A Mouse Model of Oxaliplatin-induced Neuropathic Pain

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BACKGROUND

Chemotherapy-induced neuropathy pain resulting from toxic effects of chemotherapy agents is a burden for cancer patients and causes unquantifiable side effects. Therapies such as pain-limited narcotics, nerve blocks or physical therapy have been reported, but unfortunately cause more damage and irreversibility prior to using chemotherapy. To develop such medications, we need to have a suitable animal model which simulates conditions of chemotherapy-induced neuropathy pain. There is a need for suitable animal models which better simulate clinical features in these conditions. In our study, we developed a chronic oxaliplatin neuropathic pain model which shows sensitivity to cold/cool challenges. In this study, we followed mice up to 18 weeks (4.5 months) and evaluated various outcomes by using two different behavioral tests - the Tail immersion/flick test and the Acetone cooling test. Statistical analysis was performed to evaluate the response and the validity of the outcomes in both conditions.

MATERIALS AND METHODS

Animals. All experiments were performed on male C57BL/6 mice obtained from Charles River Discovery Services, Kuopio, Finland. Animals were maintained in a light-controlled environment with access to food and water.

Chemotherapy. After the first injection, mice were treated with oxaliplatin 1 mg/kg, 3 mg/kg, or 10 mg/kg every 3 days for 9 times, so that the last injection was given 27 days after the first injection. Vehicle for oxaliplatin was 5% glucose in saline, which was injected subcutaneously into mice on the back. Acetone was applied to the plantar surface of the hindpaw of the animal. The initial cooling sensation was observed after 40 seconds. The cumulative time spent with acetone was quantified using the Stopwatch or a manual timer. The timer is stopped when the mouse stops or increases the severity of the response to acetone.

Statistical analysis. Analysis of variance (ANOVA) followed by Dunnett’s multiple comparison test was used for all comparisons. Differences were considered statistically significant when p ≤ 0.05.

RESULTS

Acetone Test Responses Over Time

<table>
<thead>
<tr>
<th>Acetone Test Responses Over Time</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M6</th>
<th>M10</th>
<th>M16</th>
<th>M19</th>
<th>change %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail slowly curves ventrally</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tail shakes from side to side</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Tail vibrates with increasing urgency</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tail is motionless, pointing downwards</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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</table>

Pharmacological responses were found in selected acetone cooling test in which both pregabaline and duloxetine alleviated allodynia responses. Data suggests the usefulness of this model to examine therapies against chemotherapy-induced neuropathy.

CONCLUSIONS

This study explored the use of oxaliplatin induced neuropathic pain model in mice. Chronic and repeated exposure to oxaliplatin induced persistent cold allodynia as evidenced by acetone test. Tail immersion test, on the other hand, gave a more variable outcome than cold allodynia responses over time with occasional failure to show statistically significant difference in tail flick response between control and oxaliplatin mice. Furthermore, tail immersion test was found to be more variable also in control mice, suggesting that with repeated testing normal responses may vary significantly.

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Neurological Index test did not indicate clear side effects with the oxaliplatin treatment, suggesting that there are no other clear neurobehavioral changes resulting from oxaliplatin treatment than cold-tail allodynia.

Future studies will focus on further optimization of the model with modified exposures to oxaliplatin, but also by introducing other measures of allodynia such as mechanical and thermal allodynia tests as well as functional motor residua.