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## **Early changes in tests of peripheral nerve function during oxaliplatin treatment and their correlation with chemotherapy-induced polyneuropathy symptoms and signs**

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Running title: Early changes in tests of peripheral nerve function during oxaliplatin treatment

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## Abstract

**Background:** Assessment of the severity of chronic peripheral neuropathy during oxaliplatin treatment is based on symptoms. Efforts to adjust the total dose of oxaliplatin to prevent severe neuropathy can be complicated by worsening of neuropathy symptoms following treatment. Objective measures of the structure and function of peripheral nerves during early phases of treatment may aid in determining the optimal oxaliplatin dose in individual patients. Intraepidermal nerve fibre density (IENFD) has been suggested as an early marker of peripheral neuropathy.

**Methods:** Sixty patients were examined before treatment and following 25% and 50% of the total planned oxaliplatin dose. Fifty-five of them were also examined at completion of chemotherapy and six months later. IENFD in skin biopsies from the distal leg, nerve conduction studies (NCS), and quantitative sensory testing at the dorsum of the foot was performed. Forty-six healthy subjects were examined at baseline and after six and 52 weeks for comparison.

**Results:** IENFD was not reduced during treatment. Sural nerve amplitude and conduction velocity, vibration detection thresholds (VDT), mechanical detection threshold (MDT), and cold detection threshold (CDT) were significantly reduced during treatment. Compared to reference values and spontaneous changes in healthy subjects, the largest proportions of patients with deterioration were found for VDT followed by NCS, MDT, CDT, and IENFD.

**Conclusions:** Significant changes were most pronounced for measures of large nerve fibre

function, especially vibration sensation. Skin biopsies do not seem to provide a clinically relevant objective measure of peripheral nerve deterioration during oxaliplatin treatment.

**Keywords:** Intraepidermal nerve fibre density, nerve conduction studies, oxaliplatin, peripheral neuropathy, quantitative sensory testing.

## **Introduction**

Chronic chemotherapy induced peripheral neuropathy (CIPN) following oxaliplatin treatment is a common side effect which affects the quality of life<sup>1</sup> and may cause neuropathic pain.

Attempts are made to titrate oxaliplatin dose to optimize the balance between the antineoplastic effect and side effects such as chronic CIPN. This is complicated, however, by the so-called coasting phenomenon, which implies that symptoms can progress even after the cessation of treatment.<sup>2</sup> Measures of subclinical peripheral nerve damage during the early phases of treatment could aid in determining the optimal dose for individual patients.

Intraepidermal nerve fibre density (IENFD) is reduced in subjects with diabetes even before symptoms or signs of peripheral neuropathy and could be a marker for early, subclinical diabetic neuropathy.<sup>3</sup> A prospective study of eight patients treated with oxaliplatin showed a reduction in IENFD during and after treatment.<sup>4</sup>

The aim of the present study was to prospectively examine changes in IENFD and other markers of peripheral nerve function including nerve conduction studies (NCS) and quantitative sensory testing (QST) during oxaliplatin treatment to determine if there are early changes and to correlate these changes to symptoms.

## **Methods**

### *Patients*

Patients scheduled for treatment with oxaliplatin against gastrointestinal cancers at the Department of Oncology at Odense University Hospital were screened for inclusion. Exclusion criteria were pre-existing peripheral neuropathy, diabetes, CNS or bone metastases, vascular diseases of the lower extremities, significant spinal degenerative disease with symptoms of radicular affection or spinal stenosis, hereditary disposition for peripheral neuropathy, previous or current alcohol abuse, previous or current treatment with medications known to cause peripheral neuropathy and age less than 18 or more than 80 years.

#### *Healthy subjects*

To evaluate the spontaneous changes in measures of peripheral nerve function, 46 healthy control subjects were examined three times: At inclusion, and after 6 and 52 weeks.

#### *Study procedures*

Patients were examined five times at the Department of Neurology. Baseline examination took place before initiation of oxaliplatin therapy. The second examination was performed at least 10 days after the patient had received 25% of the total planned dose of oxaliplatin (6 weeks of treatment). The third examination took place after 50% of the planned dose (12 weeks of treatment), and the fourth after completion of treatment (24 weeks). If the patient did not receive more than 50% of the planned dose, the fourth examination was left out. The final examination took place six months after completion of treatment.

Neuropathy symptoms and signs were assessed using Neurological Symptom Score (NSS),<sup>5</sup> Neuropathy Impairment Score (NIS),<sup>6</sup> Inflammatory Neuropathy Cause and Treatment disability sum score (INCAT DS),<sup>7</sup> and Inflammatory Neuropathy Cause and Treatment sensory sum score (INCAT SS).<sup>8</sup>

Skin biopsies were obtained from the lateral aspect of the lower leg (10 cm proximal to the lateral malleolus). They were processed according to EFNS and PNS guidelines.<sup>9</sup> IENFD was determined using bright field immunohistochemistry and classified as reduced if below the 0.05 quantile of the comprehensive normative data.<sup>10</sup>

QST was performed according to DFNS standards<sup>11</sup> and included evaluation of cold detection threshold (CDT), warmth detection threshold (WDT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), and vibration detection thresholds (VDT) at the dorsum of the right foot. CDT, WDT, and HPT were determined using a TSA-II – NeuroSensory Analyzer (Medoc Ltd, Israel). Furthermore, vibration sense was assessed using a Biothesiometer (BIO-MEDICAL INSTRUMENTS CO., Newbury,

Ohio) balanced on the tip of the first toe with a pressure corresponding to the weight of the instrument.

Sural, tibial and peroneal NCS were performed bilaterally using a Dantec KeyPoint (Natus Medical Incorporated, San Carlos, CA, USA). NCS was considered abnormal if any parameter (F-wave latencies excluded) was abnormal in two nerves, one of them being the sural nerve.<sup>13</sup>

The study was approved by The Regional Ethical Committee for Southern Denmark (reference number S-20120077), and written informed consent was obtained from all patients.

#### *Data analysis*

Data from patients completing at least three study examinations were included in the analysis. Linear regression analysis was used to estimate the weekly changes in IENFD, and NCS and QST variables. Estimates were adjusted for age, sex, and the total oxaliplatin dose. Separate estimates were obtained for the treatment period (weeks -1 to 24) and the follow up period (weeks 24 to 52). As changes during treatment were not linear for all parameters (Figures 2 and 3) an additional analysis of each of the examinations after administration of 25% and 50% of the planned dose, after completion of treatment, and six months after treatment were compared to baseline measurements using paired students t-tests. The test results of individual patients were compared to normative values as described above and the proportion of abnormal tests at each examination calculated. Furthermore, changes in individual patients at examinations during and following treatment compared to baseline values were compared to two standard deviations of the numerical spontaneous variation in healthy subjects from baseline examination to examination after 6 weeks. The proportion of patients with a deterioration were determined. Correlations between changes in neuropathy scores and IENFD and NCS and QST parameters from baseline to the examination after completion of treatment were examined using linear regression. Stata/IC v. 15 (StataCorp LLC, College Station, Texas, USA) was used.

## Results

Sixty patients completed the first three examinations, and were included in the analysis (Supplementary figure 1). The patient population had a median age of 66 years, and was dominated by males (70%). Details regarding oxaliplatin treatment and neuropathy scores six months after treatment are presented in Table 1.

Changes in neuropathy scores were quite similar during and after treatment (Figure 1). There was an almost linear increase in the neuropathy symptom score (NSS) during treatment, and small increases after six weeks of treatment followed by almost linear increases during the rest of treatment period for scoring of neurological signs (NIS and INCAT SS) and neurological disability (INCAT DS).

IENFD did not change significantly during or following oxaliplatin treatment in the linear regression analysis (Table 2), but comparison of IENFD six months after treatment (week 52) to baseline IENFD revealed a significant reduction (Figure 2).

Sural nerve conduction velocity and amplitude were significantly reduced during treatment. Compared to baseline values SNAP was significantly reduced at completion of treatment (week 24) and six months after treatment. Sural nerve SNCV was significantly reduced after administration of 50% of the planned dose of oxaliplatin (week 12), at completion of treatment, and six months after treatment. There were no significant changes in other NCS parameters (data not shown).

Of the QST variables (Figure 3), the earliest changes were found for the vibration sense assessed by VDT and the biothesiometer. There was also a significant increase in MDT, but this change only occurred after completion of treatment and six months after treatment. There

was a significant reduction in CDT. There were no changes in other tests of small fibre function, except for a reduction in MPT after 25% of the planned dose, but this change was not found in the rest of the study period. Linear regression analysis revealed significant changes in CDT and MDT during treatment and highly significant changes in sural nerve SNAP and SNCV and vibration sense during treatment. There were no significant changes following treatment.

There were no significant changes in IENFD, NCS or QST variables for the healthy control subjects during the study period.

Comparing the test results of individual patients to normative values (Figure 4) the highest proportion of abnormal tests was found for VDT. However, more than 30% of patients had abnormal test results for VDT before treatment. The fraction of abnormal CDT results increased from 7% before treatment to 14% after 25% of the planned dose and increased to 24% six months after treatment. During treatment there was a steadily increasing fraction of abnormal NCS to 9% after 50% of planned dose and 31% after complete treatment. The fraction of abnormal IENFD increased to 12% after 25% of planned dose. After treatment, the fraction of abnormal tests increased to 20%.

Compared to spontaneous changes in healthy subjects (Supplementary table 1) vibration sensation also had the highest proportions of deterioration. Sural nerve conduction also deteriorated for a relatively large proportion, whereas changes in IENFD of more than two standard deviations were only found in 10% of patients at completion of treatment.

Statistically significant correlations were found between decreasing IENFD and VDT and increasing INCAT SS (Supplementary figure 2). Similar correlations were found for changes in other measurements of nerve function and neuropathy scores (e.g. IENFD, VDT, sural nerve NCS and NIS), but these correlations were not statistically significant.

## **Discussion**

We performed the largest and most comprehensive prospective study of oxaliplatin-induced peripheral neuropathy regarding measures of peripheral nerve function to date. Neuropathy scores were affected during early phases, and increased almost linearly during treatment. This suggests that affection of peripheral nerves caused by oxaliplatin occurs with a relatively



similar intensity during treatment, and does not depend on a specific “threshold” of oxaliplatin dose, as could be assumed by the clinical impression that it is only the very last administrations of oxaliplatin which cause neuropathy.

We could not demonstrate any significant early reduction in IENFD during oxaliplatin treatment. As previously shown,<sup>4</sup> we did find a reduction of IENFD, but it was not significant until six months after end of treatment.

The earliest significant changes were found for vibration sensation, significant after 25% of the planned dose, followed by cold detection thresholds and sural nerve conduction studies, significant after 50% of the planned dose.

Our results suggest that assessment of vibration sense using the calibrated tuning fork (VDT) and the biothesiometer are equally suitable for the detection of early changes. These measurements are rapidly and easily performed, but as the calibrated tuning fork will be readily available to oncologists as well as neurologists, this methods could have the largest potential for implementation in routine clinical use.

Significant changes were found for CDT, but not for WDT or HPT, which remained stable during and after treatment. The difference may be explained by the fact that cold detection is conveyed by thinly myelinated A $\delta$ -fibres, whereas warmth detection is conveyed by unmyelinated C-fibres. This suggests that different types of nerve fibres are not equally affected by oxaliplatin treatment. However, it is known from healthy subjects that WDT has a higher inter-individual variation than CDT<sup>14</sup> which may mask small changes in WDT in a subgroup of patients in our study.

Correlations between changes in IENFD and WDT, and not CDT have been shown in Gullain-Barré syndrome<sup>15</sup> and stronger correlations between IENFD and WDT than IENFD and CDT in diabetic neuropathy<sup>16</sup> suggesting that intraepidermal nerve fibres quantified in skin biopsies are primarily C-fibres. This may explain why there was a reduction in CDT, but not IENFD during treatment.

NCS of the sural nerves were affected during treatment. in concordance with a study of two groups of patients tested during and following oxaliplatin treatment, respectively, which found reduced sural SNAP and SNCV, but no change in peroneal nerve NCS during treatment and no changes following treatment.<sup>17</sup> In contrast, a study of 20 patients found a reduction in sensory nerve amplitudes, but not conduction velocities.<sup>18</sup>

Comparison of changes in tests of small (IENFD, thermal detection thresholds) and large (vibration sense and NCS) nerve fibre function suggest that oxaliplatin primarily affects large, myelinated nerve fibres. This is supported by previous findings of early changes in vibration sense, but not thermal detection thresholds during treatment.<sup>19</sup> However, the same study found that early thermal hyperalgesia, which we did not examine, was a marker for severe, chronic neuropathy. On the other hand, a study of 20 patients with chronic oxaliplatin-induced peripheral neuropathy showed that skin biopsies were more often abnormal than NCS and QST.<sup>20</sup> This discrepancy may be explained by patient selection resulting from recruitment of patients with an established peripheral neuropathy in the latter study.

The predominance of large fibre dysfunction in a condition often clinically dominated by neuropathic pain is interesting. One explanation may be that although small fibres were mostly structurally intact as assessed by IENFD, functional changes in small peripheral nerve fibres causing pain, which we were not able to demonstrate, may have been present. Alternatively, central nervous system synaptic plasticity including phenotypical changes in neurons normally not involved in processing of noxious stimuli may play a role in oxaliplatin-induced neuropathic pain. In this case, large nerve fibre dysfunction may also be involved in the pathophysiological changes leading to neuropathic pain.

We found significant correlations between changes in vibration sense and IENFD and INCAT SS, which is a rating of neurological signs. There was no significant correlation with neuropathy symptoms (NSS). This is probably due to the very limited range of the scale in our study population.

Analysis of measures compared to normative values reveals that although vibration sense is the earliest to deteriorate during treatment, it also has the highest fraction of abnormal results before oxaliplatin treatment. Abnormal results before treatment were not found for NCS, and very infrequently for IENFD. Serial measurements of vibration sense before and during treatment, rather than comparison of single measurements to reference values, will probably be necessary to evaluate the impact of oxaliplatin treatment. It is a limitation to this study that controls were significantly younger and had a higher proportion of women, and comparison of changes to those found in controls must be interpreted with caution.

In conclusion, QST, specifically quantification of vibration sense, and NCS demonstrate significant changes during the early phases of oxaliplatin and these measures may be useful in

clinical practice and in studies of prediction of and neuroprotection against oxaliplatin-induced peripheral neuropathy. There were no significant early changes in IENFD.

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## Legends

Figure 1: Neuropathy scores before (week -1), during (weeks 6 and 12), after (week 24), and at examination six months after (week 52) treatment. NSS: Neurological Symptom Score; NIS: Neuropathy Impairment Score; INCAT DS: INCAT disability sum score; INCAT SS: INCAT sensory sum score.

Figure 2: Results of skin biopsies and sural nerve conduction studies before (week -1), during (weeks 6 and 12), after (week 24), and at examination six months after (week 52) treatment. IENFD: Intraepidermal nerve fiber density; SNAP: Amplitude of the sensory nerve action potential; SNCV: Sensory nerve conduction velocity. \*\*:  $P < 0.01$ ; \*\*\*:  $P < 0.001$ .

Figure 3: Results of quantitative sensory testing before (week -1), during (weeks 6 and 12), after (week 24), and at examination six months after (week 52) treatment. CDT: Cold detection threshold; WDT: Warmth detection threshold; HPT: Heat pain threshold; MDT:

Mechanical detection threshold; MPT: Mechanical pain threshold; VDT: Vibration detection threshold. \*:  $P < 0.05$ ; \*\*:  $P < 0.01$ ; \*\*\*:  $P < 0.001$ .

Figure 4: The proportion of patients with abnormal test results before (week -1), during (weeks 6 and 12), after (week 24), and at examination six months after (week 52) treatment. IENFD: Intraepidermal nerve fiber density; NCS: Nerve conduction studies; CDT: Cold detection threshold; MDT: Mechanical detection threshold; MPT: Mechanical pain threshold; VDT: Vibration detection threshold.

Supplementary figure 1: Screening and inclusion of patients. Baseline examination (week -1) was performed at inclusion at the Department of Neurology. The second, third, fourth and fifth study examinations were performed 6, 12, 24, and 52 weeks after initiation of treatment, respectively.

Supplementary figure 2: Examples of correlations between changes in skin biopsies and vibration thresholds and neuropathy scores between baseline and examination at completion of treatment. INCAT SS: INCAT sensory sum score; NIS: Neuropathy Impairment Score; IENFD: Intraepidermal nerve fiber density; VDT: Vibration detection threshold.

**Disclosures**

The authors have no conflicts of interests to disclose.

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Table 1. Characteristics of patients and healthy controls.

	Oxaliplatin (n=60)	Controls (n=46)
Age (years), median (range)	66 (37-78)	51 (40-80)
Sex, M/F	42/18	18/28
Total dose (mg/m <sup>2</sup> ), median (range)	748 (260-1084)	
Neuropathy scores six months after treatment		
NSS, median (range)	1 (0-5)	
NIS, median (range)	6 (0-24)	
INCAT DS, median (range)	1 (0-4)	
INCAT SS, median (range)	2 (0-9)	

NSS: Neurological Symptom Score; NIS: Neuropathy Impairment Score; INCAT DS: Inflammatory Neuropathy Cause and Treatment disability sum score; INCAT SS: Inflammatory Neuropathy Cause and Treatment sensory sum score.



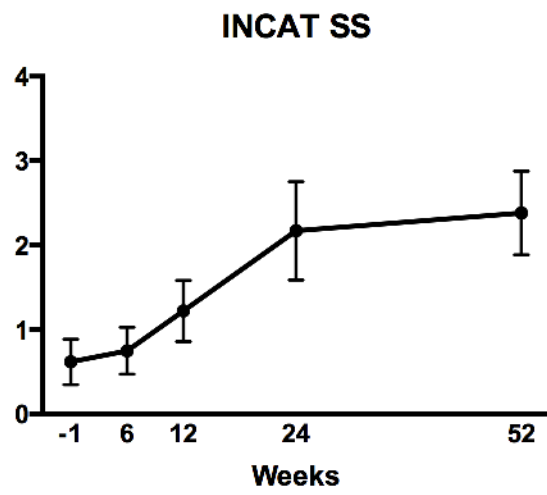
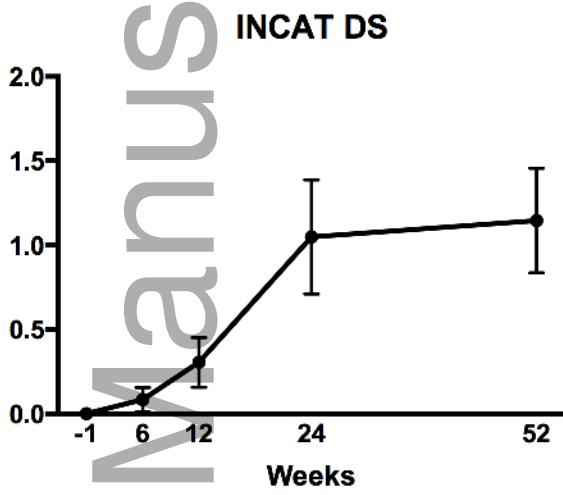
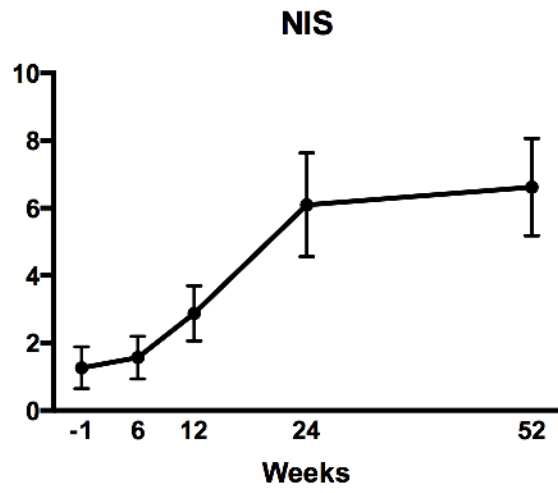
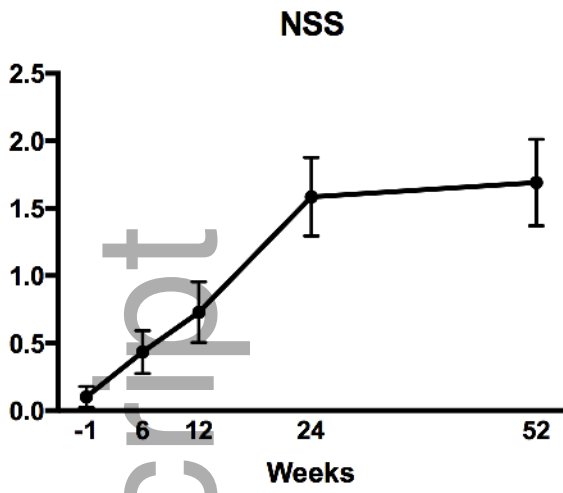
Table 2. Linear regression analysis of changes in measures of nerve function during and following

	During treatment (weeks -1–24)		Following treatment (weeks 24-52)	
	Change/week (95% CI)	P	Change/week (95% CI)	P
IENFD (nerves/mm)	0.012 (-0.048 - 0.073)	0.686	-0.045 (-0.095 - 0.006)	0.083
Sural SNAP ( $\mu$ V)	-0.154 (-0.229 - -0.080)	<0.000	-0.042 (-0.106 - 0.022)	0.195
Sural SNCV (m/s)	-0.192 (-0.266 - -0.118)	<0.000	0.003 (-0.061 - 0.067)	0.924

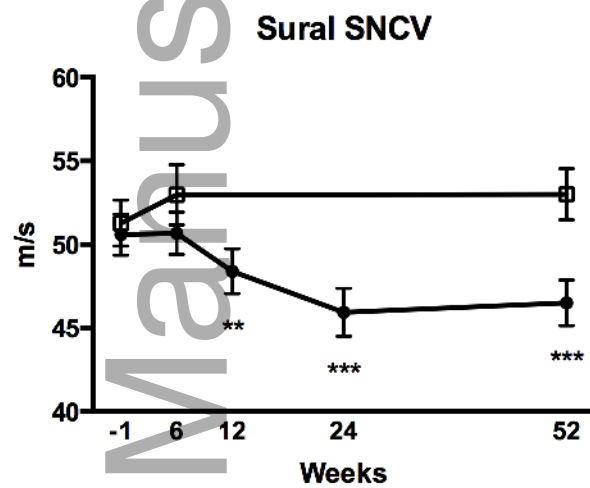
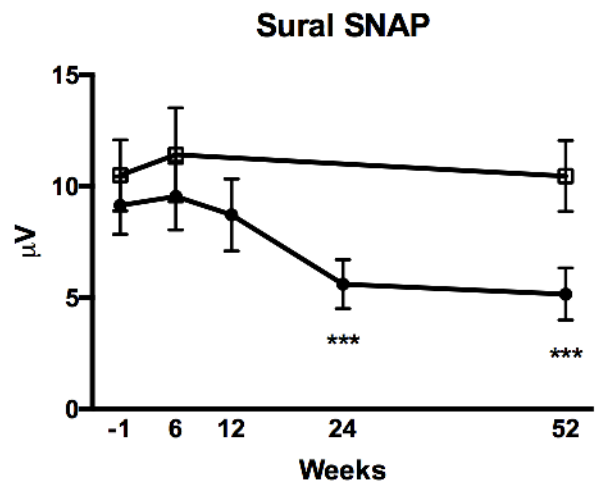
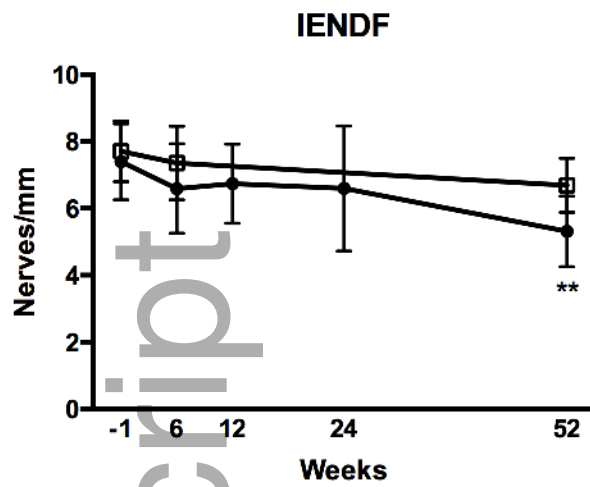
treatment.

CDT (°C)	-0.088 (-0.174 - -0.002)	0.043	-0.041 (-0.113 - 0.030)	0.255
WDT (°C)	0.029 (-0.024 - 0.083)	0.277	0.000 (-0.044 - 0.045)	0.990
HPT (°C)	0.003 (-0.037 - 0.043)	0.878	0.013 (-0.019 - 0.047)	0.425
MDT (mN)	0.303 (0.028 - 0.578)	0.030	-0.026 (-0.257 - 0.203)	0.818
MPT (mN)	0.372 (-0.404 - 1.148)	0.346	-0.175 (-0.824 - 0.473)	0.594
VDT (/8)	-0.090 (-0.122 - -0.057)	<0.000	0.004 (-0.023 - 0.032)	0.756
Biothesiometer	0.625 (0.430 - 0.820)	<0.000	-0.032 (-0.194 - 0.130)	0.699

CDT: Cold detection threshold; HPT: Heat pain threshold; IENFD: Intraepidermal nerve fibre density; MDT: Mechanical detection threshold; MPT: Mechanical pain threshold; SNAP: Sensory nerve action potential; SNCV: Sensory nerve conduction velocity; VDT: Vibration detection threshold; WDT: Warmth detection threshold.

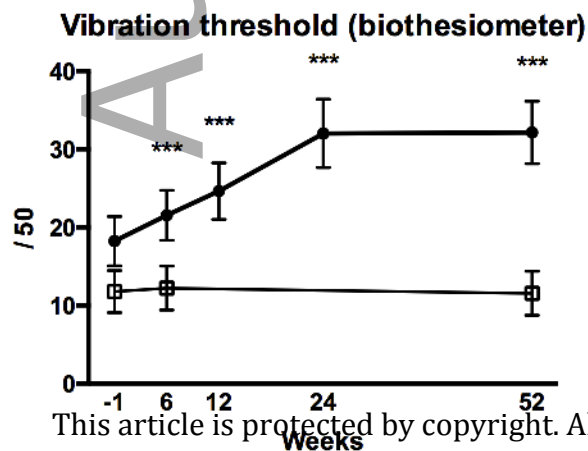
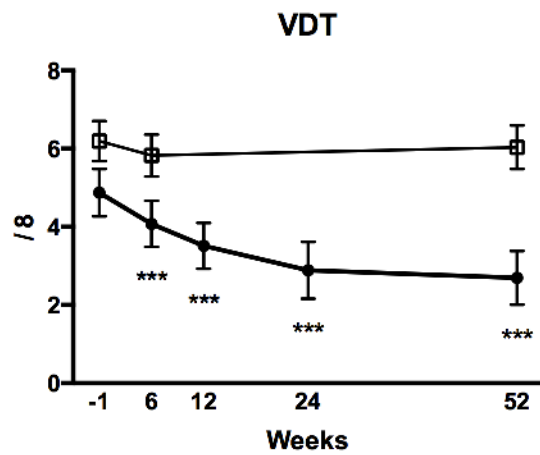
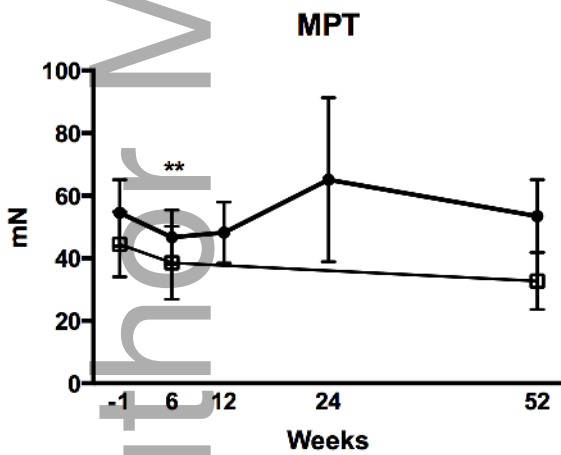
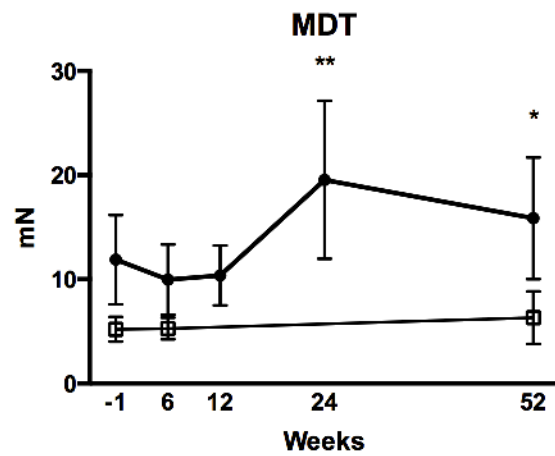
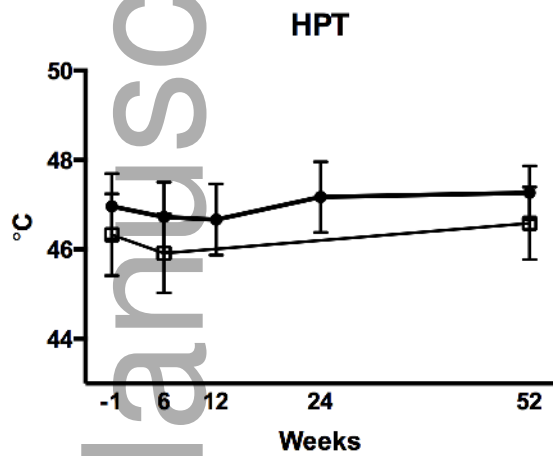
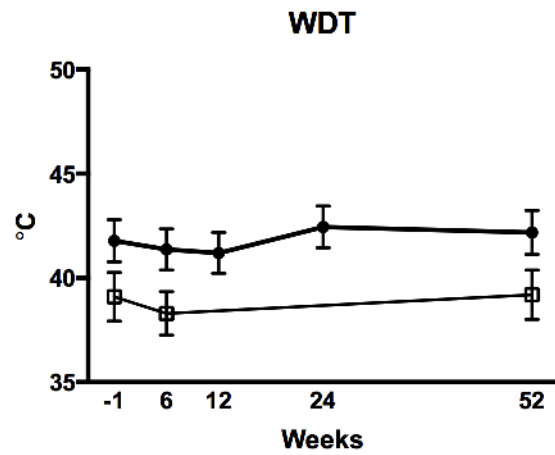
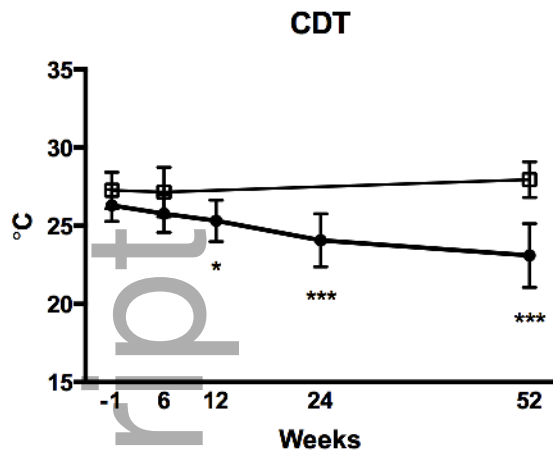


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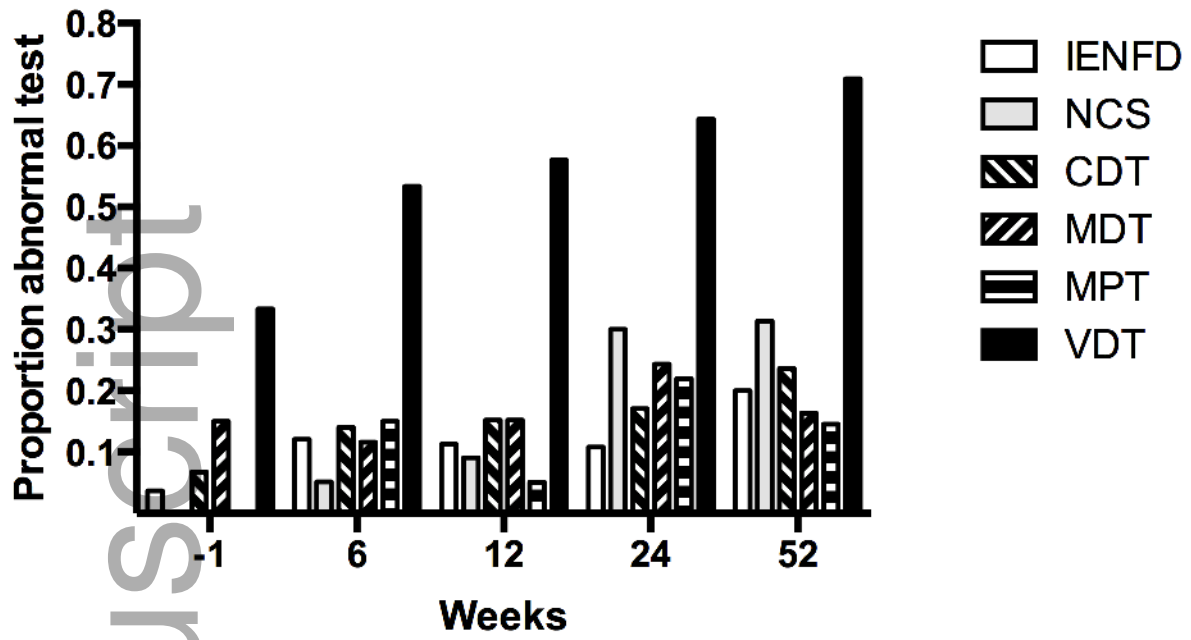


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 □ Controls

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● Oxaliplatin  
 □ Controls



ene\_14035\_f4.tif

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