, among the promising candidate neuroprotectants in the CIPN context as well.[105] However, SARM1 inhibitors were ineffective in preventing bortezomib-induced axon degeneration in human-induced pluripotent stem cell derived neuronal models.[106]

Relating to dysfunction of intra-axonal Ca^{2+} homoeostasis, which seems to greatly contribute to axonal degeneration in the context of CIPN, it was demonstrated in vitro that targeting cADPR signalling with the use of pharmacological antagonists might be a potential therapeutic approach for treating paclitaxel-induced peripheral neuropathy, through Ca^{2+} modulating effects.[55]

Additional studies are needed for other promising compounds for their ability to pharmacologically improve Bclw levels/activity or IP3R1 function in order to maintain a thorough Ca^{2+} signalling to prevent axon degeneration in CIPN. Broad-spectrum MMP inhibitors, such as biphosphonates and Marimastat, might also merit clinical testing in light of their current use in the clinical setting as also based on experimental evidence demonstrating that inhibiting MMP-13 acted prophylactic against paclitaxel-associated axonal degeneration in a zebrafish model.[47] Finally, although novel sigma-1 receptor ligands have been tested clinically, additional studies are needed to better understand molecular mechanisms and validate it a potential therapeutic target.[107]

Conclusively, successful gene or pharmacological inhibition of SARM1/Bclwand IP3R1 and MMP-13-mediated axonal degeneration might open new horizons in the management of CIPN, while longitudinal testing of NfL with the use of ultrasensitive techniques, such as single molecule immunoassay arrays, in neuroprotection trials could offer quantification of response to a given drug to objectively demonstrate inhibition of axonal degeneration and prevention of CIPN.

CONCLUSIONS

CIPN is a significant toxicity of cancer treatment, associated with potentially long-lasting effects on quality of life and patient function. Both preclinical and clinical evidence emphasises the key pathogenic role of axonal degeneration in CIPN. However, studies have also highlighted differences in underlying pathophysiological mechanisms between agents. The likelihood of multiple mechanisms of toxicity involving both axonal and neuronal components suggests that multiple preventative strategies may be required to prevent CIPN. The rapidly evolving molecular understanding of the key mechanisms underlying axonal degeneration, specifically SARM1 and downstream pathways, has yielded multiple potential therapeutic targets for intervention. Further, the development of plausible biomarkers such as serum NfL will enable objective assessment of axonal degeneration in CIPN in real-time, supplying a platform for future monitoring studies. Understanding the onset, timeline and post-treatment trajectory of axonal degeneration in CIPN will also provide critical information relevant to improve understanding, monitoring and eventual treatment of axonal degeneration across a wider range of neurological disorders.

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Contributors SBP, AAA, AC-F and PA drafted the manuscript. GC and AH revised the manuscript for intellectual content. SBP, AC-F, GC and PA prepared figures. All authors reviewed and edited the manuscript and gave final approval for manuscript publication.

Funding AH and AC-F are supported by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation. GC would like to acknowledge the support of AIRC grant IG 2021 ID 25788. PA is recipient of Bicocca Starting Grant 2021-ATESP-0007.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

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Supplementary Information

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