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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