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Mini review

Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms?

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HIGHLIGHTS

- Platins, taxanes, vincalkaloids, proteasome inhibitors are effective anticancer drugs.
- Clinical use causes peripheral neurotoxicity impairing patients' quality of life.
- Several mechanisms are involved in the development of peripheral neurotoxicity.
- Mechanisms knowledge is useful for the development of neuroprotective strategies.

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ABSTRACT

Cisplatin, oxaliplatin, paclitaxel, vincristine and bortezomib are some of the most effective drugs successfully employed (alone or in combinations) as first-line treatment for common cancers. However they often caused severe peripheral neurotoxicity and neuropathic pain. Structural deficits in Dorsal Root Ganglia and sensory nerves caused symptoms as sensory loss, paresthesia, dysaesthesia and numbness that result in patient' suffering and also limit the life-saving therapy. Several scientists have explored the various mechanisms involved in the onset of chemotherapy-related peripheral neurotoxicity identifying molecular targets useful for the development of selected neuroprotective strategies. Dorsal Root Ganglia sensory neurons, satellite cells, Schwann cells, as well as neuronal and glial cells in the spinal cord, are the preferential sites in which chemotherapy neurotoxicity occurs. DNA damage, alterations in cellular system repairs, mitochondria changes, increased intracellular reactive oxygen species, alterations in ion channels, glutamate signalling, MAP-kinases and nociceptors ectopic activation are among the events that trigger the onset of peripheral neurotoxicity and neuropathic pain. In the present work we review the role of the main players in determining the pathogenesis of anticancer drugs-induced peripheral neuropathy.

Contents

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1. Introduction

Platinum (Pt) analogues (*i.e.* cisplatin, CDDP, oxaliplatin, OHP), taxanes (*i.e.* paclitaxel, PACLI) vinca alkaloids (*i.e.* VINCRI) and proteasome inhibitors (*i.e.* bortezomib, BTZ) are the most common antineoplastic drugs successfully employed as first-line treatment for several solid and blood cancers, including breast, lung, colorectal, gastric cancers and multiple myeloma. As summarized in Table 1, although these compounds have different chemical structures and mechanisms of action, they all have the development of chemotherapy-induced peripheral neurotoxicity (CIPN) as one of their common side effect.

CIPN is a relatively common and serious consequence of cancer treatment and, since it is often the main reason for reduction or discontinuation of therapy, it may limit the employment of life-saving agents: symptoms are frequently disabling, they may affect patients' daily activities and severely impact on their quality of life. Generally, clinical signs of CIPN involve the peripheral nervous system (PNS) and lead to predominantly sensory axonal peripheral neuropathy (PN) with a "stocking and glove" distribution characterized by sensory loss, paresthesia, dysesthaesia, numbness, and tingling often aggravated by neuropathic pain [1,2]. The development, the incidence and the severity of CIPN with its relative clinical symptoms depend not only on individual risk factors but also on the cumulative dose, treatment duration, drug chemical structure and combination therapies. The supposed pathogenesis of CIPN is related to the onset of axonopathy through dying back axonal damage and neuronopathy in which the cell bodies of the Dorsal Root Ganglia (DRG) are involved. The exact pathophysiology, however, is not clear and various different underlying mechanisms have been proposed for different classes of anti-cancer drugs.

2. Pathophysiological mechanisms of CIPN

Different scientists have explored the various mechanisms involved in the development of CIPN. The chemotherapy drugs' mechanisms of action responsible for cytotoxicity are often linked also to the development of their neurotoxicity, implying the obvious difficulty in reducing toxicity without diminishing their anticancer efficacy. These mechanisms are diverse, targeting several sites of the PNS. The DRG, lacking an effective Blood–Brain Barrier (BBB [3]), are particularly vulnerable to neurotoxic damage explaining the mainly sensory symptoms in CIPN. Pt compounds, inducing DNA damage through the formation of Pt adducts, exert toxic changes in the nucleoli of DRG sensory neurons inducing changes in the transcription machinery [4]. Taxanes and vinka-alkaloids, however also seem to accumulate in the DRG of animal models producing nucleolar abnormalities [5], changes in neurofilament aggregation [6,7]. Interference with microtubule structure, exerted through tubulin alterations by taxanes [8], BTZ [9] and vinca-alkaloids [10], can lead to alterated axonal transport by interrupting the supply of trophic factors, by disrupting energy mechanisms or by inducing Wallerian-degeneration-like nerve degeneration and permanent neurological damages. Alterations in energy mechanisms in the axon through damage of some intracellular organelles such as mitochondria may also contribute to PACLI [11], CDDP [12], VINCRI and BTZ [13] neurotoxicity. The affecting of endoplasmic reticulum integrity induced by BTZ, particularly in Schwann cells [14], may lead to primary myelin sheet degeneration causing demyelinating PN. Alterations in peripheral vascularization caused by taxanes [15] and CDDP [16] can lead to a reduction in nerve blood supply. The modulation of axonal ion channels may also be implicated in CIPN. Dysfunctions in Na^+ channels, mediated mainly by OHP, but also by PACLI and VINCRI, can lead to an increase in Na^+ currents in DRG predisposing to paresthesia [17–19]. Moreover Ca^{2+} and K^+ channels are related to PACLI [20] and OHP toxicity [21], respectively. Moreover, alterations in proteins involved in Ca^{2+} signalling (such as calpains and caspases) lead to apoptotic phenomena in DRG [22]. The expression changes in Transient Receptors Potentials (TRPV, TRPA and TRPM) as well as in molecules related to glutamate signalling induced by Pt compounds, PACLI and BTZ [23–27] result in hyper-responsiveness of nociceptors predisposing to neuropathic pain and PN development. The overexpression of Mitogen Activated Protein Kinases (MAPKs) is also present in PACLI, VINCRI and OHP neurotoxicity [28,29]. Inflammatory events such as an increased release of pro-inflammatory cytokines in the peripheral nerves as well as the number of antigen presenting cells in the skin are also linked to VINCRI, BTZ and PACLI-induced PN [30–32]. Moreover, the production of free oxygen radicals, secondary to increased Ca^{2+} in DRG is common after chemotherapy treatment and determines neuronal cytotoxicity [33–36]. In this paper, we review the state-of-art of these previously cited mechanisms, a more comprehensive knowledge of which would be useful in setting up effective supportive management of neuropathic symptoms. For each chemotherapy drugs we report the most significant mechanisms by which they exert their toxic effect on the PNS, focusing also on the development of CIPN features (see Table 2 and Fig. 1).

3. Pt compounds

Pt drugs belong to a family of compounds used in the treatment of several solid tumours (*e.g.* breast, colon, lung, testicular cancers). They act by interacting with DNA forming Pt–DNA adducts that finally results in the apoptotic cell death of cancer cells. Even if CDDP, OHP and carboplatin are the most effective Pt drugs, their use is associated with several side effects such as nephrotoxicity and neurotoxicity [37]. However, differences in their toxicity profiles, related to their chemical structures and pharmacokinetic properties, have been reported [1]. DRG are considered to be the primary targets of Pt drugs where they cause apoptosis in sensory neurons [38,39] and morphological alterations in the nucleolus reflecting DNA damage due to Pt–DNA adduct formation. The DNA of PNS neurons is exposed to chemically-induced damage

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Table 1
Cisplatin, oxaliplatin, vincristine, paclitaxel and bortezomib: chemical structures, first site of action, peripheral neuropathy.

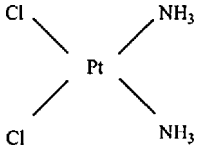
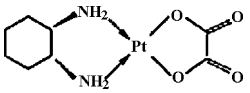
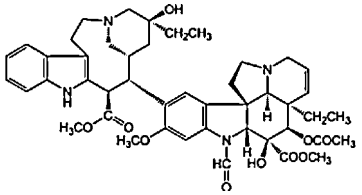
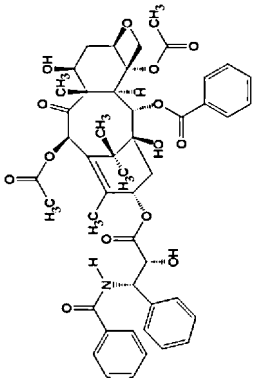
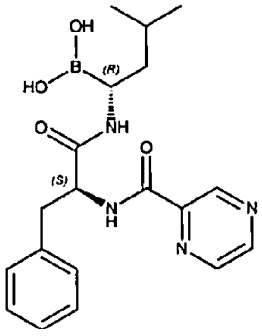
Features/drugs	Chemical structure	First site of action	Peripheral neuropathy
Cisplatin		DNA	Sensory
Oxaliplatin		DNA	Sensory proprioceptive painful
Vincristine		β-Tubulin	Sensory motor painful
Paclitaxel		β-Tubulin	Sensory motor
Bortezomib		Proteasome	Sensory painful

Table 2
Summary of some of the possible mechanisms involved in chemotherapy-induced peripheral neuropathy.

Drugs/mechanisms	Cisplatin [Refs]	Oxaliplatin [Refs]	Vincristine [Refs]	Paclitaxel [Refs]	Bortezomib [Refs]
Nuclear DNA and repair systems	[50,51,53–56]				
Mitochondria	[65,67–71]			[118,181–184,186]	[13,14,210,211]
Oxidative	[12,55,72–75,78,80,81]	[33,112,115,117,118]			[211,216,219]
Transient potential receptors	[23,82]	[24,109–111]		[195]	[25]
Glutamate	[27]			[27]	[27]
Membrane transporters	[60,83–91,93]	[84,87,92]			
Ion channels		[21,28,99–102,104–107]		[18,193]	
Caspases		[22]			
Calcium signalling		[20,108]	[20,164–166]	[109,187,189–191]	
Map-kinases		[28,177]	[167]		
Protein-kinase C		[119]			
Central glia		[124–126]	[145,148]		
Opioid receptors			[137–139]		
Synaptic plasticity			[130,131,141]		
Inflammation			[151–153]	[20,31,197–199]	[32,200,213–215]
Serotonin			[157,159,160,162,164]		
Tubulin polymerization					[9,209]

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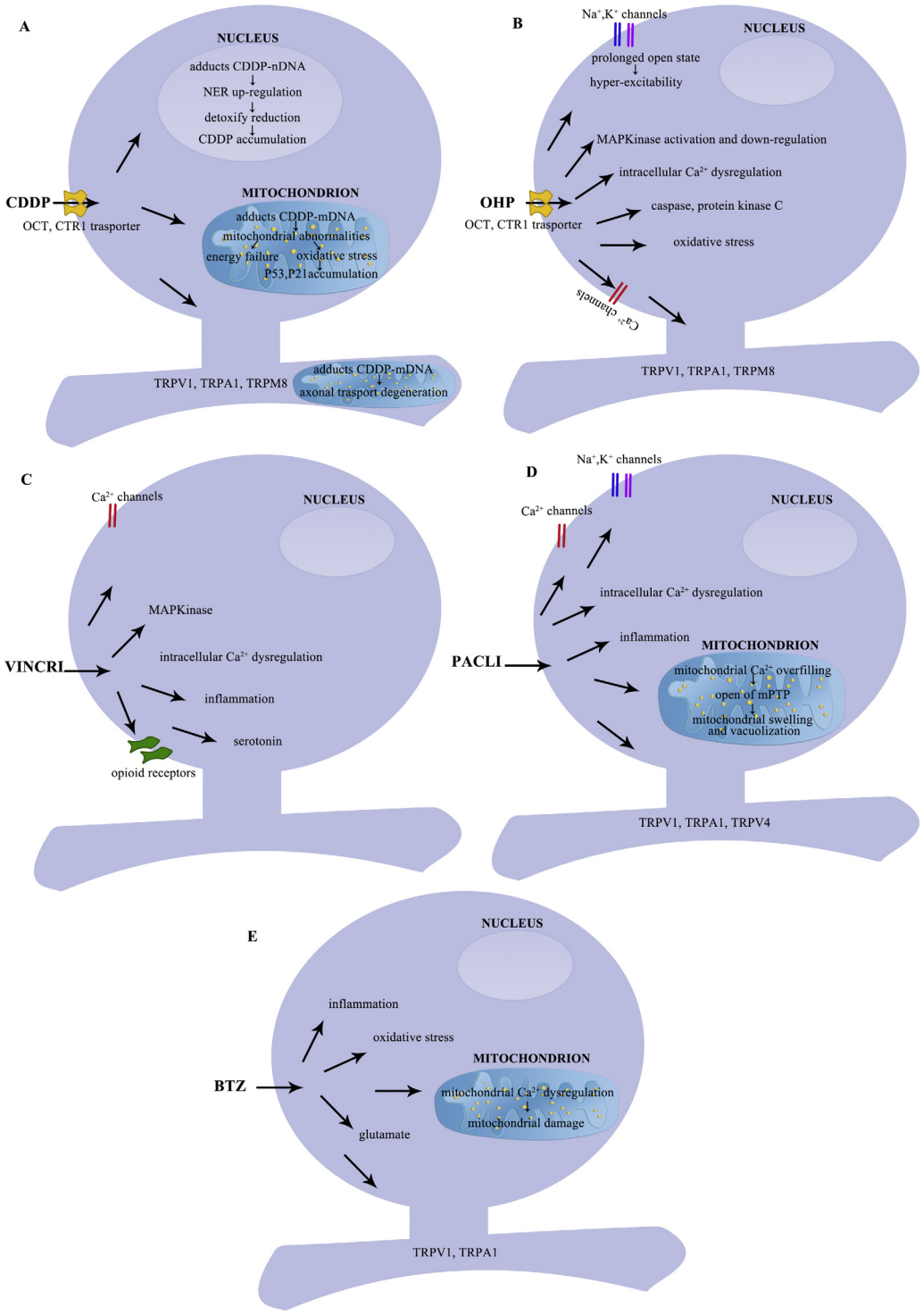

Fig. 1. Graphical summary of chemotherapy-induced mechanisms of neurotoxicity on the somatosensory pathway (OCT = organic cation transporters, CTR = copper transporters, CDDP = cisplatin, OHP = oxaliplatin, VINCRI = vincristine, PACLI = paclitaxel, BTZ = bortezomib, TRPV = transient potential receptor vanilloid, TRPA = transient potential receptor ankyrin, NER = nucleotide excision repair, Na^+ = sodium, Ca^{2+} = calcium, K^+ = potassium).

because of the lack of BBB protection. DRG are vascularized by fenestrated capillaries that render them more accessible to circulating compounds [40] including also exogenous toxic substances such as Pt drugs. Pt-induced PN is a sensory neuronopathy determined by primary damage to DRG sensory neurons that leads to an anterograde axonal degeneration, hardly and auspicious feature in neuroprotective treatment design. Generally, Pt-induced PN is characterized by paresthesia in the distal extremities, progressing to proprioceptive loss, areflexia and sensory ataxia [41,42]. Neuropathic pain symptoms have been reported, often even after treatment discontinuation [43]. While nephrotoxicity has been partially ameliorated by aggressive pre-hydration before Pt-drugs administration, interventions to reduce or avoid neurotoxicity have proved to be unsuccessful [44].

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3.1. Cisplatin

Since the 1980s, CDDP (cis-diamminedichloroplatinum), alone or in combination with other chemotherapy drugs, is mostly used to treat testicular, ovarian and small cell lung cancers [45]. It acts by forming platination products with the nuclear DNA structurally identified mainly as guanine–guanine intra-strand cross-links cis-Pt(NH3)2d(pGpG)[Pt-(GG)] [46]. Neuropathic symptoms appeared in patients receiving cumulative doses above 300 mg/m^2 [37,47] and in 50–90% of patients with a cumulative dose over 500 mg/m^2 [37,43]. Recovery from CDDP-induced neurotoxicity is often incomplete, persisting in 55% of patients up to 15 years after the cessation of treatment [4]. Even if some patients demonstrate functional improvement, neurophysiological abnormalities only rarely recover to normal [37], suggesting a sort of adaptation to symptoms by patients. Besides neurophysiological impairment (evident as a reduction in nerve potential amplitudes and partly in nerve conduction velocity [37,43]), nerve biopsies demonstrated loss of large fibres with secondary damage to myelin sheath [48,49].

3.1.1. Mechanisms of CDDP-induced neurotoxicity (see Fig. 2A)

3.1.1.1. Nuclear DNA (NDNA) and repair systems. The ability of CDDP to form cross-links with NDNA forming Pt-NDNA adducts compromises NDNA integrity and RNA transcription in differentiated cells determining alterations in cellular function. Since CDDP-induced removal of cross-links is mostly carried out by the Nucleotide Excision Repair (NER) pathway that relies in part on proteins involved in NDNA replication, it is less effective in neurons [50]. Since CDDP was found to accumulate in rat [51] and human DRG, nucleolar abnormalities in DRG neurons have been reported leading to abnormal transcription of ribosomal NDNA and a subsequent deleterious reduction in protein synthesis [52,53]. It is conceivable that this should be particularly deleterious considering the intense synthesis of ribosomal RNA indispensable for functioning in the highly metabolic DRG neurons. Since there is a relationship between the levels of CDDP-induced cross-links and the severity of PN [54], the capacity of removal of Pt-NDNA cross-links and the integrity of the NDNA repair system are of crucial importance in determining CDDP toxicity. Decreased Pt-NDNA adduct formation as well as enhanced repair are in fact correlated with cellular resistance to CDDP effects in cancer cells [55]. As a consequence, a reduced ability to repair NDNA correlates with CDDP sensitivity: a disruption of the p53 function in breast cancer cells is linked to a reduced capacity of the NER pathway [56]. NER is the main cellular defence against CDDP-induced intra-strand cross-links [57] and requires the cooperative action of several factors including xeroderma pigmentosum (XP) proteins A and C. Testicular cancer cells are hypersensitive to CDDP treatment as they are defective in XPA protein [58]. Some years ago, McDonald and co-workers demonstrated that Pt-NDNA binding in cultured DRG cells was 10 times higher than in dividing pheochromocytoma (PC12) cells [59]. The authors hypothesized that this could be due an increased uptake of the drug in the DRG or to a decreased ability to metabolize and detoxify CDDP once inside the cells. The first hypothesis is nowadays supported by the evidence that DRG sensory neurons express specific membrane transporters (Organic Cation Transporters, OCTs) able to enhance Pt-compounds transport into the cells [60]. The second possibility is related to a demonstrated decreased amount of glutathione in DRG compared to PC12 cells [59], glutathione being a protein able to bind and inactivate CDDP by forming a complex that is removed from the cell by an ATP-dependent export pump [61]. Moreover, it is possible that the increased Pt-NDNA adducts in DRG are due to an up-regulation of components in the NER pathway. Dzagnidze and co-workers in 2007 studied this possibility comparing the formation and removal of Pt-NDNA cross-links in DRG and in the spinal cord (which is protected by the BBB) of wild-type mice (WT), and mouse models lacking the core NER proteins XPA or XPC [54]. They demonstrated that the formation of intra-strand cross-links was about two-fold higher in DRG than in the central neurons of the spinal cord and, in the DRG, they were mostly in satellite cells rather than in sensory neurons. This was probably due to a demonstrated general down-regulation of NDNA repair mechanism systems in terminally differentiated neuronal cells [62]. Using animals deficient in XPA and XPC proteins, Dzagnidze and co-authors demonstrated that the NER system is essential in removing CDDP intra-strand cross-links from the genomic NDNA of PNS cells. After a functional loss of XPA or XPC proteins, Pt-NDNA adducts were inefficiently removed resulting in an increased formation of NDNA lesions. Interestingly, however, about 30% of CDDP cross-links were removed also in XPA deficient mice, suggesting the presence of other NDNA repair processes that may also contribute to the resolution of these adducts [54]. Interestingly, translocation was most pronounced in the apex of the spiral ganglion, suggesting differential regional susceptibilities to CDDP-induced NDNA damage in the PNS. Moreover, not only the NER system but also the Base Excision Repair (BER) pathway was demonstrated to be involved in CDDP cross-link formation in PNS cells. Jing demonstrated that CDDP exposure stimulated the repair function of apurinic/apyrimidinic endonuclease 1 (Ape1), a central BER enzyme, in DRG neurons augmenting their survival [63]. The involvement of the NER and BER systems in response to CDDP damage in DRG was linked to p53 and Gadd45 signalling pathways.

3.1.1.2. Mitochondria and mitochondrial DNA (MDNA). MDNA is a circular 1600 bp piece of DNA that encodes for 13 proteins essential for the synthesis of the electron transport chain subunits [64] involved in cellular energy homeostasis. Although the effect of CDDP on NDNA damage has been widely investigated (see previous paragraph), its interaction with MDNA was partly mapped by Podratz and collaborators [65]. While in NDNA CDDP-DNA adducts are partly removed by NER and BER mechanisms, in MDNA these mechanisms are not present [66]. Podratz demonstrated that CDDP forms adducts with MDNA at a similar rate to NDNA and that these adducts induce severe effects such as inhibition of MDNA replication, disruption of transcription and morphological abnormalities within mitochondria [65] in DRG neuronal cells. So, the effects of CDDP on MDNA may produce a gradual energy failure and also prolong neurotoxicity after the removal of CDDP, thus providing a possible explanation for the worsening of the symptoms of CDDP-induced PN in patients after CDDP discontinuation ("coasting" [67]). Since 95% of mitochondria in the PNS reside in the axons, mitochondrial dysfunction would be predicted to cause degeneration of axonal transport which is an energy-dependent process. It has been demonstrated that genetic abnormalities in mitofusin 2 and KIF1A, key proteins in mitochondrial homeostasis and axonal transport respectively, are known to be involved in the development of inherited axonal PN [68]. The correct functionality of mitochondria is mandatory for the maintenance of several inter-related pathways such as regulation of intracellular Ca^{2+} [69], apoptotic signalling pathways [70] and the generation of reactive oxygen species (ROS [71]).

3.1.1.3. Oxidative stress. CDDP-induced mitochondrial dysfunctions often lead to cellular oxidative damage in the PNS. Some *in vitro* and *in vivo* studies have demonstrated that CDDP is able to enhance the levels of ROS such as superoxide anion that cause lipid peroxidation, reduction in glutathione peroxidase and catalase activities, nitric oxide synthase expression, nitrosamine formation and alters the levels of reduced and oxidized glutathione. CDDP, moreover, induces apoptosis by activating of caspase 3 and 7 pathways [72], through the Bax-mitochondrion-cytocrome c pathway, by binding to MDNA or by the inhibition of the transcription and

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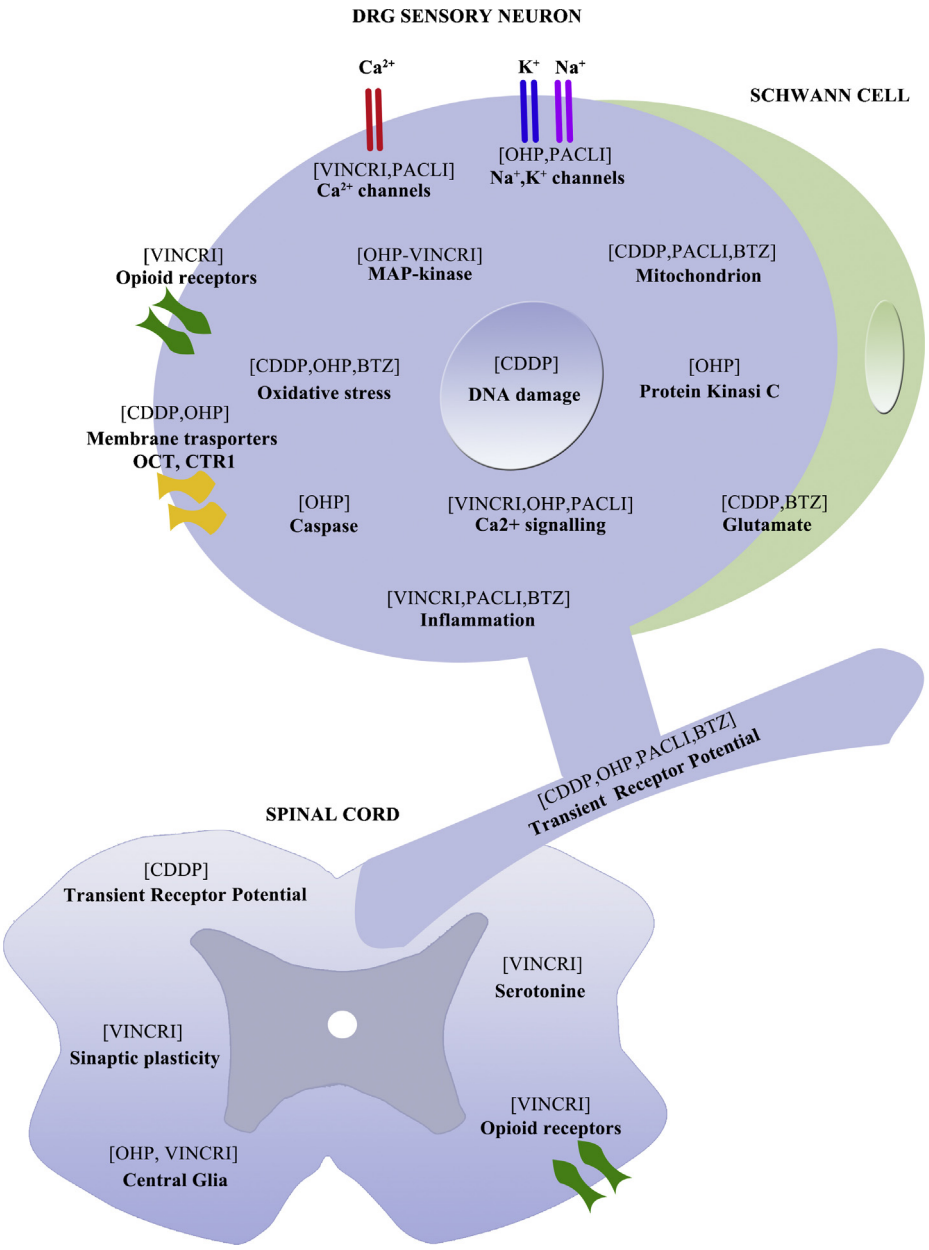

Fig. 2. Cisplatin, oxaliplatin, vincristine, paclitaxel and bortezomib primarily affect dorsal root ganglia neurons and peripheral nerve fibres (OCT = organic cation transporters, CTR = copper transporters, CDDP = cisplatin, OHP = oxaliplatin, VINCRI = vincristine, PACLI = paclitaxel, BTZ = bortezomib, Na^+ = sodium, Ca^{2+} = calcium, K^+ = potassium).

synthesis of mitochondrial proteins leading to mitochondrial loss of function [73]. After exposure to toxic concentrations of CDDP, cultured DRG sensory neurons show a reduction in functional mitochondria, a loss of mitochondrial membrane potential and ultra-structural changes suggesting subcellular vacuolar degeneration [12]. Cytoskeleton dysfunction and degeneration is the final phenomenon resulting from the alteration of the mitochondrial membrane potentials, abnormalities in electron transport chains and energy failure affecting mitochondrial transport along axons. Miller and Sheetz suggested that, since membrane-bound vacuoles containing degenerative mitochondria appear after CDDP treatment, it probably causes an autophagosome induction in DRG neurons [74]. Recent studies have demonstrated that CDDP is able to induce mitochondrial damage through the impairment of frataxin, an essential mitochondrial protein with anti-oxidant and chaperone properties [12]. This implies that some frataxin-induced cellular anti-oxidant events, such as glutathione peroxidase activation, are abolished after CDDP treatment thus decreasing cellular resistance to CDDP-induced oxidative stress [12]. Jiang demonstrated also that the increase of Ape1 expression, a protein involved in the BER DNA repair system (see previous paragraph), correlates with the increase in ROS concentration in DRG neurons while, by contrast, Ape1 silencing significantly reduces ROS generation [63]. Starting from the observation that the treatment of animals affected by CDDP-induced PN [75] with exogenous glutathione is neuroprotective, it could be speculated that, after its uptake from the plasma, glutathione is degraded by membrane-bound gamma glutamyl transpeptidase, transported into the cells and re-synthesized by gamma-glutamyl-cisteine and glutathione synthase [76]. Exogenous glutathione administration has been demonstrated to increase intracellular glutathione levels in DRG where these enzymes are particularly present [77] leading to a decrease in Pt concentration [78]. Park and colleagues, using an *in vitro* model of mouse DRG sensory neurons-neuroblastoma hybrid cell line (N18D3) demonstrated also that CDDP induced an accumulation of some apoptosis-related molecules such as p53 and p21, but not

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Bax and Bcl-2 [79]. The apoptosis induced by CDDP in DRG sensory neurons is mediated through a p53 activation-dependent pathway. Treatment with N-Acetyl-Cysteine, a precursor to the formation of glutathione, blocks, or at least, attenuates, the accumulation of p53 and p21 proteins, protecting neurons from programmed cell death [80]. The treatment of PC12 cells (neuron-like cells) with Acetyl-L-Carnitine was able to potentiate the effect of NGF by enhancing the expression of different NGF-dependent genes and promoting PC12 neurite outgrowth that was impaired by treatment with CDDP. In particular, the exogenous administration of Acetyl-L-Carnitine may indirectly modulates the process of acetylation of histones by regulating the nuclear levels of Acetyl Co-A [81]. The hyper-acetylation of histones after Acetyl-L-Carnitine treatment in the presence of low levels of NGF as occurs in CDDP-induced PN, may lead to an up-regulation of those genes required to counteract its neurotoxicity.

3.1.1.4. Receptors, neuropeptides and glutamate. It has been demonstrated that treatment with CDDP results in an increase of mRNA in the Transient Receptors Potential (Vanilloid, TRPV1), Ankyrin 1 (TRPA1) and Melastatin (TRPM8) in cultured DRG neurons [23]. These receptors have been shown to play a functional role in pain and neurogenic inflammation induced by several drugs, including toxic compounds. The up-regulation of TRPV1 and TRPA1 after *in vivo* treatment with CDDP has been reported leading to increased responsiveness in the nociceptors that contribute to the molecular mechanisms of the thermal hyperalgesia and mechanical allodynia observed in CDDP-treated animals. Lending support to the suggestion that these receptors may play a role in the development of CDDP-induced PN, it has been reported that TRPV1 null mice treated with CDDP at the same doses as WT animals, develop only mechanical allodynia but not heat-evoked pain responses. This suggests that the expression and function of TRPV1 plays a crucial role in CDDP-induced thermal hyperalgesia [23]. Immunohistochemical studies have shown that in CCDP-induced PN, there is an increase in the release in the DRG and spinal cord of some neuropeptides, activated by TRPV signalling and involved in nociceptive transmission such as substance P and Calcitonin-gene-Related-Neuropeptide (CGRP) [82].

Excitotoxic glutamate release is known to lead to excessive glutamatergic neurotransmission, neuronal cell damage and death both in PNS and central nervous system (CNS) disorders [27]. It has been demonstrated that the pharmacological inhibition of the enzyme Glutamate Carboxipeptidase II (GCPII) that hydrolyses N-acetyl-aspartyl-glutamate to produce glutamate is neuroprotective in a rat model of CDDP-induced PN [27].

3.1.1.5. Drug membrane transporters. As mentioned before, CDDP toxicity is linked to the amount of Pt accumulation inside the DRG leading to atrophy in DRG sensory neurons. Higher levels of Pt accumulate in the DRG compared to peripheral nerves, spinal cord, brain and dividing cancer cells [60]. It was previously thought that CDDP, as well as other Pt drugs, entered DRG neurons mainly through passive diffusion [83]. However, in recent years, current data have indicated that CDDP uptake may be mediated by specific membrane transporter proteins called Copper Transporters (CTRs), Organic Cation Transporters (OCTs) and Electroneural Organic Cation Transporters (OCTNs) [84].

3.1.2. Copper transporter 1 (CTR1)

CTR1 belongs to the CTR (or SLC31A) family that includes CTR1/2 and P-type copper transporting ATPases (ATP7A and B). It is a 23-kDa channel-like transporter which has a unique pore for the transport of copper and three trans-membranes domains that oligomerize to form a functional trimer [85]. Synergistically, CTR1 has been shown to mediate the cellular uptake of CDDP [86]. Various cell lines overexpressing CTR1 accumulate significantly higher levels of CDDP in comparison with WT cells [86]. CTR1 has been identified in rat DRG sensory neurons but not in their nerve fibres or other tissue elements of the DRG [87]. It localizes on the neuronal surface and in cytoplasmic vesicular structures. Underlining its involvement in CDDP neurotoxicity, it has been reported that the expression of CTR1 is more intense in the sub-population of large-size neurons, *i.e.* those that mostly undergo atrophy in response to Pt drugs. Conversely, the smaller CTR1-negative DRG neurons are less atrophic after CDDP treatment [88]. The cellular uptake of copper and CDDP may critically determine their cytotoxicity. Rat DRG neurons display a substantial capacity for accumulating copper *via* a transport process mediated by CTR1. Copper induces cytotoxicity by generating ROS, such as hydrogen peroxide, superoxide and the hydroxyl radical, which then damage proteins, lipids and DNA within cells [89].

3.1.3. Organic cation transporters (OCTs)

OCTs have been assigned to the SLC22A family that includes also electroneutral organic cation transporters (OCTNs [90]). Recent studies have indicated that they play a role also in the onset of CDDP [91] and other Pt drugs neurotoxicity [92]. The transport of the three OCT subtypes (OCT1, OCT2 and OCT3) is electrogenic, Na^+-independent and reversible. OCTs can have a stronger activity than CTR1 with respect to the transport of Pt derivatives [93]. In particular, OCT1 and OCT2 are among those most likely to be involved in the influx of Pt drugs into DRG neurons. Cavaletti and collaborators described that OCT1, OCT2 and also OCTN1 and OCTN2 mRNAs are expressed in embryonic rat DRG neurons and are modulated by CDDP treatment [91]. OCT2 expression was confirmed in *ex vivo*-cultured rat DRG [91]. While nerve conduction velocity was impaired in animals chronically treated with CDDP, mRNA expression of these molecules was increased in DRG neurons, thus suggesting that a negative correlation would reflect an attempt by DRG neurons to limit the CDDP influx thereby preventing severe damages.

3.2. Oxaliplatin

OHP [trans-R,R-cyclohexane-1,2-diamine oxalato-Pt (II)] is a third generation Pt drug characterized by the presence of 1,2-diamminecyclohexane (DACH) Pt carrier ligand that confers on OHP a reduced cross-reactivity with DNA [94]. However, while OHP produces fewer Pt–DNA adducts compared to CDDP, these are more effective in causing DNA damage and in evading DNA repair systems [94]. OHP is effectively used as a first-line therapy against colorectal cancer in both the adjuvant and advanced settings [94]. Its neurotoxicity may develop in two distinct clinical fashions: one is acute, rapidly reversible neurosensory neurotoxicity (in up to 90% cases) that occurs immediately or shortly after the drug infusion. It is characterized by paresthesias and dysaesthesia of the hands, feets and peroral region, with jaw tightness [95]. These symptoms are usually transient and last only a few hours but may be cold-triggered and may increase with repeated administration. The second syndrome is a chronic sensory neuropathy that develops after a cumulative dose of OHP (540 mg/m^2 over four cycles or more of therapy) and has similar features to CDDP-induced PN. Patients present distal paresthesia, sensory ataxia, functional impairment, jaw pain, eye pain, ptosis, leg cramps and visual and voice changes [95]; OHP-PN is dose-dependent with 10–20% of patients developing severe neurotoxicity at 750–850 mg/m^2 [96] and up to 10% who demonstrate persistent symptoms two years post-treatment [97]. The duration of therapy and consequently the cumulative dose of OHP may influence the different distribution of grades 1–2 *versus* 3–4 of neurotoxicity [95]. Neurophysiological assessments of OHP-induced PN reveal a reduction in the sensory action potentials with

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preserved motor amplitudes and conduction velocities [98] in the chronic syndrome but no changes in peak amplitudes in the acute form. However, prominent spontaneous activity was evident, suggesting an immediate effect of the drug on the axonal excitability rather than structural damage [1]. This is the event that confirms that OHP induces an acute alteration in axonal excitability induced by ion-channels dysfunctions, known as "channelopathy" [1]. The role of ion channels such as Na^+-, Ca^{2+} and K^+-channels is, therefore, central in OHP-induced PN.

3.2.1. Mechanisms of OHP-induced neurotoxicity (see Fig. 2B)

3.2.1.1. Ion channels. Na^+-channels play a central role in the development of pain induced by OHP. This evidence has been supported by the results of some researchers who have demonstrated that the administration of Na^+-blockers, such as lidocaine and mexiletin, is able to relieve OHP-induced cold allodynia in rats [99]. Previously reported experiments showed also that the treatment of DRG with OHP induced an increase in the Na^+ current that was antagonized by the Na^+-channel blocker carbamazepine [100]. Moreover, OHP slowed axonal Na^+-channels inactivation kinetics, shifted the voltage dependence of inactivation and activation and reduced the overall Na^+ currents [100]. These alterations induced by OHP are explained by its chemical structure and its intracellular degradation: oxalate, one of its metabolites, can alter the functional properties of voltage-gated Na^+-channels resulting in a prolonged open state of the channels and hyper-excitability of DRG sensory neurons [101]. These changes induced ectopic discharges leading to the typical symptoms of paresthesia induced by OHP [102]. The worsening of neuropathic symptoms observed in patients when exposed to cold is similar to that which occurs when Na^+-channel kinetics are further affected by cold exposure [28]. The alterations in voltage-gated Na^+-channels underlying changes in axonal excitability seem to predict the development of a chronic form of PN: in clinical studies, abnormalities in Na^+ currents were detected in 78% of patients who subsequently underwent chronic symptoms of OHP-induced PN [103]. Pharmacogenomics studies also support the idea that abnormalities in Na^+-channels play a central role in developing OHP peripheral neurotoxicity: the polymorphism 2SCN 2A R19K in the SCN2A gene that encodes for the voltage-gated Na^+-channel type II alpha polypeptide seems to be responsible for a channel dysfunction [104]. SCN4A-rs2302237, rs2302237 and SCN10A-rs1263292 polymorphisms also appear to be related to the development of acute OHP-induced PN [105].

Through *in vitro* studies on sciatic nerve fibres, Kagiava and collaborators [106] demonstrated that OHP is able to induce functional abnormalities also in voltage-gated K^+-channels by lowering the expression of TREK-1 and TRAAK channel types and by increasing the expression of the pro-excitatory K^+-channels such as the hyperpolarization-activated channels (HCNs) [21]. TRK1-TRAAK null mice were used and treated with an HCN inhibitor (ivrabradine) which abolished OHP-induced hypersensitivity. Moreover, the OHP-induced hyperexcitability was reduced following the activation of slow axonal K^+-channels (Kv7) [107].

3.2.1.2. Ca^{2+} signalling. It has been suggested that a dysregulation of Ca^{2+} homeostasis may play a key role in the pathogenesis of OHP-associated nerve damage. This was demonstrated by observational studies in which intravenous administration of Ca^{2+} gluconate and Mg^{2+} sulphate, given 1 h pre/post each OHP infusion, was prescribed for reducing subsequent neuropathy. Also treatment with Ca^{2+} channel blockers, which work by limiting the Ca^{2+} influx across the plasma membranes, has been clinically employed [20]. These findings are encouraging considering that Ca^{2+} is a critical intracellular messenger involved in several neuronal functions including survival, death, synaptic plasticity and neurotransmitter release. The possibility of modulating Ca^{2+} signals means gaining control over all these cellular processes. Shulze and collaborators studied the mechanisms involved in OHP toxicity on a neuron-like cell line (Sh-Sy5y) and on DRG neurons cultures. They found that although acute exposure to OHP had no effect on neuronal cells, 24 h after the treatment, intracellular Ca^{2+} signalling was significantly altered. They observed that prolonged exposure to OHP produced spontaneous changes in intracellular Ca^{2+} and that the amplitude of phospho-inositide-mediated Ca^{2+} responses was increased, probably due to an alteration in the endoplasmic reticulum Ca^{2+} load [108].

3.2.1.3. Transient receptors potential (TRP). As previously cited for CDDP, it has been demonstrated that treatment with OHP results in the up-regulation of the mRNA of the TRPV1 and TRPA1 as well as melastatin 8 (TRPM8) in cultured DRG neurons. OHP-induced cold allodynia *in vivo* was found to enhance the sensitivity and expression of TRPM8 and TRPA1 [24,109]. In fact, TRPM8 is expressed only in DRG after exposure to innocuous cool and noxious cold (<15 °C) temperatures. In mice TRPM8 was significantly increased within 3 days after injection of a therapeutic dose of OHP [109]. To support this thesis, Gauchan demonstrated that by blocking the TRPM8 function by administering capsazepine, OHP-induced cold allodynia was inhibited in mice [109]. Although the transcriptional level of TRPM8 mRNA returned to normal values ten days after OHP discontinuation, cold allodynia persisted till the 25th day suggesting that also other TRPM8-independent neuronal mechanisms maintain OHP-induced hypersensitivity to cold. By contrast, 5-iodoresiniferatoxin, a selective TRPV1 blocker [110], did not alleviate the allodynia but seemed to have a partial TRPV1 agonistic activity and to cause hypothermia [111]. These considerations suggest that TRPV1 antagonistic and partial agonistic actions do not affect cold allodynia induced by OHP [109].

3.2.1.4. Oxidative stress. Several lines of evidence suggest a relationship between OHP-induced neurotoxicity and oxidative stress [112]. This has been particularly well supported by data that have demonstrated that antioxidant regimens are helpful in reducing neuropathic symptoms both in pre-clinical models and in clinical practice. However, the relationship between the increased generation of ROS after Pt-treatment and other mechanisms of OHP-neurotoxicity remains poorly understood. Some researchers have linked the TRPA1 and oxidative patterns, both influenced by Pt drug exposure, in determining painful hypersensitivity to cold. Because TRPA1 is a sensor of both oxidative stress [113] and cold temperatures [114], it can be hypothesized that TRPA1 may play a key role in mediating cold hypersensitivity provoked by OHP *via* oxidative stress-related events [112]. In fact, the role of TRPA1 as a sensor of electrophilic and reactive compounds, such as those generated during oxidative stress at sites of tissue injury and inflammation, has been solidly established. Indeed, oxidative stress by-products generated after OHP exposure [115] could gate TRPA1, produce nociceptive responses and neurogenic inflammation. These reactive agents include H_2O_2, nitroleic acid [116], hypochlorite [113] and other endogenous molecules. Different oxidative stress by-products, *via* their action on TRPA1, have been reported as replicating the ability of OHP to produce mechanical and cold [117] hypersensitivity. So, the effect of OHP on TRPA1 is indirect, probably mediated by oxidative stress by-products. The antioxidants, Acetyl-L-Carnitine, α-lipoic acid, or vitamin C inhibit OHP-induced hyperalgesia in rats [33] suggesting a critical role for oxidative stress in OHP-induced PN and neuropathic pain. Joseph and collaborators in 2008 hypothesized that also IB4 receptors seem to be involved in this: *in vivo* intrathecal administration of neurotoxin for IB4-positive nociceptors (IB4 saporin) induced a marked decrease in the IB4 positivity in the dorsal horn of the spinal cord and prevented OHP-induced hyperalgesia in mice, thus

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suggesting that OHP acts on IB4 nociceptors to induce the oxidative stress [33]. The ROS generated by OHP treatment have been shown also to modulate Na^+-channel activity, thus influencing the sensitivity of nociceptors.

Moreover, Zheng and collaborators reported that OHP is able to produce deleterious effects on axonal mitochondria leading to electron transport chain disruption and cellular energy failure in DRG neurons [118]. The mitochondrial damage could be the starting point for increased ROS generation. In fact, prophylactic treatment with the antioxidant compound Acetyl-L-Carnitine inhibits the development of OHP-evoked hyperalgesia by preventing damage to the respiratory chain thus leading to preservation of the mitochondrial integrity [118].

3.2.1.5. Caspases, MAP-kinases and protein kinase C. The involvement of the caspases in OHP-induced PN was demonstrated by Ta and collaborators in 2006 when using a caspase inhibitor (z-VAD-fmk); they demonstrated an increase in Tunel-positive cells in rat DRG thus suggesting a caspase-mediated apoptosis [22]. On *in vitro* rat DRG sensory neurons, the prolonged exposure to OHP induces early activation of the MAP-kinase proteins p38 and ERK1/2 which in turn mediate apoptosis-mediated cell death [29]. Conversely, protective JNK/Sapk are down-regulated thus increasing OHP neurotoxic effects [28]. Restoring MAP-kinases' physiological function, achieved through a treatment of DRG cells with NGF or retinoic acid, is neuroprotective against *in vitro* OHP neurotoxicity [29].

Furthermore, the involvement also of PKC was evidenced by Norcini and Galeotti [119] who observed an attenuation of mechanical hyperalgesia in animals co-treated with OHP and calphostin C, a PKC inhibitor. In fact, OHP was able to induce up-regulation of the gamma isoforms of PKC and increase in the phosphorylation of gamma/epsilon PKC isoforms in some regions of the brain. Similar results were obtained also injecting another PKC inhibitor (hypericin) [119].

3.2.1.6. Drug membrane transporters. The ability of CTRs and OCTs to mediate the uptake of OHP is of neurological interest because their expression can influence OHP influx and efflux in- and out of DRG cells. ATP7A and B contribute by regulating the level of copper in cells because excess copper is deleterious for cell metabolism [120]. ATP7A and B seem to transport Pt out of cells or into specific subcellular compartments [121]. The expression of ATP7A, ATP7B, and CTR1 was investigated by using by real-time quantitative PCR, RT-PCR, immunohistochemistry and Western blot analysis in the DRG of healthy control and OHP-treated rats. It was found that ATP7A was expressed into the cytoplasm of smaller DRG neurons without any staining of satellite cells and nerve fibres, while CTR1 was detected at high levels in the plasma membranes and vesicular cytoplasmic structures of large DRG neurons without co-localization with ATP7A. ATP7B was not detected [87]. Since ATP7A facilitates the cellular efflux of OHP, reducing its availability for forming Pt–DNA adducts, the authors' hypothesis was that ATP7A-expressing DRG neurons are less sensitive to OHP neurotoxicity. In contrast, DRG neurons expressing high levels of CTR1 would be expected to take up more OHP leading to toxic effects in this neuronal subtype [87].

OCT2 protein was also present in human and mouse DRG [92] and its role was investigated by Sprowl and co-workers employing WT and OCT1 or 2 null mice. The authors demonstrated that there was no difference in sensitivity to cold in naïve mice. Following a single dose of OHP, WT, but not null mice, experienced significant increased sensitivity to cold and to mechanical stimulation. To support these results, the authors reported that the same results could be obtained in WT mice by dosing with cimetidine, a selective pharmacological inhibitor for OCT2. These results demonstrate that the OCT2 function is required at the onset of acute OHP-induced peripheral neurotoxicity and can be considered as an initial regulator for the accumulation of Pt in PNS target sites.

3.2.1.7. Central glia. Neuronal and glial cells contribute to normal functioning, maintaining homeostasis in the PNS and CNS. Spinal glial cells have been shown to contribute to the development of chronic pain in various conditions including surgery, inflammation, and nerve injury. This is substantiated by the evidence that pharmacological treatments able to prevent glial activation reduce neuropathic pain (*i.e.* minocycline [122]; fluorocitrate [123]). Even if OHP has no access to the CNS, dramatic oxidative damage in the spinal cord of rats treated with OHP has been described [123], coincident with glial cell activation and pain [125]. Increased numbers of Iba1 (microglia) and GFAP (astrocyte) immune-positive cells were evident in the dorsal horn of the spinal cord concomitantly with a pain threshold decrease and with an increased glia density also in the various supra-spinal sites involved during neuropathy [125]. The relationship between OHP-induced pain development and an increased number of glial cells in the spinal cord is supported also by the evidence that minocycline treatment electively prevents microglia activation and the development of hypersensitivity (data not published). Some recent research has demonstrated that not only microglia, but also astrocytes are involved in OHP-induced neuropathic pain. The expression of the astrocyte-specific gap junction protein Cx43 was increased in the spinal cord of rats treated with OHP, suggesting an enhancement in the function of spinal astrocytes through gap junction connections. The spinal application of carbenoxolone to block gap junction connections between astrocytes was able to prevent the OHP-induced mechanical hypersensitivity and activation of astrocytes [126].

These observations, taken together, suggest that different cellular patterns are inter-linked and may influence the development of OHP-induced PN and neuropathic pain.

4. Vinca-alkaloids

4.1. Vincristine

VINCRI is a chemotherapy agent that was approved by the United States Food and Drug Administration (FDA) in July 1963. It is one of the most common anticancer drug clinically employed in paediatric oncology for the treatment of a variety of malignancies, including paediatric acute lymphoblastic leukaemia. However, its clinical use is accompanied by severe side effects, including PN and chronic neuropathic pain that in many patients are the main reason for treatment discontinuation. It is reasonable to suggest that this greatly impacts on the survival of cancer patients [127]. VINCRI-induced PN is characterized by disturbances in both sensory and motor functions [127,128], and the incidence and severity of symptoms are closely correlated with the duration and therapeutic doses received by patients. VINCRI's mechanism of action is due to its high binding affinity to β-tubulin, leading to aborted cell division and cell death [129]. The disruption of the β-tubulin assembly and disassembly leads to severe alterations in axonal microtubules leading to axonal swelling in myelinated and unmyelinated fibres [130,131] and to nervous fibre damage. Moreover, C-fibre nociceptors enhance their responsiveness [130,131] to nociceptive and non-nociceptive stimuli leading to a chronic painful diseases that are functionally and structurally due to changes in the CNS and PNS (for review, see [132]). *In vivo* and *in vitro* experimental models have been developed to study the mechanisms of VINCRI-associated PN and neuropathic pain.

4.1.1. Mechanisms of VINCRI-induced neurotoxicity (see Fig. 2C)
4.1.1.1. Opioid receptors. Opioid receptors in the spinal cord play a critical role in modulating nociceptive transmission and their

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signalling, mediated by opiate ligands through the mu-opioid receptor (MOR) [133]. Endomorphin-1 (EM1) and endomorphin-2 (EM2) are newly isolated endogenous opioid peptides and are identified as the endogenous ligands of MOR [134]. While EM1 is primarily expressed into the brain, EM2 is found mainly in the spinal cord is thought to modulate pain signalling at that level [135]. In rat models of neuropathic pain, the administration of exogenous EM2 into the spinal cord results in a much stronger analgesic effect than that from morphine [136]. Recently, Yang and collaborators investigated the role of EM2 in the pathobiology of VINCRI-induced neuropathic pain demonstrating that decreasing levels of EM2 in the spinal cord and DRG of VINCRI-treated animals contribute to the development of allodynia and central sensitization leading to hypersensitivity of C-fibre nociceptors and abnormal activity of the wide dynamic range neurons in the dorsal horn of the spinal cord [137]. Chronic pain might be due to the loss of the inhibitory effect of pain signal transmission [137]. Surprisingly, in this study it was demonstrated that MOR expression remains unchanged in the spinal cord after VINCRI treatment, suggesting that the reduction in the spinal EM2 level does not induce a compensatory increase in MOR expression, suggesting that spinal MOR may not be involved in the initiation and maintenance of VINCRI-induced chronic pain. Therefore, the causal relationship between decreased spinal EM2 and pain behaviour could not be established. These results were corroborated by the evidence that intrathecal administration of EM2 was able to attenuate mechanical allodynia elucidating the contribution of the decreased spinal EM2 levels to the decreased endogenous inhibitory influence on pain transmission. Moreover, the authors detected a significant increase in a serine proteinase that inactivates the endomorphins, after VINCRI treatment. We confirmed this by demonstrating that systemic treatment with diprotin A (an inhibitor of the serine protease) can block the down-regulation of spinal EM2 [137]. Oxidative stress, generated after the impaired mitochondrial function and the production of excessive amounts of ROS following VINCRI treatment, may influence the activity of the serine protease [138] thus suggesting that the oxidative stress is a key mechanism in the activation of the molecular cascades determining VINCRI neurotoxicity. The involvement of opioid receptors in VINCRI-induced neuropathic pain was investigated also by Thibault and collaborators [139]. They observed that oxycodone, a semi-synthetic opioid analgesic used clinically employed since 1917 [140] acting through the activation of the mu-opioid receptor, has a longer-lasting effect than morphine in counteracting VINCRI-induced neuropathic pain. Through a DNA microarray technology, they also demonstrated that, in chronic VINCRI-exposed animals, oxycodone specifically induced an up-regulation of GABA-B2 receptor in the superficial layers of the dorsal horn, particularly in glutamatergic presynaptic terminals containing CGRP. The up-regulation of GABA-B receptors in DRG neurons leads to an increase in inhibitory transmission tonus and a decrease in excitatory transmission tonus that can counteract the increased neuronal excitability induced by VINCRI treatment.

4.1.1.2. Spinal synaptic plasticity. Since chronic pain diseases are mainly due to functional and structural changes in the PNS as well in the CNS, the plasticity of the synaptic connections of the nociceptive system is an important topic in the study of VINCRI-induced neuropathic symptoms. In 2013 it was observed that c-Fos, a marker of active pre-synaptic elements, was increased in neurons in the deep layers of the spinal cord in VINCRI neuropathic animals, suggesting increased neuronal activity and a structural reorganization of pre-synaptic elements [141]. Piccolo, a molecule that plays a pivotal role in maintaining the synaptic plasticity in supra-spinal areas [142], was increased in intermediate laminae (III–IV) and also in the superficial laminae (I–II) after VINCRI treatment, thus confirming an increase in both the neuronal activity and the number of active pre-synaptic elements. The increased number of active pre-synaptic elements (Piccolo positive) in superficial laminae could be the result of enhanced spontaneous activity [143] and/or morphological and/or electrophysiological modifications in unmyelinated fibres induced by VINCRI [130].

4.1.1.3. Central glia. As previously cited, spinal glia (astrocytes and microglia) play key roles in the initiation and maintenance of neuropathic pain. Therefore, inhibiting spinal glial cell activation may be a potential strategy to alleviate neuropathic pain [144]. Recently, it was demonstrated that spinal astrocytic activation contributed to mechanical allodynia in VINCRI treated rats through a mechanism involving the up-regulation of IL-1β which, in turn, may induce NMDA receptor phosphorylation in spinal dorsal horn neurons to enhance neuronal activity and pain transmission [145]. Since GFAP (astrocyte marker) rather than OX42 (microglial marker) was increased in the spinal cord of VINCRI-treated rats, the treatment with L-α-aminoadipate (astrocytic inhibitor) but not with minocycline (microglial inhibitor) significantly attenuated allodynia, suggesting that astrocytic but not microglial activation contributes to the development of VINCRI-related mechanical allodynia [145]. It was widely postulated that much of chemotherapy-induced PN, included that induced by VINCRI, was a result of a severe toxic effect on neuronal mitochondria [11]. Considering that the primary afferent sensory terminals and spinal dorsal horn are the regions of high metabolic demand, they contain high concentration of mitochondria [146]. As previously cited, toxic impairment of mitochondria produces an excessive amount of ROS, which increases oxidative stress [147], that seems to be able to influence the morphology and cell viability of primary cultured astrocytes of rat [148]. It can be hypothesized that VINCRI-induced oxidative stress may be a key mechanism for the development of spinal astrocytic activation. In fact, a systemic co-treatment of VINCRI-exposed rats with an antioxidant drug significantly reduced GFAP overexpression and also astrocyte activation [145]. In parallel, glutametergic transmission seems to be involved in VINCRI-induced neuropathic pain: the increased levels of IL-1β released by astrocytes, consequential to their activation, enhance the rate of binding with their endogenous receptor (IL-1R) that causes the phosphorylation of the NMDA NR1 subunit in spinal neurons leading to neural excitability and pain transmission enhancement [149].

4.1.1.4. Inflammation. The role of inflammatory events in determining VINCRI-induced PN and neuropathic pain is still controversial. Siau and collaborators demonstrated an increase in Langerhans cells (LC) in the skin as a consequence of inflammatory mechanisms leading to intraepidermal nerve fibres loss. There are two main mechanisms by which the increased number of LC may contribute to pain development: one is mediated by an increased release of nitric oxide [150] and the other is mediated by pro-inflammatory cytokines and neurotrophic factors [151,152], both causing sensitization of nociceptors, spontaneous discharge and mechanical hypersensitivity. However, Jaggi in 2010 demonstrated that VINCRI administration did not produce an elevation in TNF-α level in rat sciatic nerve indicating that inflammatory reactions do not play a role in the pathobiology of neuropathic pain. To corroborate this result, the authors reported that spironolactone, an aldosterone receptor antagonist with anti-inflammatory properties, has a beneficial effect in ameliorating VINCRI-related pain [153].

4.1.1.5. Serotonin transporters (5-HTT). The development of pain behaviour in mice may be modulated also by the efficiency of the serotonin transporter (5-HTT) [154] because serotonin (5-HT) plays several roles in pain processing and modulation [155]. It has been demonstrated that 5-HT acts on C-fibres [156] and, in the

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ventral regions of the spinal cord, after being released from mast cells and from descending neurons [157], respectively, it can facilitating nociception. In fact, 5-HTT null mice with a complete deficiency of 5-HTT showed a reduced 5-HT content in tissues [158] and an attenuated thermal hyperalgesia in mechanical nerve damage [154] and after treatment with VINCRI [159]. Behavioural observations showed that 5-HTT null mice were protected from pain thanks to the reduced content of 5-HT in the CNS and PNS areas. Under physiological conditions, when 5-HT is released from descending neurons from the rostral-ventral medulla, it may activate 5-HT3 receptors localized on the nerve terminals of a sub population of small-diameter afferents, by enhancing neurotransmitter release in the dorsal horn [157]. Considering that 5-HT in VINCRI-treated mice has an influence on pain transmission, also on the mechanically-evoked responses of dorsal horn neurons [157], the reversed pain behaviour in 5-HTT null mice may be attributed to a lack of spinal 5-HT. 5-HTT null mice however, were not protected by a VINCRI-induced increase in ATF3-immunoreactive nuclei in DRG neurons and by macrophage invasion, thus suggesting that peripheral nerve injury and macrophage infiltration in the DRG are not influenced by the deletion of the 5-HTT function in VINCRI-induced PN [157].

Furthermore, Fallah demonstrated that tropisetrone, a highly selective 5-HT3 receptor antagonist with immune-modulatory and anti-inflammatory properties [160], is able to ameliorate VINCRI-induced nerve injury in rats. In fact, considering that after nerve lesion, damaged Schwann cells initiate a cascade of events leading to the release pro-inflammatory cytokines, macrophage chemotaxis, IL-2 secretion from infiltrated T-cells, production of nitric oxide, ROS and the up-regulation of TNF-α in the PNS and CNS culminating in neuroinflammation and neuropathic pain, tropisetrone is able to modulate these events in several ways: it inhibits IL-2 gene transcription and proliferation in antigen-stimulated T-cells *via* a blockade of calcineurin/NFAT-dependent signalling pathway [161]. The increase of intracellular Ca^{2+} after VINCRI nerve injury leads to calcineurin activation, NFAT phosphorylation and translocation into the nucleus leading to cytokine and TNF release and neuronal apoptotic cell death [162].

4.1.1.6. Ca^2 signalling. Ca^{2+} is a key regulator of major cellular processes and its intracellular concentration is mediated mainly by an extracellular Ca^{2+} influx, internal release from vesicles and mitochondrial uptake. An increase in cytosolic Ca^{2+} concentration influences a great variety of neuronal and glial functions including membrane excitability, neurotransmitter release, synaptic plasticity, gene expression, and excitotoxicity [163]. In fact, VINCRI is able to affect Ca^{2+} movement through the mitochondrial membrane, reducing both the amount and rate of Ca^{2+} uptake and decreasing Ca^2 efflux [164]. So, it is conceivable that VINCRI alters Ca^{2+} homeostasis through a dysregulation and structure modification of neuronal mitochondria [165]. These changes may result in heightened neuronal excitability and impaired glial function. However, reducing the availability of extracellular Ca^{2+}, blocking Ca^{2+} release from intracellular stores, or chelating cytoplasmic-free Ca^{2+} would be expected to reverse some of the adverse consequences of impaired mitochondrial Ca^{2+} regulation. Siau demonstrated that neuropathic pain produced by VINCRI is significantly ameliorated by drugs that decrease the extracellular and intracellular availability of Ca^{2+} (TMB-8, Quin-2, EGTA, and EGTA-am [20]). Other experimental models of neurological disorders have shown a reduction in the Ca^{2+} influx, and intracellular Ca^{2+} loading may cause a reduction in the contribution of NMDAR to central sensitization [166]. This could explain the effectiveness of the Ca^{2+} decreasing drugs in reducing VINCRI-evoked pain.

4.1.1.7. MAP-kinases. The role of the MAP-kinase cascade in VINCRI-induced PN and neuropathic pain was postulated by Jaggi in 2012 by studying the antinociceptive effects of treatment with farnesyl thiosalicylic acid, a novel Ras inhibitor with potent analgesic effects and with GW5074, a c-Raf1 kinase inhibitor [167]. Ras is a key element in activating the intracellular signal transduction pathway involving MAP-Kinase family member such as Ras/Raf/MEK/ERK2. In addition to several MAP-kinase inhibitors [168], farnesyl thiosalicylic acid has been shown to activate TRPA1 [169] suggesting that this effect may alter its anti-nociceptive effects in neuropathic pain. Moreover, the intrathecal injection of GW5074 also attenuates various VINCRI-induced pain manifestations. These results suggest that MAP-kinase modulation might be an important mechanism for the onset of VINCRI-related neuropathic pain. The intrathecal delivery of farnesyl thiosalicylic acid and GW5074 attenuates hyperalgesia and allodynia in VINCRI-induced neuropathic pain in rats, suggesting that Ras and c-Raf-1 may serve as potential targets for inhibiting neuropathic pain [167].

5. Taxanes

5.1. Paclitaxel

PACLI (Taxol®) is a microtubule-binding antineoplastic drug that is commonly used in the management of various solid tumour like lung, breast and ovarian cancers. PACLI is able to bind the lumen of microtubules stabilizing the microtubule lattice and suppressing dynamic instability and depolymerisation [170–172]. The loss of microtubules' dynamic instability leads to the arrest of cellular mitosis at the G2/M phase and, consequently, to cellular death by apoptosis [172]. PACLI is highly effective against proliferating cancer cells; however neurons, that are not dividing cells, are vulnerable to PACLI. The treatment with PACLI affects the PNS and leads to a predominantly sensory axonal PN with sensory loss, paresthesia and, occasionally, pain [1]. PACLI disturbs all sensory modalities with greater involvement of the large fibres, while the motor system is less frequently affected [173,174]. Sensory symptoms usually start symmetrically in the feet, but may also appear simultaneously in both hands and feet [174]. This is reflective of a dying-back neuropathy, in which the distal sensory axons degenerate [175]. Biopsies obtained from peripheral nerves have evidenced a pathology of axonal degeneration, secondary demyelination, and, in cases of severe neuropathy, nerve fibre loss has also been observed [176]. However, though PACLI-induced PN affects primarily large fibres, rat models have demonstrated that neuropathic symptoms may be present with degeneration of only the very distal intraepidermal fibres [30]. Cultured dissociated neurons and explants treated with PACLI are susceptible to the drug and it results in a reduction in neurite length and morphology changes that are dependent on time and dose [177]. Moreover, if PACLI is added directly to the axons, axon length is reduced suggesting direct action of PACLI on the axon and the development of axonal degeneration through local mechanisms [178]. These results indicate that the cumulative doses of PACLI are associated with the intensity of PN.

5.1.1. Mechanisms of PACLI-induced neurotoxicity (see Fig. 2D)

5.1.1.1. Mitochondria. Over the past decade, it has been suggested that mitochondria could play an active role in axonal degeneration and they have been identified as a potential mediator of PACLI toxicity. In fact, in several neurodegenerative conditions mitochondrial permeability changes have been observed and these modifications happen after mitochondrial Ca^{2+} overfilling, accompanied by adenine nucleotide depletion, oxidative stress and elevated free PO_4 level [179]. As a result of these changes

the mitochondrial permeability transition pore (mPTP), which is a multi-molecular complex containing trans-membranous proteins such as the voltage-dependent anion channel (VDAC), the adenine nucleotide translocator (ANT), and the peripheral benzodiazepine receptor as well as the mitochondrial membrane-associated proteins, opens. The opening of the mPTP is followed by a loss of mitochondrial membrane potential, increased generation of reactive ROS, a reduction in ATP level, Ca^{2+} release and mitochondrial swelling [180]. *In vitro* studies have evidenced that PACLI treatment leads to immediate mitochondrial depolarization and Ca^{2+} release in non-neuronal cells [181] and cultured brain stem neurons [182]. Various studies have demonstrated that PACLI acts directly on mitochondria isolated from human cancer cells to release cytochrome c that initiates caspase activation during apoptosis [183]. PACLI is able to open the mPTP and it results in vacuolated, swollen and functionally compromised mitochondria [11,183]. The release of cytochrome c is stopped by cyclosporin A, an inhibitor of mPTP which prevents the mitochondrial permeability transition pore from opening suggesting that PACLI may activate the mPTP [184]. In addition, the mitochondrial anti-apoptotic protein Bcl-2 is a PACLI-binding protein; plausible mechanisms exist for the action of PACLI on the mPTP and on mitochondrial status that might be either tubulin dependent or independent. In addition, mitochondria in peripheral neurons might turn over more slowly or their repair mechanism may be less efficient than those in other tissues [185].

Moreover, in 2006 Flatters and Bennett observed in rats treated with PACLI the development of an evoked painful PN associated with a significant increase in the number of vacuolated and swollen mitochondria in the axons of peripheral nerves [11]. These data are the first confirmation of functional damage of peripheral nerve mitochondria obtained from rats with established PACLI-evoked painful peripheral neuropathies. The presence of vacuolated and swelling mitochondria in the peripheral nerve axons of PACLI-treated animals suggests the mitotoxicity hypothesis, which proposes that PACLI causes a chronic sensory axonal energy deficiency that is the primary cause of the pain and neuropathy symptoms and, moreover, it causes degeneration of the intraepidermal nerve fibres, the distal tips of sensory axons [11,186]. Zheng and colleagues in 2011 measured mitochondrial respiration and ATP production in sciatic nerves collected from PACLI-treated rats and they observed significant deficits in Complex I-mediated and Complex II-mediated respiration together with a significant ATP depletion. Moreover, prophylactic treatment with Acetyl-L-Carnitine, which inhibits the development of peripheral neurotoxicity, prevented mitochondrial function deficits suggesting mitotoxicity as a possible cause of PACLI-evoked chronic sensory peripheral neuropathy [118]. Mitochondria are involved in intracellular Ca^{2+} homeostasis and if mitochondria are damaged or mitochondrial Ca^{2+} uptake is impaired, this may be responsible for the increased propagation of Ca^{2+} signals and thus, the Ca^{2+}-dependent processes in neuropathic pain induced by PACLI. Jaggi and co-workers in 2012 suggested that an increase in Ca^{2+}-mediated neuronal excitability was due to changes in mitochondrial structure induced by PACLI treatment [2].

5.1.1.2. Ca^{2+} signalling. It is well known that Ca^{2+} is important in the development of neuropathic pain such as chemotherapy-induced pain; it has been demonstrated in some studies that the administration of an antagonist to Ca^{2+} channels (*e.g.* ethosuximide a T type channel Ca^{2+} channel blocker and gabapentin) induces a reduction in PACLI-induced neuropathic pain [187]. Additionally, Siau and Bennett in 2006 [20] observed that the decrease in extracellular and intracellular Ca^{2+} levels due to treatment with different types of membrane impermeable Ca^{2+} chelators that act by chelating extracellular Ca^{2+} with a reduction in Ca^{2+} influx, induced an attenuation of PACLI-induced neuropathic pain [20]. Ca^{2+} channels contains a $\alpha 2\delta$ subunit and it has been demonstrated that PACLI treatment increases the $\alpha 2\delta$-1 mRNA level in the dorsal spinal cord [109,187] and, accordingly, it has been proposed that the inhibitory effect of gabapentin on PACLI-induced pain acts on the $\alpha 2\delta$-1 subunit in the DRG and spinal dorsal horn [188]. Boehmerle and his collaborators identified a neuronal Ca^{2+} sensor 1 (NCS-1), a Ca^{2+} binding protein that interacts with the inositol 1,4,5-trisphosphate receptor (InsP3R), as a conceivable PACLI-binding protein. They observed that there was no direct interaction between tubulin and the InsP3R, and that PACLI treatment was able to increase binding of NCS-1 to the InsP3R [189]. Acute treatment of cultured neuroblastoma cells (SH-SY5Y cell line) and primary rat DRG neurons with sub-micromolar concentrations of PACLI rapidly induced cytosolic Ca^{2+} oscillations that were independent of extracellular and mitochondrial Ca^{2+} but dependent on intact signalling *via* the phosphor-inositide signalling pathway and on endoplasmic reticulum (ER) Ca^{2+} stores [189,190]. NCS-1 binding to InsP3R modulates Ca^{2+} fluctuations and the interaction between NCS-1 and InsP3R increases upon PACLI treatment. In contrast, prolonged exposure to therapeutic concentrations of PACLI activates calpain, a calcium-activated protease implicated in PACLI-induced degeneration [191], which leads to a reduction in InsP3R-mediated Ca^{2+} signalling with a decrease in NCS-1 protein levels. This reduction was also found in peripheral neuronal tissue collected from PACLI-treated animals [190]. Since calpain activation is thought to be an effector of axon degeneration rather than an early trigger, it is probably a response to upstream signalling events. The involvement of Ca^{2+} channels and the interaction among PACLI, NCS-1, InsP3R and calpain is an early step in the mechanism leading to the production of PACLI-induced peripheral neuropathy.

5.1.1.3. Ion channels. It has been demonstrated that also voltage-gated Na^+ channels play a critical role in neuronal function under both physiological and pathological conditions [192]; in particular it plays a very important role in the development of pain due to anticancer agents. *In vivo* studies conducted by Nieto and colleagues in 2008 evidenced that acute systemic tetrodotoxin (TTX) administration inhibited the development of PACLI-induced cold and mechanical allodynia and heat hyperalgesia suggesting that TTX-sensitive Na^+ channels play a very significant role in generating and maintaining PACLI-induced neuropathic pain [18].

Recent studies have shown that in DRG neurons of PACLI-treated animals there are alterations in the expression of some neuronal ion channel genes including the up-regulation of Na^+ channels Nav1.7, hyperpolarization-activated cyclic nucleotide-gated channel 1 and down-regulation of K^+ channel Kir channels [193].

5.1.1.4. TRP. As previously described, a subset of primary sensory neurons expresses several members of the TRP family of ion channels which convey various sensory modalities including mechano-/osmo-, thermo-, and chemical sensations [194]. Studies of co-localization performed in sub-populations of DRG neurons evidenced that TRPV1 co-localizes with TRPA1 and has a functional role in pain development and inflammation resulting from different compounds including ROS, nitrogen species and irritant compounds. There is evidence that TRPV4, which has been implicated in the process of osmo-mechanical transduction, plays a significant role in inducing mechanical hyperalgesia produced by PACLI treatment in mice and rats [195].

Studies conducted on TRPV4 knock-out mice treated with PACLI demonstrated a reduction in mechanical hyperalgesia; moreover this reduction was observed also after spinal intrathecal administration of antisense oligodeoxynucleotides to TRPV4, suggesting an involvement of TRPV4 in the development of PACLI-neuropathic pain [195].

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In 2012 Materazzi and collaborators, using both pharmacological and genetic studies, hypothesized that, in addition to TRPV4, TRPA1 also contributes to PACLI-induced mechanical and cold hypersensitivity and targets these TRP channels associated with the production of oxidative stress. Data show that in mice both TRPV4 and TRPA1 contribute to the reduction in mechanical allodynia, whereas only TRPA1 reduced the cold hypersensitivity developed after PACLI treatment [196].

5.1.1.5. Inflammation. Growing evidence suggests that various inflammation phenomena (increase in LC, regulation of pro-inflammatory cytokines, macrophage accumulation, microglia activation) are involved in the development of neuropathic pain due to chronic treatment with PACLI.

Studies conducted by Siau and his collaborators in 2006 demonstrated an increase in LC in PACLI-treated rat skin suggesting the involvement of these cells in the development of pain [30]. LC cells play a role in pain development acting on nitric oxide release [150], neurotrophic factors [152] and pro-inflammatory cytokines [151]; the results of these actions are the sensitization of remaining nociceptors and this leads to mechano-hypersensitivity. Growing evidence supports the hypothesis that also pro-inflammatory cytokines, such as IL-1β, TNF-α, are critical in enhancing PACLI-induced neuropathic pain [31].

Ledeboer and collaborators demonstrated that PACLI up-regulates these pro-inflammatory cytokine gene expressions in the lumbar DRG. Moreover, the administration of plasmids carrying IL-10 genes attenuated PACLI induced up-regulation of pro-inflammatory cytokines along with a decrease in the mRNA expression of CD11b, a macrophage/dendritic cell marker [31]. Moreover, also macrophage accumulation and activation in the DRG of PACLI-treated rats were observed in PACLI-induced neuropathic pain. In 2007 Peters and colleagues observed that intravenous PACLI administration in rat induced a sensory PN characterized by macrophage infiltration and injury to DRG cells [197]. They also reported an initial up-regulation of Activating-Transcription-Factor 3 (ATF3) in the DRG and Schwann cells, followed by macrophage activation in the DRG and sciatic nerve and microglial and astrocyte activation in the spinal cord [197]. In 2008 Nishida and co-workers, using a cDNA microarray technique, demonstrated that mRNA expression for both metallo-protease MMP-3 and macrophage marker CD163 significantly increased in PACLI-treated animals. MMP-3 up-regulation occurs prior to macrophage accumulation suggesting it is an important event in activating a series of reactions involved in the development of neuropathic pain induced by PACLI treatment [198]. Moreover, *in vivo* treatment with different glial cell inhibitors such as minocycline, propentofylline and thalidomide is able to reduce PACLI-induced neuropathic pain with the prevention of mechanical hyperalgesia [199].

5.2. Bortezomib

BTZ is an antineoplastic drug that shows a high degree of activity against multiple myeloma and some types of solid tumour [200]. BTZ was first described as an inflammation inhibitor but its cytotoxic effects rapidly shifted its use to cancer therapy. This drug was approved by the Food and Drug Administration in May 2003 for the treatment of advanced myeloma considering the benefits observed in patients in phase 1 and 2 trials [14]. BTZ was originally approved as a single agent but now is mostly used in combination with other drugs [201,202]. BTZ is generally well tolerated but, despite its efficacy, its clinical use is frequently limited by the onset of severe painful PN [203,204] that is characterized by paresthesias, burning sensations, dysaesthesias, numbness, sensory loss, reduced proprioception and vibratory sensation [205]. Deep tendon reflexes and autonomic innervation in the skin of BTZ-treated patients are reduced [206]. In patients with newly diagnosed multiple myeloma, grade 1 and 2 PN occur in 25–33% of cases and grade 3 and 4 in 0–18% of cases; in patients with recurrent multiple myeloma, grade 1 and 2 occur in 27–75% of cases and grade 3 and 4 in 0–30% of cases [13]. BTZ inhibits protein degradation binding specifically and reversibly to the 26S proteasome subunit [207] leading to the inhibition of the cell cycle and an increase in apoptosis [200,208].

5.2.1. Mechanisms of BTZ-induced neurotoxicity (see Fig. 2E)

5.2.1.1. Tubulin polymerization. Two different *in vitro* and *in vivo* studies showed that BTZ acts by inducing a tubulin polymerization and microtubule stabilization that contribute to cytotoxicity [9,209]. Both these studies showed that BTZ induces an increase in the polymerized fraction of α-tubulin suggesting that this alteration of tubulin dynamics contributes to induce the onset of PN.

5.2.1.2. Mitochondria. As previously described for other chemotherapeutic drugs, mitochondrial changes play a critical role in the development of various neurological disorders inducing neuropathic pain. DRG of animals treated with BTZ show intracytoplasmic vacuolation which can be ascribed to mitochondrial and endoplasmic reticulum enlargement [14]. These changes are able to induce the activation of the apoptotic pathway, triggering the activation of caspases and the dysregulation of Ca^{2+} homeostasis [210]. Moreover, alterations in several genes that might have an involvement in mitochondrial changes have been identified (enzymes involved in the transport of hydrophobic fatty acid chains into mitochondria, CPT1C): genes involved in apoptosis and Ca^{2+}-ion binding (RASGRP1), in the DNA repair pathway (BRCA1) and in the development and function of the nervous system [13]. This is supported by another study performed in rats used to study the cytotoxic and morphological effects of BTZ administration. After treatment with BTZ, RT4-D6P2T Schwannoma and RSC96 Schwann cell lines showed perinuclear inclusion bodies and vacuoles in the cytoplasm suggesting the induction of macroautophagy [211]. In these cells, BTZ induced endoplasmic reticulum stress that caused macro-autophagy and cell death [212].

5.2.1.3. Inflammation. BTZ is an inhibitor of NFkB that is able to block the transcription of genes involved in proliferation, angiogenesis and the suppression of apoptosis [202]. NFkB is constitutively localized in cytoplasm where it binds with the inhibitory protein IkB in its inactive state; pro-inflammatory signals or other forms of cellular stress induce the degradation of IkB and a translocation of NFkB to the nucleus where it induces the expression of pro-inflammatory genes [209]. For this reason the inhibition of NFkB results in the production of TNFα that is associated with the development of neuropathic pain [213] by the activation of heat-shock proteins and the generation of ROS [200,214]. Mangiacavalli observed an imbalance in $CD4^+$ sub-population Th1 and Th2 with a shift towards Th2 in neuropathic patients treated with BTZ; this shift results in a significant increase in IL6 blood levels [32] suggesting that neural damage could be related to inflammation [215] and that the inhibition of NFkB plays a role in the development of PN.

5.2.1.4. Oxidative stress. BTZ is able to induce excessive production of ROS that induces mitochondrial damage and a caspase-independent cell death [216]. ROS promote mitochondrial permeabilization through oxidative modifications of mitochondrial lipids or proteins that regulate the permeability transition membrane pore [217]. The over-production of ROS contributes to the depletion of energy and oxidative damage associated with neurodegenerative disorders [218]. It is important to note that oxidative stress and mitochondrial changes induced by proteasome inhibition can persist when the proteasome function is restored

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and are critical in determining the survival of neuronal cells [216]. A recent study demonstrated that BTZ is able to induce an increase in ROS in DRG neurons and ROS plays a crucial role in the initiation of the BTZ-induced apoptotic cascade [219]. Moreover, the administration of vitamin C or N-Acetyl-L-Cysteine is able to alleviate cytotoxicity in Schwann cells treated with BTZ [211]. These agents act by inhibiting the accumulation of the ubiquitinylated proteins induced by BTZ treatment contributing to the formation of inclusion bodies and vacuoles in Schwann cells leading to the onset of PN. These compounds reduce the ER stress and act as potent antioxidants reducing the ROS-mediated cytotoxic effects induced by BTZ [211,216,219].

5.2.1.5. Glutamate. As previously reported for cisplatin, the inhibition of GCPII, the enzyme that produces glutamate by hydrolysing the neuropeptide NAAG, is associated with neuroprotective effects in animal models also of BTZ-induced PN [27]. High concentrations of NAAG are able to activate NMDA receptors and play a key role in the glutamatergic mechanisms of axon–glia signalling [220]. The beneficial effects of the inhibition of GCPII are exerted by both the decrease in excitotoxic glutamate and the increase in the levels of the neuroprotective NAAG [27]. This leads to the inhibition of glutamate release from Schwann cells and decreases the excitability of damaged peripheral afferents [27].

5.2.1.6. TRP. Recently it has been found that acute and chronic administration of BTZ in rats induces an increase in TRPV1 protein levels compared to controls; in particular it has been found that TRPV1 protein levels increase in DRG when BTZ is administered acutely while when BTZ is administered chronically the TRPV1 protein levels increase in DRG and spinal cord [25]. In this work they also found down-regulated levels of TRPV1 mRNA and they observed that treatment with BTZ induced an increased immunoreactivity to TRPV1 in the DRG neurons and spinal dorsal horn, inducing a significant decrease in TRPV1/neuropeptide co-localization in DRG neurons. These neurochemical changes in DRG neurons and the spinal cord induced by BTZ-administration may contribute to the development of painful PN [25].

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