Oxaliplatin-Induced Peripheral Neuropathy

Subjects: Oncology

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Oxaliplatin-induced peripheral neurotoxicity (OIPN) is a severe and potentially permanent side effect of cancer treatment affecting the majority of oxaliplatin-treated patients, mostly with the onset of acute symptoms, but also with the establishment of a chronic sensory loss that is supposed to be due to dorsal root ganglia neuron damage. The pathogenesis of OIPN is still largely unknown. This lack of information is a limitation in the identification of effective strategies to prevent or limit OIPN incidence and severity. So far, no treatment is available for the prevention of OIPN, although duloxetine showed moderate evidence of efficacy in the reduction of OIPN symptoms. On this background, several neuroprotection clinical trials are ongoing in oxaliplatin-treated patients, although only part of them relies on solid preclinical evidence supporting the study hypothesis. Based on the available literature it can be concluded that dose and schedule modification is currently the most effective approach to limit the severity of OIPN since pharmacological prevention and treatment of OIPN still remains an unmet clinical need.

Keywords: oxaliplatin ; neurotoxicity ; acute ; chronic ; prevention ; treatment ; pain ; neuropathy

1. Introduction

Oxaliplatin (OHP) is a platinum-based antineoplastic drug used for colorectal cancer treatment whose main dose-limiting side effect is peripheral neurotoxicity, a disabling and potentially permanent consequence which could impair life quality of patients during and after therapy [1][2]. The main target of peripheral nervous system (PNS) damage due to OHP antineoplastic therapy is believed to be dorsal root ganglia (DRG), as a result of platinum accumulation [3][4][5].

Oxaliplatin (OHP)-induced peripheral neurotoxicity (OIPN) produces two distinct manifestations of peripheral neuropathy: an acute cold-enhanced form and a chronic distal sensory neuropathy [4][5].

The acute neurotoxicity, affecting the majority (80-90%) of OHP-treated patients [6], is a transient form ensuing hours after OHP administration and lasting 1-3 days, characterized by cold-induced paresthesias/dysesthesias, with predominant oropharyngeal and limbs distribution, frequently associated with cramps and fasciculations. Although of short duration, acute OIPN is disturbing for the patients. Moreover, it has been reported that patients with more severe acute OIPN are more likely to develop severe chronic neurotoxicity [7]. Although this observation does not certainly imply a direct causal relationship, it might however be considered an evidence of higher susceptibility of some individuals to PNS injury.

The incidence of chronic OIPN is variable, also because of the different assessment methods for its diagnosis, however it can be considered a frequent side effect, which might seriously impair the quality of life of the most severely affected patients. The first symptoms are generally numbness and tingling in hands and feet, with progressive distal-to-proximal limb involvement after increasing OHP exposition. Peripheral neurotoxicity may then progress toward sensory ataxia, with difficulty in manipulating small objects and necessity to base widening in standing; these symptoms are more evident in all the situations where defective proprioceptive input cannot be compensated by visual input, such as in poorly lit environments. Cranial and motor nerve impairment or autonomic disorders have very rarely been reported as manifestations of chronic OIPN [8].

The clinical features of acute and chronic manifestations of OHP neurotoxicity may be helpful in understanding the basic mechanisms of their onset. Acute OIPN is a typical feature of OHP treatment, while chronic OIPN, a cumulative and dose-dependent peripheral neurotoxicity, is common to other platinum-based drugs, in particular cisplatin.

2. Basic mechanisms: acute OIPN.

The time course of acute OIPN, with rapidly onset and reversal of symptoms, clearly suggests a functional, rather than structural, impairment.

A possible mechanism to explain acute OIPN is reversible neuronal plasma membrane ion channels dysfunction in the dorsal root ganglia (DRG). In fact, OHP can slow the inactivation of voltage-gated Na+ channels, an effect that may be enhanced by exposure to cold [9][10][11][12][13], and cooling may also slow the activation of axonal slow K+ (Kv7) channels, ensuing axonal excitability modification [14]. This pathogenetic hypothesis involving ion channel-interference has been demonstrated in animal studies [15], and validated in small cohorts of OHP-treated patients through a non-standard neurophysiological technique, the Nerve Excitability Test, which gives indirect information about ion-channel activity [16][17].

However, other hypotheses have been raised to explain the mechanism at the basis of acute OIPN. It has been recently reported, both in mouse DRG neuron culture and *in vivo*, that OHP causes an acidification of the cytosol and this in turn is responsible for sensitization of TRPA1 channels [18]. In the *in vitro* study a concentration of OHP like those found in plasma of treated patients has been employed.

Investigating OHP effects on the PNS, additional and unexpected targets were discovered. For instance, it has been demonstrated that OHP leads to a reduction of intracellular pH by forming adducts with neuronal hemoglobin. This observation is in agreement with the concept that hemoglobin in non-hematopoietic cells has non-iron-related activities. For instance, in neurons it can act as a proton buffer, an activity impaired by OHP binding. Moreover, it has been demonstrated that OHP neurotoxicity is sensitive to the activity of carbonic anhydrase, an enzyme that is linked to hemoglobin in intracellular pH homeostasis. The potential relevance of this latter observation is highlighted by the report that drugs such as topiramate and acetazolamide, able to inhibit carbonic anhydrase activity, can revert OHP-induced cytosolic acidification of DRG of treated animals and acute OIPN, without affecting OHP-induced cytotoxicity on cancer cells [19].

3. Basic mechanisms: chronic OIPN

The anticancer effect of OHP is mainly due to its binding and subsequent damage of nuclear DNA. In particular, the cytotoxicity is thought to result from platinum derivatives entering the cell nucleus with formation of both inter- and intra-strand cross-links, which prevent DNA replication and transcription; the inhibition of DNA synthesis leads to cell death, similarly to other platinum compounds (e.g., cisplatin, carboplatin).

The lack of blood-brain barrier in DRG allows platinum accumulation in DRG sensory neurons. The first descriptions of OIPN in rodent animal models evidenced DRG nucleolar, nuclear, and somatic size changes [20], and since then, many other preclinical studies investigated the effect of OHP administration and the related mechanisms of OIPN onset. Recently it was also demonstrated that OHP, although unable to cross the blood-brain barrier, could also affect the spinal cord, since wide dynamic range neurons hyperexcitability [21] and central glial activation [22] have been reported in OIPN rodent models.

Other studies suggest that also mitochondrial dysfunctions and oxidative stress could represent important pathogenetic mechanisms, since platinum metabolites can cause a significant reactive oxygen species (ROS) generation. The consequent oxidative stress can impair metabolic activity, both in cancer and healthy cells. Podratz and colleagues [23] reported in an *in vitro* study that cisplatin binds mitochondrial DNA with the same binding affinity observed for nuclear DNA in DRG neurons. However, since mitochondrial DNA is not provided with systems of DNA repair like those of nuclear DNA (e.g., base excision repair, nucleotide excision repair pathways), platinum adducts cannot be removed, leading to problems in mitochondrial DNA replication and transcription and protein synthesis, dysfunction of respiratory chain and, eventually, energy failure of neurons and oxidative stress. Other authors confirmed the presence of dysfunction in mitochondrial respiration and a decrease of ATP production in the sciatic nerves of rats treated with OHP [25]. In agreement with these data, Xiao and Bennet [24] pathological observations demonstrated swollen and vacuolated mitochondria in saphenous nerves of rats treated with OHP compared to controls. Therefore, the mitotoxicity hypothesis has gained a prominent position to explain the pathogenesis of chronic OIPN.

Other pathological events which may play an important role in chronic OIPN onset are neuroinflammation, either related to or independent from oxidative stress [26][27], and modulation of voltage-gated Na+ channels. Finally, the mechanisms allowing intracellular accumulation of OHP must be considered. Under this perspective, the DRG neurons selective expression of plasma membrane transporters' (e.g., copper transporters such as CTR1, organic cation transporters such as OCT1 and 2) and their activity might explain their peculiar sensitivity to the toxic effects of OHP [28][29].

A clinically relevant aspect of OIPN is the marked difference in its severity in different individuals with the same oncological and neurological conditions and treated with the same OHP schedule. Evidence of different susceptibility to OIPN in different mice strains suggests a possible role of genetic background , and this hypothesis has been investigated

in several clinical trials in OHP-treated patients, but they failed so far to provide firm confirmation, also in view of several methodological flaws in their design [30]

4. Conclusion

The lack of conclusive pathophysiologic evidence to explain OIPN clinical features must be clearly acknowledged, and this is one of the main reasons at the basis of the current incapacity to effectively treat this very serious condition. Currently, the only recommended treatment for OHP-induced painful peripheral neuropathy is the serotonin-norepinephrine reuptake inhibitor duloxetine [31], even though this drug is not effective for everyone and its treatment schedule is still under investigation in clinical trials.

Based on the available data, it can be stated that OHP dose and schedule modification is currently the most effective approach to limit the severity of OIPN, and that pharmacological prevention and treatment of OIPN still remains an unmet clinical need. This leads to the conclusion that more accurate and reliable preclinical investigation of the causes of OIPN is mandatory.

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