Early predictors of peripheral neurotoxicity in cisplatin and paclitaxel combination chemotherapy

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Background: We investigated the possible use of clinical signs of chemotherapy-induced peripheral neurotoxicity (CIPN) or of nerve growth factor (NGF) circulating levels to predict the final outcome of CIPN.

Patients and methods: Sixty-two women affected by locally advanced squamous cervical carcinoma treated with TP (paclitaxel 175 mg/m² over a 3 h infusion plus cisplatin 75 mg/m²) or TIP (TP plus ifosphamide 5 mg/m²) were examined and scored according to the Total Neuropathy Score (TNS), before and during chemotherapy.

Results: A correlation with the final severity of CIPN was observed with vibration perception and deep tendon reflex evaluation, while pin sensibility, strength, and autonomic symptoms and signs were not informative. A highly significant correlation existed between the decrease in circulating levels of NGF and the severity of CIPN ($r = -0.579; P < 0.001; 95\%$ confidence limits $-0.702$ to $-0.423$). However, circulating levels of NGF were not effective as predictors of the final neurological outcome of each patient.

Conclusion: Our study indicates that a precise clinical evaluation of the peripheral nervous system of patients treated with platinum and taxane combination polychemotherapy not only gives reliable information regarding the course of CIPN, but also can be used to predict the final neurological outcome of the treatment.

Key words: chemotherapy, cisplatin, neuropathy, paclitaxel

Introduction

No general agreement has been reached [1–3] concerning which is the most effective method for assessing the severity of chemotherapy-induced peripheral neurotoxicity (CIPN). Besides accurately evaluating the severity of CIPN, another major point of concern when using platinum–taxane combination therapy is the absence of reliable clinical, neurophysiological or biological early predictors of the final outcome of each patient.

Moreover, evidence that nerve growth factor (NGF) may play a role in the course of CIPN has recently been reported [4–9], but this result has not yet been confirmed in prospective studies on patients followed using clinical and neurophysiological methods.

The main aim of this study was to investigate the possible use of the Total Neuropathy Score (TNS) or of individual TNS items to predict the outcome of CIPN in patients undergoing cisplatin and paclitaxel combination chemotherapy, and to assess circulating NGF levels in relationship to the neurological status in order to determine whether a correlation exists between biological and clinical indicators of the final neurological outcome.

Patients and methods

Following approval by all institution review boards and the provision of patients’ written informed consent, 62 women without any clinical evidence of peripheral neuropathy at baseline and who were affected by locally advanced squamous cervical carcinoma treated at the Departments of Gynecological Oncology of the S. Gerardo Hospital in Monza ($n = 39$) and the European Institute of Oncology in Milan ($n = 23$) were examined. Patients were treated every 3 weeks with cycles of chemotherapy using either TIP (paclitaxel 175 mg/m² over a 3 h infusion plus ifosphamide 5 mg/m² plus cisplatin 75 mg/m²) or TP (paclitaxel 175 mg/m² over a 3 h infusion plus cisplatin 75 mg/m²).
All the patients participating in this study, some of whom belonged to the cohort reported in the TNS validation study [3], were examined at the Department of Neurology of the S. Gerardo Hospital. Neurological examinations were performed before chemotherapy, after three and five cycles, and 3 months after the end of chemotherapy. The severity of CIPN was assessed by a single examiner (G.C.) and the TNS score (Table 1) was calculated.

The presence of sensory, motor and autonomic symptoms was assessed by interviewing the patients. The neurological examination was based on: (i) standard evaluation of strength; (ii) standard evaluation of deep tendon reflexes (DTR); (iii) examination of pin sensibility using a sterile disposable needle; and (iv) evaluation of vibration sensibility using a 128 Hz tuning fork in upper and lower limbs. The tuning fork contained two triangles on the weight, with a scale ranging from 0 (minimum) to 8 (maximum). When the tuning fork was vibrating maximally, the triangles appeared double and the intersection of the two virtual triangles moved from 0 to 8 with decreasing vibration amplitude [10]. Vibration sensibility was normal if the patient perceived a vibration leading to a score of 7 or 8. Vibration detection threshold (VDT) was assessed by a trained examiner using a Vibrameter type IV device (Somedic AB, Stockholm, Sweden) at the base of the first metatarsal bone of the right foot using the method of ‘limits’ [11]. Nerve conduction studies were performed with a Medelec Premiere Plus electromyograph (Vickers Medicals, Woking, UK) using standard methods [10, 12–14].

At the time of each neurological examination, a venous blood sample was obtained and plasma was stored at $-80^\circ$C until determination of the NGF level by enzyme-linked immunosorbent assay using a commercial kit (Emax ImmunoAssay System (Promega, Madison, WI)) [9].

The correlations existing between total TNS and circulating levels of NGF were assessed using the Spearman test for non-parametric data (significance level $P<0.05$), and the 95% confidence limits were also calculated using PRISM (GraphPad Software, Inc., CA).

### Results

#### Clinical results

Thirty-four patients underwent all four of the scheduled neurological examinations and were evaluable. They were divided, according to the highest TNS score reached during the period of observation, into three groups: those with a score <5 (better outcome, $n=14$), those with a score $\geq5$ but $<10$ ($n=5$), or those with a score $\geq10$ (worst outcome, $n=15$). In each patient, the changes in the score observed in total TNS and individual items at the visit performed before the observation of the maximum severity of CIPN were determined, and the results obtained in the two groups with the best or worst neurological outcome were compared.

During the examinations performed before the maximum severity of CIPN had been reached, the total TNS score increased by 3–8 points in the group that eventually had the worst final neurological signs and symptoms, and by 0–5 points in the group with the better overall outcome. However, the most interesting correlation with the final severity of CIPN (Table 2) was observed in the subscore obtained for the items regarding vibration perception and DTR, while pin sensibility, strength, and autonomic symptoms and signs were not informative. In fact, in the examination performed before the onset of worst neuropathy signs, 14 of the 15 patients with a final

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**Table 1. Description of the scales used in the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total neuropathy score</th>
<th>Sensory symptoms</th>
<th>Motor symptoms</th>
<th>Autonomic symptoms</th>
<th>Vibration sensibility</th>
<th>DTR</th>
<th>Pin sensibility</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Normal</td>
<td>NVR</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Slight difficulty</td>
<td>Normal</td>
<td>Reduced to ankle</td>
<td>Reduced to ankle</td>
<td>NVR</td>
<td>Reduced to ankle</td>
<td>Reduced to ankle</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Moderate difficulty</td>
<td>Reduced to wrist/ankle</td>
<td>Reduced to wrist/ankle</td>
<td>Reduced to wrist/ankle</td>
<td>NVR</td>
<td>Reduced to wrist/ankle</td>
<td>Reduced to wrist/ankle</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Severe difficulty</td>
<td>Reduced to elbow/knee</td>
<td>Reduced to elbow/knee</td>
<td>Reduced to elbow/knee</td>
<td>NVR</td>
<td>Reduced to elbow/knee</td>
<td>Reduced to elbow/knee</td>
</tr>
<tr>
<td>4</td>
<td>4 or 5</td>
<td>Paralysis</td>
<td>Paralysis</td>
<td>Paralysis</td>
<td>Paralysis</td>
<td>NVR</td>
<td>Paralysis</td>
<td>Paralysis</td>
</tr>
</tbody>
</table>

**Note:** MRC, Medical Research Council; DTR, deep tendon reflexes; QST, quantitative sensory test (n.v. <2 mm); ULN, upper limit of normal; LLN, lower limit of normal; SAP, amplitude of the sensory potential (n.v. >6 μV); CMAP, amplitude of the compound muscular potential (n.v. >2 mV).
Table 2. Incidence of the most relevant changes in Total Neuropathy Score (TNS) items occurring in the visit performed before the maximum severity of CIPN is observed

<table>
<thead>
<tr>
<th>Increase in combined vibration perception+DTR scores ≥2</th>
<th>Patients with better outcome (maximum TNS &lt;5; n = 14)</th>
<th>Patients with worst outcome (maximum TNS &gt;10; n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in vibration perception scores ≥1</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Absent bilateral ankle and patellar reflexes</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Increase in combined VDT+DTR scores ≥2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Decrease in sural SAP &gt;50% compared with baseline value</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Change from normal to pathological SAP value (26 μV)</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

DTR, deep tendon reflexes; VDT, vibration detection threshold; SAP, amplitude of the sensory potential.

TNS of ≥10 had a change of ≥2 points in the score obtained by adding together the vibration score obtained with the tuning fork and the DTR examination. Interestingly, in 12 of these 14 patients, the change in the score was due to both vibration perception and DTR impairment. This observation is relevant since a change in the combined score (i.e., vibration + DTR impairment ≥2 points) was also observed in seven of the 14 patients in the group with the better neurological outcome, but none experienced any change in vibration perception at the examination performed before the maximum TNS score was reached. Another possible early indicator for worse neurological outcome was the complete disappearance of DTR in the lower limbs, which was observed in seven of the 15 patients, while only one patient in the better outcome group had this clinical sign. The results of the VDT score were in agreement with the tuning fork results, while the neurophysiological assessment of sural nerve potential amplitude changes was less effective than clinical or VDT examinations in predicting the final outcome of the CIPN (Table 2).

Nerve growth factor results

A total of 129 serial plasma samples was available. The circulating levels of NGF determined for the baseline samples were comparable to, and not significantly different from, those measured in 36 healthy volunteers (personal observation). The baseline determinations were used to calculate changes from baseline levels induced by treatment, and a highly significant correlation existed between the decrease from baseline value in circulating levels of NGF and the severity of CIPN as scored using the TNS ($r = -0.579$; $P <0.001$; 95% confidence limits 0.702 to $-0.423$) (Figure 1).

However, the circulating levels of NGF, which were closely associated with the actual neurological status, were not effective as predictors of the final neurological outcome of each patient.

Discussion

The identification of reliable early predictors of the final outcome of the neurotoxicity of platinum-derived drugs, particularly when they are used in polychemotherapy schedules, would be extremely useful in the clinical management of cancer patients.

General agreement regarding the best way to investigate and grade the peripheral neurotoxicity of platinum drugs has not yet been reached [1–3, 10, 13, 14].

In our study, careful examination of changes in vibration sensibility and DTR was found to be an early predictor of the outcome of CIPN. Moreover, vibration impairment, assessed using a tuning fork in the semiquantitative manner described in our study, was particularly effective. Neurophysiological assessment allows reproducible results to be obtained, but these methods are most useful for grading an established neuropathy rather than for predicting a better or worse outcome, as the present study has also confirmed. Neuroradiological methods [15] of studying spinal cord dorsal columns still need to be validated in large series to assess sensitivity and reliability. Sural nerve biopsy is no longer an acceptable method for investigating well established chemotherapy schedules. Skin biopsy, however, might be a useful tool in the future. In fact, in diabetic patients, skin biopsy changes in the intraepidermal innervation occur very early in the course of the disease, and the procedure is simple and well tolerated by patients [16, 17]. However, until now no validation of skin biopsy results has been performed in the course of CIPN.

In searching for a biological marker for CIPN, and possibly for a predictor of the neurological outcome, we investigated a large number of serial NGF samples obtained during the course of the study. NGF, a neurotrophic factor of the neurotrophin family, has been investigated as a putative neuroprotectant in several in vitro and in vivo models of cisplatin and paclitaxel peripheral neurotoxicity [5–8, 18, 19]. Moreover, a previous small clinical study performed in an unselected cohort of patients undergoing various chemotherapy schedules, suggested that circulating NGF levels might be correlated with clinical status [9, 20]. These results have already
been reproduced in cisplatin and oxaliplatin rat models [21], while no data are available on taxanes. Our study made it possible to confirm that cisplatin–paclitaxel chemotherapy determines a clinically related decrease in NGF circulating levels, but it failed to demonstrate that determining NGF is a biological predictor of final neurological outcome.

In conclusion, our study indicates that a precise clinical evaluation of the peripheral nervous system of patients treated with platinum–taxane combination polychemotherapy yields reliable information not only about the course of CIPN, but that it can be also be used to predict the final neurological outcome of the treatment.

References