Oxaliplatin and Axonal Na\(^+\) Channel Function \textit{In vivo}

Arun V. Krishnan,1,3 David Goldstein,2 Michael Friedlander,2 and Matthew C. Kiernan1,3

Abstract

\textbf{Purpose:} The aim of the study was to investigate the pathophysiology of oxaliplatin-induced neurotoxicity using clinical nerve excitability techniques that provide information about axonal ion channel function.

\textbf{Experimental Design:} Excitability studies were combined with standard nerve conduction studies and clinical assessment in 22 patients undergoing treatment with oxaliplatin.

\textbf{Results:} Excitability studies recorded before and immediately after oxaliplatin infusion for 89 treatment cycles revealed significant increases in refractoriness and relative refractory period postinfusion in all patients, consistent with an effect of oxaliplatin on axonal Na\(^+\) channels. However, those patients that developed chronic neuropathy had significantly greater changes. Following cessation of oxaliplatin treatment, 41% of patients had persistent symptoms and nerve conduction abnormalities consistent with the development of chronic neuropathy.

\textbf{Conclusion:} The present study provides evidence that oxaliplatin-induced neurotoxicity is mediated through an effect on axonal Na\(^+\) channels. Clinical nerve excitability techniques may prove beneficial in monitoring for early signs of neurotoxicity and in the assessment of future prophylactic therapies.

Oxaliplatin is a novel chemotherapeutic agent effective against advanced colorectal cancer (1, 2). Unlike other platinum-based agents, it does not induce dose-limiting nephrotoxicity; dose limiting bone marrow toxicity is uncommon (3) but it causes considerable neurotoxicity (4–7). Oxaliplatin-induced neurotoxicity manifests as rapid-onset neuropathic symptoms exacerbated by cold exposure and as chronic neuropathy that develops after several treatment cycles (1, 2).

The incidence of oxaliplatin-induced neurotoxicity has been defined by clinical studies that graded neurotoxicity using the National Cancer Institute Common Toxicity Criteria, with grade 3 neuropathy (severe sensory loss that interfered with function) reported in 12% to 18% of patients (1, 2, 8). Early identification of neurotoxicity may allow for alterations in dose or schedule to prevent the development of chronic symptoms, which, once established, may take many months or years to resolve (7). The development of chronic neurotoxicity becomes especially problematic in the setting of adjuvant therapy where long-term neurologic deficit is an unacceptable outcome. Whereas preliminary \textit{in vitro} studies have documented changes in voltage-dependent Na\(^+\) channel function (9–11) following oxaliplatin, mechanisms responsible for nerve dysfunction in patients have not been established.

Nerve excitability techniques, recently adapted for clinical use (12–14), provide information about axonal membrane ion channel function. Axonal excitability in human subjects is assessed using “threshold tracking,” where threshold indicates the stimulus current required to produce a target potential, which can be adjusted online by computer (i.e., tracked) to assess excitability. Excitability studies have shown alterations in axonal Na\(^+\) channel function in toxic and metabolic neuropathies (15, 16) and in patients with genetic mutations in Na\(^+\) channels (17). Such information cannot be gained using standard nerve conduction studies, which provide information about the number of conducting fibers (amplitude) and the speed of the fastest conducting fibers (latency and conduction velocity). More critically, nerve conduction studies may not manifest abnormalities until significant fiber loss has occurred and are therefore unsuitable for predicting the development of neuropathy.

Given that excitability studies undertaken in patients who developed neuropathy following completion of oxaliplatin therapy provided supportive evidence for an effect on axonal Na\(^+\) channels (7), the aim of the present prospective study was to establish whether acute neurotoxicity was mediated by effects on axonal Na\(^+\) channels, and if so, whether axonal excitability measures undertaken in a prospective fashion may help to identify those patients at greatest risk of developing neurotoxicity.

Materials and Methods

Nerve excitability studies were recorded in 22 consecutive patients treated with oxaliplatin for advanced colorectal cancer for a total of 89 treatment cycles. Patients received 2 to 12 cycles of oxaliplatin (Table 1).
Table 1. Clinical and nerve excitability data, oxaliplatin dosages, presence of neuropathic symptoms, and reason for oxaliplatin cessation for each patient

<table>
<thead>
<tr>
<th>#</th>
<th>Clinical and nerve excitability data, oxaliplatin dosages, presence of neuropathic symptoms, and reason for oxaliplatin cessation for each patient</th>
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<tbody>
<tr>
<td></td>
<td>Single dose range (mg)</td>
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<tr>
<td>#1</td>
<td>110-140 (15)</td>
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<td>#2</td>
<td>180 (6)</td>
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<tr>
<td>#3</td>
<td>110-170 (9)</td>
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<tr>
<td>#4</td>
<td>125-160 (8)</td>
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<tr>
<td>#5</td>
<td>190 (2)</td>
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<tr>
<td>#6</td>
<td>123-162 (10)</td>
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<tr>
<td>#7</td>
<td>135-175 (10)</td>
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<tr>
<td>#8</td>
<td>180-220 (4)</td>
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<tr>
<td>#9</td>
<td>177-236 (6)</td>
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<td>#10</td>
<td>100-132 (9)</td>
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<td>#11</td>
<td>100-180 (13)</td>
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<td>#12</td>
<td>250 (7)</td>
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<td>100-150 (12)</td>
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<td>#14</td>
<td>105-140 (10)</td>
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<td>136 (12)</td>
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<td>96-157 (8)</td>
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<td>#18</td>
<td>155 (9)</td>
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<td>#19</td>
<td>165 (10)</td>
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<td>140-175 (9)</td>
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<tr>
<td>#21</td>
<td>90-150 (8)</td>
</tr>
<tr>
<td>#22</td>
<td>110-170 (7)</td>
</tr>
</tbody>
</table>

NOTE: Maximal single infusion dosage is calculated using body surface area to correspond to a dosage of 100 mg/m² and the total number of cycles of treatment is indicated in brackets after range of single infusion dose. Chronic symptoms are those which were present at the time of the first review following completion of oxaliplatin treatment. The neurosensory scale of the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 1) was used with the following grading system (21): 0, no neuropathy; 1, mild paresthesias, loss of deep tendon reflexes; 2, mild or moderate objective sensory loss or moderate paresthesias; and 3, severe objective sensory loss or paresthesias that interfere with function. The number of cycles after which chronic symptoms were first noted is given in brackets. Two patients (#4 and #7) developed chronic symptoms 4 and 2 weeks after the completion of oxaliplatin therapy, respectively. Relative refractory period (RRP) duration was >4 ms in 78% patients with chronic neuropathy and the cycle at which this change was first noted is shown. Two patients (#5 and #10) died 4 to 6 weeks after completion of oxaliplatin therapy. Although nerve conduction studies were not undertaken, there were no clinical signs of neuropathy.

Results

Acute symptoms, defined as those occurring immediately following oxaliplatin infusion and typically lasting for less than a week, occurred in 90% patients. Neurupathy, defined as a National Cancer Institute Common Toxicity Criteria neurosensory grade of ≥0 and accompanied by nerve conduction abnormalities (21), developed in 41% of patients (see Table 1). Baseline relative refractory period values before the first dose of oxaliplatin were normal in all subjects (reference range, 3.1 ± 0.1 ms; age range, 23-59 years; mean, 39.4 years; n = 29) when compared with previously established normative data (13). Following oxaliplatin therapy, alterations were noted in relative refractory period duration and refractoriness, illustrated for a single representative patient in Fig. 1A. When compared with preinfusion recordings for all 89 cycles, postinfusion recordings showed increases in the duration of the relative refractory period (postinfusion, 3.83 ± 0.1 ms; preinfusion, 3.1 ± 0.1 ms; n = 89; P < 0.0005; paired t test) and refractoriness (postinfusion, 52.0 ± 6.5%; preinfusion, 26.1 ± 4.4%; n = 89; p < 0.001).
Novel findings demonstrate that oxaliplatin-induced neurotoxicity is mediated through an effect on axonal voltage-gated transient Na⁺ channels. The acute excitability changes induced by oxaliplatin were greater in patients who subsequently developed neuropathy compared to those without neuropathy. Furthermore, the finding that patients with a pretreatment relative refractory period of >4 ms invariably developed neuropathy suggests that excitability measures may be of clinical use in determining which patients are at highest risk for developing chronic neuropathy. Such incremental changes cannot be diagnosed on clinical grounds alone given that almost all patients treated with oxaliplatin manifest acute neurotoxic symptoms, yet not all develop chronic neuropathy. Furthermore, the finding that patients with a pretreatment relative refractory period of >4 ms invariably developed neuropathy suggests that excitability measures may be of clinical use in determining which patients are at highest risk for chronic neurotoxicity.

Findings from the present study also provide a rationale to the hypothesis that reduction in acute neurotoxicity may potentially reduce the development of chronic neuropathy (22). The only Na⁺ channel found at the node of Ranvier in the
peripheral nervous system (Na\(^+\), 1.6) colocalizes with the Na\(^+\)/Ca\(^{2+}\) exchanger at sites of axonal injury (23). Alterations in axonal Na\(^+\) concentrations may trigger reverse flow of the Na\(^+\)/Ca\(^{2+}\) exchanger, which activates damaging Ca\(^{2+}\)-mediated processes, leading to axonal loss (23, 24). Reductions in membrane-bound Ca\(^{2+}\) may contribute to the axonal hyperexcitability, which underlies paraesthesia, cramp, and tetany (25), common symptoms immediately following oxaliplatin infusion, providing a rationale for prophylactic Ca\(^{2+}\) infusions. Furthermore, the fact that the excitability abnormalities preceded the onset of clinical symptoms by an average of seven cycles provides a window for prophylactic therapy to be initiated.

The recent report of a randomized trial with xaliproden may have identified an effective prophylactic therapy (26). The use of a predictive test such as ours may enable more focused use of such strategies in addition to maximizing the benefit of the intervention in a cost-effective manner. Recent studies, such as the OPTIMOX trial (27), suggest that one strategy for increasing the duration of progression-free interval may be to recycle the oxaliplatin regimen at regular intervals for a fixed duration. Such an approach does, however, run the risk of increased neurotoxicity. Data from the present study suggest that it may be possible to identify which patients can be safely reexposed to an oxaliplatin-based regimen in a recycling strategy to maximize the benefit of each line of therapy.
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