Vinorelbine neurotoxicity: clinical and neurophysiological findings in 23 patients

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Abstract

Vinorelbine (5'-nornoradvinblastine) is a new semisynthetic antineoplastic vinca alkaloid which interferes with axonal transport, inducing spiralisation of axonal microtubules and resulting in peripheral neurotoxicity. A prospective detailed neurological and electrophysiological evaluation was performed in 23 patients treated with 25 mg vinorelbine a week. All patients developed a sensory-motor distal symmetric axonal neuropathy. The neurotoxicity increased with cumulative vinorelbine doses and peripheral neuropathy was mild or moderate in most patients. After discontinuation of vinorelbine treatment, neuropathic signs and symptoms were partially reversible.

(Materials and methods

From April to November 1994, 23 patients affected by advanced breast carcinoma and treated with vinorelbine were enrolled. Patients were eligible if not pretreated with other neurotoxic drugs. Patients presenting with other risk factors for neuropathies, such as diabetes mellitus, alcoholism, and paraneoplastic or dismetabolic syndromes were not included. We adopted an unconventional intensified schedule of vinorelbine (25 mg a week given intravenously sequentially for 24 weeks, plus granulocyte colony stimulating factor). Five interrupted the treatment after the 12th administration of vinorelbine because of progression of disease.

Patients were aged between 32 and 70 years and had measurable disease, performance status between 0–1 on the Eastern Cooperative Oncology Group criteria1 in 19 patients, between 2–3 in four, normal bone marrow, hepatic, and renal function, and a life expectancy of at least 12 weeks. They gave informed consent.

Neurological examination and electrophysiological examination were performed before and after 4, 12, and 24 cycles of therapy and (in six patients) six months after the end of therapy. Clinical neurological examination, performed independently by two neurologists (AP or LB), included a standardised history for detection of neuropathic symptoms and a complete evaluation of pinprick and vibratory sensation, strength, and deep tendon reflexes. Neuropathic signs and symptoms were scored using a questionnaire designed for detection of sensory disturbances (paraesthesia, pain, burning in feet or fingers) and symptoms of muscle weakness (upper arm, hand, thigh, and leg weakness) experienced by patients. We adopted a modified version of the neurological symptom score (NSS) by Dyck et al. grading the severity of symptoms as mild 1, moderate 2, and severe > 2.

Nerve conduction was measured in the median, peroneal, and sural nerves with surface electrodes at constant skin temperature.
Table 1 Neurotoxicity score based on clinical subjective symptoms, clinical signs, and neurophysiological findings

<table>
<thead>
<tr>
<th>Neurotoxicity score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibratory sensation</td>
<td>Normal</td>
<td>Slightly reduced</td>
<td>Reduced</td>
<td>Absent</td>
</tr>
<tr>
<td>Median sensory amplitude</td>
<td>Normal</td>
<td>AJ reduced</td>
<td>AJ absent</td>
<td>All absent</td>
</tr>
<tr>
<td>Peroneal amplitude</td>
<td>Normal</td>
<td>10-25%</td>
<td>25-50%</td>
<td>&gt; 50% reduction</td>
</tr>
<tr>
<td>Sural amplitude</td>
<td>Normal</td>
<td>10-25%</td>
<td>25-50%</td>
<td>&gt; 50% reduction</td>
</tr>
</tbody>
</table>

Mild neurotoxicity = score < 4; moderate neurotoxicity = score 5-10; severe neurotoxicity = score > 10.

NSS = Neurological symptom score; AJ = ankle jerk.

(34°C at least). Action potential amplitudes were measured from peak to peak for the motor response (MAP). Values were considered abnormal if they exceeded the normal range of our laboratory. A measurement of sympathetic skin response (surface electrode stimulation at the wrist and contralateral registration with active electrode on the palm) were also made.

The pretreatment and post-treatment values for all the variables were compared by analysis of variance (ANOVA) for repeated measures. A cumulative neurotoxicity score was calculated for each patient by scoring the severity of symptoms and clinical and electro-physiological signs using a modified version of the neuropathy score of Chaudry et al. (table 1).

The severity of neurotoxicity was graded on the basis of the obtained score as mild neurotoxicity = total score 1 to 4; moderate neurotoxicity = score 5-10; severe neurotoxicity = score > 10.

Results

NEUROPHYSIOLOGICAL STUDIES

The pretreatment evaluation showed normal neurophysiological values in all patients except a reduced amplitude of the SAP of the sural nerve in three patients and of the median nerve in one patient.

After four courses of vinorelbine the mean values of nerve conduction velocities, distal latencies, MAPs and SAPs, and sympathetic skin response values were normal. A reduction by more than 50% of baseline values was detected in peroneal amplitude in six patients, in sural amplitude in four, and in median sensory amplitude in one (table 2).

After 12 courses of treatment the mean peroneal MAP amplitude was significantly reduced by 36% of baseline values (P < 0.001); the mean median SAP amplitude was significantly reduced by 29% (P < 0.001); the mean sural SAP amplitude was reduced by 22% (P < 0.05). Conduction velocity, distal latency, and sympathetic skin response values remained unchanged. Peroneal MAP amplitude was decreased by more than 50% in seven patients, sural SAP in four, and median SAP in one.

At the end of treatment after 24 cycles of vinorelbine the mean values of peroneal amplitude obtained in 18 out of 23 patients were decreased by 47% compared with pretreatment values (P < 0.001), mean median SAP amplitude decreased by 38% (P < 0.005), and sural SAP decreased by 26% (P < 0.05). Conduction velocities, distal latencies, and sympathetic skin response were still normal. In nine patients peroneal MAP amplitude fell below 50% of baseline values, sural SAP in seven (absent response in one) and median SAP in five.

Six months after vinorelbine discontinuation electrophysiological data showed in six patients an improvement of median and sural SAP (one patient was absent at examination after 24 cycles) and partial recovery of peroneal MAP amplitudes.

NEUROPATHIC SCORE

After four cycles of vinorelbine 20 out of 23 patients (87%) showed symptoms and signs of neurotoxicity: in 16 patients (69%) the neuropathic score was < 5 (mild neurotoxicity), in four (17%) < 10 (moderate neurotoxicity).

After 12 cycles nine (39%) patients complained of mild signs and symptoms and scored < 5, 14 (60%) had moderate neurotoxicity, scores < 10. After 24 cycles of chemotherapy 12 patients (66-6%) showed moderate neurotoxicity with a score of 5 to 10.

Table 2 Mean (SD) of peroneal MAPs (mV) and median and sural SAPs (μV) before and after 4, 12 and 24 courses of therapy

<table>
<thead>
<tr>
<th>Courses</th>
<th>Normal</th>
<th>Baseline</th>
<th>4 (n = 23)</th>
<th>12 (n = 23)</th>
<th>24 (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>21 2 (4 6)</td>
<td>25 2 (11 6)</td>
<td>23 7 (9 4)</td>
<td>16 4 (7 5)</td>
<td>16 4 (7)</td>
<td>0 002</td>
</tr>
<tr>
<td>Peroneal</td>
<td>5 2 2 (2 2)</td>
<td>5 6 1 (1 8)</td>
<td>4 4 (1 9)</td>
<td>3 7 (1 7)</td>
<td>3 0 (1 4)</td>
<td>0 001</td>
</tr>
<tr>
<td>Sural</td>
<td>16 8 (6 3)</td>
<td>10 9 (6)</td>
<td>9 2 (5 4)</td>
<td>8 7 (5 5)</td>
<td>8 5 (9 3)</td>
<td>0 05</td>
</tr>
</tbody>
</table>

P value refers to amplitudes after 24 courses vs baseline.
and six (33-3%) severe neurotoxicity with a score > 10. However, in no patient did the severity of neurotoxicity require discontinuation of treatment, and no patients had a World Health Organisation (WHO) disability score > 2.

Total neurotoxicity score was significantly related to the number of cycles of vinorelbine ($r = 0.9$).

**Discussion**

Peripheral neurotoxicity due to vinorelbine treatment was described as occurring less often than after treatment with other vinca alkaloids. The reported incidence in phase II oncological studies varied from 6% to 29%.

The WHO neurotoxicity grading system commonly used in oncological series, however, does not permit the real incidence and the neuropathy profile to be evaluated.

The detailed neurological and electrophysiological evaluations and the neurotoxic score system used in our study are sensitive methods for detecting early peripheral neurotoxicity and allowed a precise neuropathy assessment.

Our data show that all the patients treated with vinorelbine developed a mild distal sensory-motor, symmetric neuropathy of axonal type. Most patients had reduced or abolished deep tendon reflexes and sensory symptoms with distal paraesthesiae, hypoesthesia, and hypopallæsthesia, showing an involvement of both small and large calibre sensory fibres; electrophysiological findings confirm the involvement of both motor and sensory fibres with decreased amplitude of MAPs and SAPs and normal conduction velocities. These findings are indicative of a distal axonopathy similar to that induced by pyridoxine.

Follow up data after six months confirmed that this kind of neuropathy may reverse, like that with distal axonal neuropathies due to vincristine and paclitaxel.

The degree of clinical and neurophysiological impairment correlates with the number of courses given ($r = -0.9$) and shows that this neuropathy is dose-dependent. At the dosage used in our study vinorelbine induced slight neuropathic signs and symptoms but did not seem to be dose limiting.

The sympathetic skin response, a simple method of assessing dysfunction of unmyelinated axons in axonal neuropathy proposed by Shahani et al., did not show involvement of small unmyelinated C fibres.

The very high incidence of vinorelbine neurotoxicity in our study could be explained by the detailed clinical and electrophysiological methods used and, perhaps, with the high dose intensity of the schedule adopted. Although the severity of vinorelbine neuropathy does not seem clinically relevant, the use of this drug in combination with other neurotoxic agents such as paclitaxel or platinum compounds, may aggravate the neurotoxic damage. Some studies suggest that administration of several neuronotrophic factors (nerve growth factor, ACTH analogues, and others) can prevent or limit neurotoxicity of many drugs. We think that to define the real incidence and the precise pathological profile of neurotoxicity from antineoplastic drugs, using standardised methods, is extremely important both for evaluating the drug itself, and in evaluating the potential benefit of neuroprotective agents.