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Editorial Comment

The pain with platinum: Oxaliplatin and neuropathy

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Oxaliplatin-induced nerve dysfunction is an important issue in clinical oncology, particularly in the setting of adjuvant therapy where long term neurotoxicity is an unacceptable outcome. There is a pressing need both to establish the mechanisms of neurotoxicity, and to identify novel diagnostic techniques that can predict preclinical damage. Through such processes, early intervention in the form of neuroprotection or alternatively appropriate dose reduction strategies may then be undertaken.

Oxaliplatin, a platinum-based chemotherapeutic agent, has demonstrated marked efficacy for the treatment of advanced colorectal cancer[1,2] and in the adjuvant setting.[3,4] Unlike other platinum derivatives, oxaliplatin does not result in significant renal impairment or ototoxicity. Oxaliplatin's dose-limiting toxicity is related to peripheral nerve function and ultimately the development of peripheral neuropathy.[5] Initial symptoms consisting of paraesthesiae and pain may develop during or soon after infusion in up to 90% of patients. Less commonly, motor symptoms such as cramp, tetanic spasm and myotonia can develop. All symptoms are worsened by exposure to cold. With continued oxaliplatin treatment, cumulative and ultimately irreversible neurotoxicity develops and patients are left with a peripheral neuropathy.

While some studies have suggested that neurotoxic symptoms are largely reversible,[6] it is becoming increasingly apparent that oxaliplatin can induce significant, long-lasting neurotoxicity.[7,8] The median recovery time for oxaliplatin-induced neuropathic symptoms is 13 weeks,[6] although symptoms can persist for 2 years or more in up to 10% of patients.[8] At cumulative dosages > 1000 mg/m^2, neuropathic symptoms may persist indefinitely.[9] In addition, the 'coasting' phenomenon has been reported with high-dose oxaliplatin treatment (130 mg/m^2) inducing the most severe neuropathic symptoms weeks after cessation of treatment.[10]

The pathophysiology of oxaliplatin neurotoxicity has not yet been clearly established.[5] The acute symptoms have been attributed to channelopathy, due to functional alterations in axonal membrane ion channels without discernible morphological changes. Preliminary *in vitro* studies have documented changes in voltage-dependent Na^+ channel function,[11–13] as have subsequent patient studies,[7,14] although the exact molecular mechanisms responsible for such an effect remain unclear. In contrast to these findings, others have suggested that acute effects on voltage-gated K^+ channels, also important in modulating axonal excitability, may be involved in oxaliplatin-induced neurotoxicity. By analogy, peripheral nerve hyperexcitability is a known feature of neuromyotonia, an acquired autoimmune channelopathy of voltage-gated potassium channels.[15,16]

In terms of preventative strategies, it has previously been suggested that neurotoxicity may be reduced through

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the use of Ca^{2+} and Mg^{2+} infusions before and after oxaliplatin administration, although again the mechanism of protection with such intervention remains to be elucidated.[12] While the chief problems encountered during oxaliplatin therapy such as paraesthesiae and pain may be reduced by Ca^{2+} and Mg^{2+} infusions prior to each treatment,[17] end organ neurotoxicity and neuropathy may not be as improved and may require discontinuation of effective treatment.

In this issue of the journal, Binder and colleagues document their findings in patients who developed painful neuropathic symptoms associated with oxaliplatin therapy.[18] Using quantitative sensory techniques, the authors have demonstrated a profile of change consistent with cold and mechanical hyperalgesia. Perhaps not surprisingly, patients from this study who did not complain of pain had already received twice as many cycles of oxaliplatin treatment. Conceivably, a simple explanation for the lack of painful symptoms in this group of patients may be that neuropathy had already developed as a result of treatment. This hypothesis would also be supported by the recent literature – when nerve conduction studies have been formally undertaken in patients receiving oxaliplatin, neurophysiological features of a neuropathy become evident despite the lessening of symptoms. This would suggest that part of the explanation for a reduction in 'positive' symptoms (such as pain and paraesthesiae) is related to large fibre loss, that may occur concurrent with the development of 'negative' features such as numbness. If true, this in turn has critical implications for the various graded clinical monitoring scales currently in widespread use, which may tend to underestimate the true nature of neurological deficit produced by oxaliplatin.[5]

Neurotoxicity and the risk of irreversible functional impairment remain dose-limiting. Early identification of at-risk patients would seem important in attempts to minimise neurotoxicity. If early identification proved possible, prophylactic treatment with neuroprotective agents may then provide the best way of preventing severe long-lasting chronic symptoms. The use of a predictive test, perhaps incorporating measures of axonal membrane ion channel function, may assist in identifying patients who will benefit most from intervention.[5,14] Additionally, genetic factors have been identified that may confer susceptibility or resistance to oxaliplatin-induced neuropathy. Several polymorphisms in the glutathione s-transferase genes, which are involved in detoxification pathways, have been associated with an increased risk of developing severe oxaliplatin-induced neuropathy.[19] Further examination of genetic predisposition to severe neuropathy may assist in targeting at-risk patients.

If the mechanism of oxaliplatin-induced neurotoxicity can be firmly established, this would mark a significant advance. Presently, neuropathy treatment trials are being undertaken with little or no scientific rationale, that may at worst, inadvertantly affect the efficacy of oxaliplatin.[20] Only when the pathophysiology of oxaliplatin toxicity has been established, can appropriate therapies be developed to prevent irreversible nerve damage.

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