Graphical Review

Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy☆

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A B S T R A C T

Peripheral neuropathy is a severe dose limiting toxicity associated with cancer chemotherapy. Ever since it was identified, the clear pathological mechanisms underlying chemotherapy induced peripheral neuropathy (CIPN) remain sparse and considerable involvement of oxidative stress and neuroinflammation has been realized recently. Despite the empirical use of antioxidants in the therapy of CIPN, the oxidative stress mediated neuronal damage in peripheral neuropathy is still debatable. The current review focuses on nerve damage due to oxidative stress and mitochondrial dysfunction as key pathogenic mechanisms involved in CIPN. Oxidative stress as a central mediator of apoptosis, neuroinflammation, metabolic disturbances and bioenergetic failure in neurons has been highlighted in this review along with a summary of research on dietary antioxidants and other nutraceuticals which have undergone prospective controlled clinical trials in patients undergoing chemotherapy.

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Introduction

Chemotherapy induced peripheral neuropathy (CIPN) remains one of the major limitations in oncology clinics due to increasing number of cancer patients, lack of effective treatment strategy, relapse of disease [1]. Around 30–40% of patients undergoing chemotherapy develop peripheral neuropathy and experience symptoms of pain and sensory disturbances [2]. According to National Cancer Institute (NCI), CIPN is one of the major reasons responsible for cessation of treatment, and hence is responsible for decreased chemotherapeutic efficacy and higher relapses [3]. Symptoms of peripheral nerve damage range from sensorimotor deficits (tingling sensation, burning pain in the arms, allodynia and hyperalgesia) to various functional deficits (impaired axonal transmission and reduced nutritive blood flow to nerves [4]). The most frequent agents causing CIPN are platinum compounds, taxane derivatives, vinca alkaloids, epothilones, thalidomide and bortezomib, which adversely affect the peripheral nervous system through dissimilar mechanisms summarized in Fig. 1 [5]. Although, the molecular pathomechanism and severity may vary with the inducing agent, physical damage to the neurons by chemotherapeutic agent is a common mechanism underlying...
the disease pathology [4]. The physical damage by chemotherapeutic drugs leads to functional impairment in neurons through oxidative stress, inflammation, apoptosis and electrophysiological disturbances. The scope of the present review is to present a basic idea on the possible role of oxidative stress and related pathomechanisms in CIPN based upon the existing experimental evidences.

**Susceptibility of peripheral nervous system (PNS) to oxidative stress**

It is a recognized fact that antineoplastic agents produce reactive oxygen species (ROS) to induce apoptosis in cancer cells [6]. However, ROS generated during chemotherapy may interfere with the normal cells and tissues and may be associated with the various toxic events like cardio toxicity, nephrotoxicity, neurotoxicity, etc. Certain structural and functional attributes of peripheral nervous system (PNS) make it more susceptible for accumulation of chemotherapeutics and some neurotoxins (Fig. 2) [5]. Lack of an efficient vascular barrier and absence of lymph drainage make the PNS more prone to toxic chemical insults. In addition mammalian nerves are known to be more susceptible to oxidative stress because of their high content of phospholipids, mitochondria rich axoplasm and also due to weak cellular antioxidant defences [7]. It has also been recently observed that structural and functional impairment caused by anti-cancer drugs enhances mitochondrial free radical production. Oxidative stress generated in this regard causes physical damage to neurons by demyelination, mitochondrial dysfunction, and neuronal apoptosis [8].

**Role of oxidative stress in the neuronal damage and incidence of neuropathic pain**

Although neurotoxicity caused by different classes of chemotherapeutic drugs differs to a significant extent, peripheral neuronal degeneration or small fiber neuropathy remains the end result of all CIPNs. It is been suspected that this might occur by a common mechanism i.e. increased neuronal oxidative stress as presented in Fig. 3. In fact, oxidative stress is identified to be responsible for the neuronal damage in different models of neuropathies such as diabetic neuropathy, acrylamide induced neuropathy and Charcot–Marie neuropathy [9–12]. These observations laid the foundation for investigating possible involvement of oxidative stress in CIPN. Chemotherapy induced mitochondrial...
Mitochondrion: an emerging target in CIPN

Several prospective experimental studies in animal models suggested that mitochondrial dysfunction is associated with chemotherapy and axonal mitotoxicity contributes to neuropathic symptoms produced by various chemotherapeutic agents such as taxanes, vinca alkaloids, platinum compounds and bortezomib [21–25]. In fact histological and microscopic observation of peripheral nerve sections of chemotherapeutic drug treated animals showed swollen and vacuolated mitochondria. These features indicate neuronal apoptosis that may be through pathways like caspase activation and Ca^{2+} dysregulation. Paclitaxel induced apoptosis is mainly due to cytochrome c (Cyt c) release and Ca^{2+} dysregulation through the opening of mPTP of mitochondria [26,27]. Frataxin deficiency, mt DNA damage, formation of defective electron transport chain (etc) components and loss in antioxidant defense enzymes has been demonstrated as mechanism for platinum compounds induced neuropathy [27]. Accumulation of dysfunctional mitochondria due to inefficient mitophagy further increases the free radical leakiness and this vicious cycle of oxidative damage to the bio molecules and mitochondria provides a feed-forward mechanism, that leads to further accumulation of ROS and RNS in the neurons during the development and progression of CIPN (Fig. 4). These experimental evidences clearly indicate that oxidative stress induced mitochondrial dysfunction is a central mediator of redox imbalance, apoptotic, autophagic and bioenergetic failure in peripheral neurons. It has also been widely observed that accumulation of oxidant damaged proteins and organelles due to inefficient autophagic pathway might be responsible for neurodegeneration, and hence therapeutic alleviation of Autophagy/Mitophagy is an unexplored potential target in peripheral neuropathies associated with nerve damage [28].

Oxidative stress in CIPN: biomarkers and therapeutic strategies

Experimental evidences support the involvement of mitochondria mediated oxidative, nitrosative stress in development of peripheral nerve damage. Identification of these mechanisms might be helpful in identifying newer biomarkers for the CIPN and thus increases the chances of getting improved therapeutic strategies. Currently diagnosis is based mainly on clinical examination and electrophysiological changes to monitor CIPN, hence identification of newer disease pathomechanisms will be helpful in identifying new candidate biomarkers through which disease progression can be identified at an earlier stage [3]. Oxidative damage to peripheral neurons can cause damage to myelin sheath, mitochondrial proteins and other antioxidant enzymes. Hence,
identification of levels of malondialdehyde, glutathione (GSH), superoxide dismutase (SOD) and activities of mitochondrial enzymes such as citrate synthase and ATP synthase can be helpful in monitoring the course of peripheral neuropathy and response of neuropathy to the treatment.

Due to the wide range of safety and tolerability, some of the dietary antioxidants and nutraceuticals have been tested for their clinical efficacy against chemotherapy induced peripheral neuropathy in large scale controlled clinical trials (Table 1). These agents were reported to have clinical utility by their protective action on neurons and they were found to alleviate functional disturbances of neurons by improving the mitochondrial function and physiology as shown in Fig. 5 [29,30].

Despite their wide usage and clinical efficacy, the available antioxidants present so far could only provide mild to moderate pain relief in peripheral neuropathy [31]. Failure of antioxidants in clinical trials might be due to their inability to reverse established oxidative damage, radical specificity and interference with physiological redox signaling pathways [28]. Targeted delivery of antioxidants and employing the mechanism based approach, clinical pathology and concentration dependent dosage schedule in antioxidant trials will help us to develop better understanding and might help us in devising newer strategies in CIPN [32]. Another possible explanation of translational failures of these trials are the common toxicity criteria (CTC) assessment scales used in CIPN trials, which should be remodeled to include necessary parametric measures, that will ensure accurate quantification of the drug induced effect [33].

**Summary**

This review highlighted the possible involvement of oxidative stress as a vital pathogenic mechanism of CIPN. Molecular insight into oxidant induced neuronal damage can probe a chance of getting an alternative therapy for CIPN in the form of natural phyto antioxidants or synthetic radical traps. Further, identification of antioxidant molecules having pleiotropic activity on other pathophysiological pathways involved in the CIPN could aid in the development of improved therapies. Since mitochondria are found to be a primary source of cellular ROS, pharmacological interventions targeted at maintenance of mitochondrial health and function is an alternative therapeutic approach for CIPN over direct scavengers of free radicals for the treatment of CIPN.
Fig. 4. Mitochondrial dysfunction in CIPN and role of its pharmacological modulation: the common factors associated with oxidative stress induced mitochondrial dysfunction are disruption of calcium homeostasis, increased mitochondrial outer membrane permeability (MOMP), defective mitochondrial ATP synthesis, alteration in the mitochondrial membrane potential ($\Delta\Psi_m$), induction of mPTP, release of Cyt c (since it loses its binding ability by oxidative induced damage to the cardiolipin), mitochondrial swelling etc. [26]. All these steps occur together or one orchestrates with other and forms a vicious cycle which further disrupts mitochondrial function. This finally leads to the cell death via apoptosis or necrosis. Pharmacological manipulation of mitochondrial toxicity with mitochondria-targeted antioxidants could help us to get the better therapeutic outcome in CIPN through alleviation of mitochondria mediated oxidative stress [20,27,38].

Table 1
List of clinical studies conducted using nutraceuticals and dietary antioxidants in patients suffering from CIPN.

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Model used</th>
<th>Treatment schedule</th>
<th>Parameters evaluated</th>
<th>Results observed</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Paclitaxel/ cisplatin induced neuropathy in patients</td>
<td>N-acetyl carnitine oral (1 g t.i.d for 8 consecutive weeks)</td>
<td>Neurological examination, total neuropathic score (TNS) and quantitative sensory testing were measured.</td>
<td>Improvement in TNS, sensory symptoms and neurophysiology were observed in N-acetyl carnitine treated patients.</td>
<td>[29]</td>
</tr>
<tr>
<td>2.</td>
<td>Cisplatin/ docetaxel induced neuropathy in patients</td>
<td>$\alpha$-lipoic acid 600 mg i.v once a week for 3–5 weeks followed by 1800 mg t.d p.o upto 6 months</td>
<td>Neurological examinations and WHO toxicity score assessment were evaluated</td>
<td>Improvement in neurological symptoms after treatment with $\alpha$-lipoic acid.</td>
<td>[30]</td>
</tr>
<tr>
<td>3.</td>
<td>Cisplatin induced neurotoxicity in women.</td>
<td>Glutathione (3 mg/m$^2$) i.v every 3 weeks for six courses.</td>
<td>A questionnaire on the subjective symptoms of peripheral neuropathy and quality of life was assessed.</td>
<td>Decreased incidence of CIPN in glutathione treated arm.</td>
<td>[39]</td>
</tr>
<tr>
<td>4.</td>
<td>Oxaliplatin induced neuropathy in patients</td>
<td>GSH (1500 mg/m$^2$ over a 15-min infusion period before oxaliplatin)</td>
<td>Electrophysiological parameters and assessment of neurological symptoms</td>
<td>Increased sural sensory nerve conduction velocity observed in GSH treated patients</td>
<td>[40]</td>
</tr>
<tr>
<td>5.</td>
<td>Paclitaxel/ docetaxel induced neuropathy in patients</td>
<td>Melatonin 21 mg daily at bedtime</td>
<td>Neurological examinations, toxicity assessment as per NCI-CTC 3.0 scale and FACT-Taxane quality of life questionnaire were evaluated.</td>
<td>FACT-Taxane quality of life end of study score was 137. Reduced incidence of neuropathy was observed in melatonin treated patients.</td>
<td>[41]</td>
</tr>
<tr>
<td>6.</td>
<td>Oxaliplatin induced neuropathy in patients</td>
<td>Oral N-acetyl cysteine (1200 mg) (arm A) or placebo (arm B).</td>
<td>Electrophysiological parameters and assessment of neurological symptoms.</td>
<td>Improved NCV (nerve conduction velocity), CMAP (compound muscle action potential) and decreased SAP (sensory amplitude potential) were observed after N-acetyl cysteine treatment.</td>
<td>[42]</td>
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Table 1 (continued)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>Paclitaxel induced peripheral neuropathy in patients</td>
<td>$\omega$-3 fatty acids 640 mg t.i.d orally/placebo</td>
<td>Electrophysiological parameters and assessment of neurological symptoms.</td>
<td>Reduced total sensory neuropathy score, improved NCV after treatment with $\omega$-3 fatty acids.</td>
<td>[43]</td>
</tr>
<tr>
<td>7.</td>
<td>Oxaliplatin induced neuropathy in patients</td>
<td>Glutamine (15 g twice a day orally for seven consecutive days every 2 weeks starting on the day of oxaliplatin infusion)</td>
<td>Electrophysiological parameters and neurological symptoms were assessed</td>
<td>Lower percentage of grade 1–2 peripheral neuropathy after 2 cycles and lower incidence of grade 3, 4 neuropathy after 4–6 cycles of glutamine administration was observed.</td>
<td>[44]</td>
</tr>
<tr>
<td>8.</td>
<td>Taxanes, platinum compounds and combination drug induced neuropathy in patients.</td>
<td>Twice daily dosing of vitamin E (400 mg)/ placebo.</td>
<td>The outcome was evaluated using the common terminology criteria for adverse events (CTCAE v 3.0) and A questionnaire on the subjective symptoms of peripheral neuropathy.</td>
<td>Significant difference in the incidence of sensory neuropathy between the two arms was not observed. Vitamin E did not appear to reduce the incidence of sensory neuropathy. Vitamin E reduced the incidence of sensory neuropathy</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Cisplatin induced neurotoxicity in patients</td>
<td>vitamin E (300/day mg/placebo)</td>
<td>The outcome was evaluated by measuring total neuropathic score (TNS) and quantitative sensory testing.</td>
<td></td>
<td>[47,48]</td>
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Fig. 5. Role of nutraceutical antioxidants in the treatment of chemotherapy induced peripheral neuropathy (CIPN): nutraceutical antioxidants exhibited significant neuroprotection towards chemotherapy induced neurotoxicity by decreasing cellular oxidative stress through their inherent free radical scavenging property (glutathione [39,40], melatonin [41], n-acetyl cysteine [42], $\omega$-3 fatty acids [43], $\alpha$-lipoic acid [30] etc) and indirectly by increasing whole blood concentrations of antioxidant enzymes (glutamine [44], n-acetyl cysteine [42]), normalizing mitochondrial functions (n-acetyl carnitine [29], $\alpha$-lipoic acid [30]), attenuating the production of proinflammatory mediators ($\omega$-3 fatty acids [43]) etc. Totally these nutraceutical antioxidants normalize the cellular functions, rescue mitochondrial impairment, inhibit neuronal inflammation, apoptosis and therefore diminish the sensory nerve degeneration [2,45].