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REVIEW

Glutamatergic system modulators as agents in prevention and management of chemotherapy- induced polyneuropathy

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Polyneuropathy is a common and important chemotherapy-induced adverse effect which often leads to dose modifications and impact on patients' quality of life. Limited treatment options for prevention and management of this neuropathology stimulate further research on the topic. Recent attention has been focused on downregulation of glial glutamate transporter expression observed in spinal region of rodents treated with cancer chemotherapy drugs. Consequent extrasynaptic glutamate overflow could be considered a key element in neuropathic pathogenesis resulting in excessive activation of glutamate receptors and neuronal hyper-excitability, finally contributing to develop neuropathic condition. Recently, the onset of neuropathy in bortezomib treated rats could be prevented by preemptive administration of drugs promoting glial glutamate transporter expression and antagonism at mGlur5, a metabotropic receptor which reinforces glutamatergic transmission in presence of high extracellular glutamate concentrations. These findings point to glial-glutamate system dysregulation as a main mechanism in the pathogenesis of anticancer chemotherapy induced neuropathy.

Keywords: anticancer drugs; neuropathy; glutamate transporter; metabotropic receptor

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Chemotherapy-induced peripheral neuropathy (CIPN) is a recurrent adverse effect related to anticancer chemotherapy treatment that involves platinum agents, vinca alkaloids, bortezomib, thalidomide, taxanes and epothilone analogs [1]. The onset of neuropathy during treatment with these drugs, results in chemotherapy dose reductions or early discontinuation detracting power to the therapy. Although CIPN frequently resolves completely after therapy, some patients had residual neuropathy even two or more years after the end of pharmacological treatment [2]. Therefore, CIPN is a cause of significant distress in cancer patients inducing decreased quality of life and reduced functional ability.

Unfortunately, effective treatments for prevention and management of CIPN have not yet been found. Many of the agents used in clinical practice for treatment of CIPN are chosen based on extrapolated data from pharmacologic studies of more common non-chemotherapy-related neuropathic pain syndromes, such as painful diabetic neuropathy and postherpetic neuralgia.

A recent study that examined the pharmacological agents currently used in CIPN, shows that clinical trials are inconclusive even in respect of symptomatic pharmacological agents used to treat CIPN as tricyclic antidepressants, gabapentin or other medications with the same mechanism of action although these agents are relatively successful in treating other neuropathic pain conditions [3]. This report also

does not recommend the use of different substances such as acetyl-l-carnitine, CaMg, glutathione and Vitamin E in clinical practice due to the lack of a clear consistency of their validity in the prevention and treatment of CIPN [3]. Presently, the mainstays of treating this neuropathy in clinical practice are confined to dose and treatment schedule modification [4].

CIPN is relatively distinct from other forms of neuropathic pain in terms of the pathophysiology and symptomatology. This pathology often occurs as a sensory rather than motor neuropathy and is characterized by higher prevalence of numbness, tingling and pain that generally starts in the toes and fingers and expands proximally. The exact mechanisms underlying CIPN are still unclear. Channel dysfunction and changes in membrane polarization have been identified as a critical mechanism for the development of neuronal hyperexcitability and acute symptoms of CIPN, especially from platinum chemotherapeutics and proteasome inhibitors. However, proposed alterations in voltage-gated sodium and potassium channel kinetics do not adequately account for CIPN symptoms [5,6].

Recent preclinical studies focused on chemotherapy induced glia alterations. A significant increase in astrocyte cell density in spinal cord was shown in oxaliplatin treated rats [7,8] . Astrocyte activation was observed within the spinal cord of paclitaxel [9,10] and bortezomib [11] treated rats. One way astrocytes affect neuronal function is through the excitatory aminoacid transporters (EAAT). Changes in the expression of glial glutamate transporters as glutamate transporter-1 (GLT-1) were examined in the spinal cord of rats with chemotherapy induced mechanical hyperalgesia [12,13]. Immunohistochemical studies showed that the expression of GLT-1 in the spinal dorsal horn was significantly decreased in paclitaxel/taxol treated rats as compared to controls [12,13].

Glutamate transport process has the ability to maintain stimulatory, but nontoxic, levels of free intrasynaptic glutamate nearby neurons [14]. Previous studies have shown the importance of these transporters in peripheral pain. Inhibition of glutamate transporters results in an elevation of spinal extracellular glutamate and spontaneous pain [15]. Pharmacological blockade of GTs, including glial GTs, in the spinal cord resulted in a hyperalgesic state in awake animals [15] and increased the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA) receptors [16,17] and group I metabotropic glutamate receptors (mGluRs) [18]. Neurophysiologic studies have also shown that impaired glial glutamate uptake and consequent extrasynaptic glutamate overflow resulted in excessive activation of glutamate receptors in the spinal dorsal horn from neuropathic rat [19,20]. Allosteric antagonist at the mGluR5, a receptor recruited only in presence of high extracellular glutamate concentrations, could effectively prevent the development of bortezomib induced neuropathy in rodent as shown by assessment of sensory nerve conduction velocity, an established neuropathy marker [21].

These findings postulate that the abnormalities induced by anticancer chemotherapy drugs on glutamate transport process underlie polyneuropathy, resulting in the accumulation of extracellular glutamate in synaptic clefts, factor that determines the activation of neurons and influence neuronal excitability [22]. On inhibition of glutamate uptake, glial cells function like excitatory interneurons, releasing glutamate to activate postsynaptic neurons in spinal pain pathways and finally contributing to the development of neuropathic condition.

Recently, CINP could be revoked when glutamate transporter expression and function was promoted in bortezomib treated rats [21]. Ceftriaxone is a beta-lactam antibiotic and its use has been shown to not affect bortezomib antitumor action in multiple myeloma cell lines [21]. In addition to its known antibacterial effect, ceftriaxone has the ability to stimulate the expression of EAATs, increasing transcription of the EAAT2 gene [23]. NF-kB binding site at the -272 position of the EAAT2 promoter was identified as responsible for the ceftriaxone-mediated EAAT2 activation in human tissue and a similar action could be realized in rodent through analogous EAAT1 gene transcription [24].

It must be pointed out that glutamate modulator pharmacological agents were unable to revert neuropathic impairment and pain associated to this pathology if administered to rodent when CIPN was already established [21]. The consideration that arises from these experiments is that CIPN can be prevented but not revoked once the glutamatergic system was overactive. Thus, preemptive co-administration of glutamate modulators with anticancer drugs is necessary to prevent CINP.

Ceftriaxone is largely prescribed in clinical practice as beta-lactam antibiotic. Thus, translational therapy administration to a significant number of CINP patients might be undertaken to validate preclinical results. The implementation of drug discovery efforts has recently focused on specific activator of glutamate transporter to provide neuroprotection in several neurodegenerative diseases [25]. Specific modulation of pharmacological target with these molecules will expected to be of therapeutic benefit in CIPN prevention and management.

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