EUROPEAN JOURNAL OF CANCER 43 (2007) 2658–2663

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Pain in oxaliplatin-induced neuropathy – Sensitisation in the peripheral and central nociceptive system

Andreas Binder[a,b,*,e], *Maike Stengel*[a,b,e], *Rainer Maag*[a,b], *Gunnar Wasner*[a,b], *Robert Schoch*[c], *Frank Moosig*[c], *Bernhard Schommer*[d], *Ralf Baron*[a,b]

[a]*Division of Neurological Pain Research and Therapy, Schittenhelmstrasse 10, 24105 Kiel, Germany*
[b]*Department of Neurology, University Hospital Schleswig-Holstein, Campus Kiel, Schittenhelmstrasse 10, 24105 Kiel, Germany*
[c]*Second Medical Department, University Hospital Schleswig-Holstein, Campus Kiel, Chemnitzstrasse 33, 24116 Kiel, Germany*
[d]*Department of Medicine, University Teaching Hospital Rendsburg, Lilienstrasse 20-28, 24768 Rendsburg, Germany*

ARTICLE INFO

Article history:
Received 15 May 2007
Received in revised form 20 July 2007
Accepted 31 July 2007
Available online 12 September 2007

Keywords:
Oxaliplatin
Quantitative sensory testing (QST)
Neuropathy
Cold
Pain
Sensitisation

ABSTRACT

Background: This study aimed to determine the somatosensory characteristics and pain types in patients with acute oxaliplatin-induced neuropathy and to relate this profile to the hereby detected underlying pathophysiological mechanisms.
Patients and methods: Sixteen patients treated with oxaliplatin for cancer were characterised with neurological assessment and a standardised and validated set for quantitative sensory testing (QST). Patients were allocated to two groups depending on the presence or absence of pain symptoms of acute neuropathy.
Results: Comparison with normative data revealed in patients with pain symptoms a characteristic somatosensory profile of cold and mechanical hyperalgesia. Group-to-group analysis revealed additional heat hyperalgesia and warm hypoesthesia.
Conclusion: Pain symptoms of acute oxaliplatin-induced neuropathy are related to signs of sensitisation within the peripheral (cold and heat hyperalgesia) and central nervous nociceptive system (mechanical hyperalgesia). This strengthens the rationale for treatment with anticonvulsants and antidepressants and fosters research on ion channel and receptor related mechanisms.

1. Introduction

Oxaliplatin is an effective platinum derivate that is used in the treatment of colorectal carcinoma[1,2] and causes neurotoxicity predominantly within the peripheral nervous system.[3,4] Two different types of oxaliplatin-induced neuropathy have been described. The acute neuropathy occurs shortly after administration and is characterised by paraesthesia, dysaesthesia or pain usually starting in the hands or feet.[4,5] Chronic peripheral neuropathy develops after longer treatment resulting in loss of sensation, dysaesthesias and functional impairment.[6]

The pathophysiology of the (acute) oxaliplatin-induced neuropathy is not completely understood. It was hypothesised that oxaliplatin interferes with axonal ion conductance and causes neural hyperexcitability,[7–10] leads to cell loss in the dorsal root ganglion[10–13] and is predicted by gene polymorphisms.[14]

* *Corresponding author:* Address: Division of Neurological Pain Research and Therapy, Department of Neurology, Christian-Albrechts-Universität Kiel, Schittenhelmstrasse 10, 24105 Kiel, Germany. Tel.: +49 431 597 8505; fax: +49 431 597 8530.
E-mail address: a.binder@neurologie.uni-kiel.de (A. Binder).
[e] The first two authors contributed equally to this manuscript (shared first authorship).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.07.030

The assessment of chemotherapy induced neuropathy mainly relies on clinical examination since conventional neurophysiological tests are often insensitive to detect neuropathy at an early stage.[15] Recently, the method of quantitative sensory testing (QST) has been validated within a standardised protocol[16] and provides the opportunity to detect and quantify positive, i.e. allodynia or hyperalgesia (pain or increased pain intensity to physiologically non-/noxious stimuli), as well as negative signs, i.e. hypoesthesia, of (acute) neuropathy non-invasively. Moreover, characteristic QST signs can be related to their underlying mechanisms within the peripheral and central nervous system,[17] e.g. peripheral and central sensitisation.

Thus, the aim of the present study was to use QST to detect the somatosensory profile in patients with acute oxaliplatin-induced neuropathy and to relate this profile to the hereby detected underlying pathophysiological mechanisms.

2. Patients and methods

2.1. Study protocol and subjects

Sixteen patients were consecutively recruited. All patients were treated with oxaliplatin and had to be examined as soon as possible after oxaliplatin application. Before quantitative sensory testing (QST) the patients were examined neurologically, filled in the McGill pain and an oxaliplatin specific questionnaire and were allocated to two groups depending on the presence (P-group) or absence of pain symptoms (non-P-group).

The study was approved by the local ethics committee and conducted according the declaration of Helsinki. The patients gave written informed consent after being adequately informed before entering the study.

2.2. Quantitative sensory testing (QST)

In all patients the dorsum of the right hand was investigated using the QST-protocol of the German Research Network on Neuropathic Pain (DFNS) as described previously.[16] This protocol has been recently validated in 180 healthy volunteers[16] and includes a standardised QST battery measuring 13 parameters non-invasively (detailed description in [16]). Summarizing, the mechanical detection- (MDT) and vibration detection threshold (VDT) represent large-fibre function (thickly myelinated A-beta-fibres). Cold detection, (CDT), cold pain, (CPT), warm detection, (WDT), heat pain threshold (HPT), thermal sensory limen (TSL), mechanical pain, (MPT) and pressure pain threshold (PPT) represent small-fibre function (unmyelinated C-fibres and thinly myelinated A-delta-fibres). Paradoxical heat sensations (PHS), i.e. having a warm sensation when applying a cold stimulus, represent dysfunction of A-delta-cold-fibres. Wind-up ratio (WUR) reflects a frequency dependent increase in excitability of spinal cord neurons and pain. Within stimulus/response-functions mechanical pain sensitivity (MPS) for pinprick stimuli and dynamic mechanical allodynia (ALL) for light tactile stimulators was assessed. All parameters were determined by repeated measurements as outlined within the standardised and validated QST-protocol.

2.3. Questionnaires

Participants subjective pain quality and intensity pain were assessed using the McGill Pain Questionnaire (MPQ; German version).[18] The MPQ consists of pain descriptors that are rated on scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Additionally, an oxaliplatin questionnaire was filled in assessing oxaliplatin specific neurotoxicity.[19] Scores of the questionnaire correspond to neurotoxicity grades (1, 2 = grade 1; 3 = grade 2, 4 = grade 3; 5 = grade 4) in three regions of the body (oral/facial; upper and lower extremity) that were calculated as a ratio of the sum score and the number of available questions for each body region.

2.4. Statistics

All QST data except PHS, CPT, HPT and VDT were transformed logarithmically before statistical analysis.[16] To create a somatosensory profile, mean values of QST parameters were calculated. QST parameters of each subject were transformed into a common z-value using the following equation: $Z\text{-score} = (\text{Value}_{\text{subject}} - \text{Mean}_{\text{controls}})/\text{SD}_{\text{controls}}$ (negative Z-score: loss, positive Z-score: gain in sensation). This procedure results in a QST profile where all parameters are presented as standard normal distributions independent of the original units of measurement. In WinStat 3.1 statistical differences of QST data, Z-scores and demographic data were tested using U-test. $p < 0.05$ was considered to be significant. QST data, demographic data and scores of questionnaires are shown as mean values with standard deviation and range.

3. Results

Nine patients (5 women, 4 men) presented with pain symptoms, all of them reporting cold evoked pain (pain evoked by cold environmental temperature or contact with cold objects, fluids or air). Two of them additionally reported spontaneous pain in both hands. The other 7 patients (6 women, 1 man) did not experience any pain symptoms. All patients received oxaliplatin (50 or 85 mg/m^2) and leucovorin (400 mg/m^2) by intravenous infusion followed by an intravenous bolus of 400 mg/m^2 and infusion of fluorouracil (600 mg/m^2) for gastrointestinal cancer (Table 1). Leucovorin and fluorouracil administrations were repeated at the same dose and schedule on the next day. Cycles were repeated every 2 weeks. Both groups did not differ significantly regarding age, disease duration, days between oxaliplatin treatment and performance of QST, the cumulative oxaliplatin dosage and the number of oxaliplatin administrations, although there is a trend towards a lower number of administrations in the P-group (Table 1).

3.1. Psychophysical parameters

The most frequently used pain descriptors of the MPQ (>33% of patients) in the P-group were tingling (in 9 of 9 patients = 9/9), cold (6/9), freezing (5/9), pricking (5/9), heavy (4/4) and piercing (4/4). The corresponding intensity scores were 2.4 ± 0.7 (1–3), 2.4 ± 0.6 (1–3), 2.3 ± 0.8 (2–3), 2.6 ± 0.6 (2–3), 2.3 ± 1.0 (1–3) and 1.8 ± 0.5 (1–2) indicating moderate to severe

Table 1 – Demographic data of both groups showed no significant differences

Demographics	P-group	Non-P-group	*p*-Value
Age (years)			
Mean	64.6 ± 12.4	61.4 ± 12.0	0.2
Range	44–75	39–74	
Primary site			
Colon	7	6	–
Oesophagus	1	0	–
Gastric	1	1	–
Disease duration (month)	13.0 ± 3.1 (1–26)	10.1 ± 2.8 (2–22)	0.28
Number of oxaliplatin administrations	4.4 ± 1.0 (2–10)	7.7 ± 1.7 (3–13)	0.07
Cumulative oxaliplatin dose (mg)	599.2 ± 176 (200–1530)	745.6 ± 163.9 (223.5–1300)	0.21
Days until QST	2.3 ± 1.7 (1–5)	1.9 ± 0.9 (1–7)	0.17

Mean values are shown with standard distribution and range (in parentheses). Using the *U*-Test $p < 0.05$ was considered to be significant. P-group, pain symptoms present; non-P-group, no pain symptoms present.

symptom intensity. The oxaliplatin questionnaire revealed for the upper extremity a score of 0.9 ± 0.9 (0.2–2.9) for intensity of symptoms and 0.9 ± 0.9 (0.2–3.2) for symptoms affecting daily activities, for the lower extremity 0.3 ± 0.6/0.3 ± 0.7 (0–2.1) and 0.2 ± 0.3/0.2 ± 0.2 (0–0.5) for the oral/facial region, respectively, indicating overall a low grade of oxaliplatin specific neurotoxicity in those patients suffering from pain.

3.2. *Neurological assessment*

Neurological assessment of the vigilance, orientation, coordination, cranial nerves and the upper extremities did not show pathological findings, especially any loss of sensation, decreased muscle tendon reflexes or weakness. At the lower extremity in 4 patients of the P-group and 3 of the non-P-group tendon reflexes were decreased or absent without muscle weakness. One patient in each group showed hypoesthesia to vibration at both malleoli mediales but no further disturbances of sensation.

3.3. *QST*

In comparison to normative data the P-group showed a pathological decrease of the CPT (Z-score: 2.17), i.e. cold hyperalgesia, and of the MPT (Z-score: 2.55), i.e. pin-prick hyperalgesia (Table 2 and Fig. 1). None of the other parameters and none of the parameters of the non-P-group showed pathological values (Table 2). Comparison of both groups revealed a significant lower CPT and MPT, i.e. cold and pin-prick hyperalgesia, lower HPT, i.e. heat hyperalgesia, and higher WDT, i.e. warm hypoesthesia in the P-group (Table 2 and Fig. 1). All other parameters did not show significant differences (Table 2).

4. Discussion

Within this study we were able to show that oxaliplatin-induced acute neuropathy presenting with pain symptoms is characterised by a specific somatosensory profile, i.e. cold and mechanical hyperalgesia. Furthermore, group analysis revealed additional heat hyperalgesia and warm hypoesthesia. Taken together, these findings display sensitisation within the peripheral and central nociceptive system as the underlying mechanisms.

Thermal and mechanical hyperalgesia are well known in the context of neuropathic pain syndromes, like postherpetic neuralgia.[17] Cold and heat hyperalgesia are thought to be caused within the peripheral nervous system by peripheral sensitisation as a result of hyperexcitability of predominantly nociceptive C-fibres following de novo expression of sodium channels or transient receptor potential (TRP) receptors.[17] Peripheral sensitisation leads consecutively to sensitisation of converging nociceptive neurons (WDR-neurons) within the spinal cord causing central sensitisation. Through this, physiological (non-)nociceptive nerve fibres such as A-fibres get access to the WDR-neurons and touching or pricking the skin results in allodynia or hyperalgesia, respectively. These findings correspond to the clinical picture of the patients presented here, all of them reporting cold hyperalgesia. This sign has been recognised as a characteristic sign in acute oxaliplatin neuropathy.[4,5] Moreover, our results resemble the clinical picture of an animal model of oxaliplatin-induced neuropathy.[20] Thus, we propose that oxaliplatin administration causes peripheral and central sensitisations that underlie the symptoms of acute neuropathy.

The question arises how oxaliplatin induces sensitisation. In an animal model of oxaliplatin-induced neuropathy[20] pain symptoms were found to be partly reversible by the administration of ion-channel and transmitter-modulating analgesics, concluding an underlying channelopathy.[20] Neurophysiological studies demonstrated hyperexcitability in peripheral nerves[10,21,22] indicating sodium channel dysfunction. Acute channelopathy of ion channels had been proposed from animal studies,[7] TTX block of oxaliplatin effects[9] and affection of sodium currents by calcium.[8] Furthermore, among others ion channel and transmitter modulating agents like gabapentin, carbamazepine and venlafaxine have been proven to prevent or alleviate acute neuropathy.[5,23,24] Interestingly, anticonvulsants and antidepressants modulate ion channels and transmitters within the peripheral and central nervous system, respectively, and are effective in neuropathic pain.[25]

However, the herein detected somatosensory profile is similar to findings in the human experimental menthol-mod-

Table 2 – Results of quantitative sensory testing (QST)

	P-group			Non-P-group			*p*-Values	
	Absolute values	Log values	Z-scores	Absolute values	Log values	Z-sores	Absolute/log values	Z-scores
CDT	29.6°C ± 1.2 (0.7–3.8)	0.31 ± 0.26	−0.69 ± 1.08	28.7°C ± 2.4 (1.2–8.2)	0.43 ± 0.28	−1.25 ± 1.15	0.30	0.21
WDT	37.9°C ± 4.5 (2.6–16.7)	0.69 ± 0.26	−1.66 ± 1.03	35.5°C +/3.0 (1.6–9.9)	0.45 ± 0.29	−0.74 ± 1.37	**0.03**	**0.04**
TSL	10.2°C ± 5.5 (4.0–19.6)	0.95 ± 0.23	−1.71 ± 0.83	7.4°C ± 3.6 (2.8–12.4)	0.81 ± 0.24	−1.30 ± 0.98	0.18	0.32
CPT	26.3°C ± 3.3 (20.8–30.1)	n.a.	**2.17 ± 0.47**	11.8°C ± 6.5 (0.7–20.9)	n.a.	0.10 ± 0.71	**0.0006**	**0.0004**
HPT	42.4°C ± 4.5 (36.6–49.8)	n.a.	0.75 ± 1.28	45.9 ± 2.7 (42.9–49.8)	n.a.	−0.56 ± 0.68	**0.03**	**0.03**
PHS	0.6 ± 1.1 (0–3)	n.a.	0.5 ± 1.09	0.3 ± 0.8 (0–2)	n.a.	−0.02 ± 0.05	0.32	0.33
MDT	14.2mN ± 17.6 (0.3–55.7)	0.72 ± 0.77	−1.76 ± 1.89	10.8mN ± 16.0 (0.3–45.3)	0.56 ± 0.79	−1.49 ± 2.40	0.28	0.32
MPT	20.1mN ± 27.5 (6.1–90.5)	1.09 ± 0.41	**2.55 ± 1.23**	58.7mN ± 49.9 (12.1–157.6)	1.63 ± 0.38	0.74 ± 0.95	**0.01**	**0.005**
MPS	3.1NRS ± 3.8 (0.2–10.2)	0.10 ± 0.66	0.81 ± 1.46	0.6NRS ± 0.4 (0.1–1.4)	−0.32 ± 0.40	−0.16 ± 0.73	0.20	0.20
ALL	–	n.a.	n.a.	–	n.a.	n.a.	n.a.	n.a.
WUR	2.50 ± 1.40 (1.2–4.8)	0.36 ± 0.21	0.11 ± 0.77	2.60 ± 2.30 (0–6.7)	0.40 ± 0.30	0.18 ± 1.10	0.40	0.43
VDT	7.5 ± 1.0 (7.2–8.0)	n.a.	−0.22 ± 1.89	7.3 ± 0.70 (6.3–8.0)	n.a.	−1.21 ± 1.84	0.13	0.08
PPT	336.3 kPa ± 107.7 (170–507)	2.50 ± 0.15	1.36 ± 1.26	393.3 kPa ± 146.3 (245–618)	2.57 ± 0.16	0.63 ± 1.09	0.28	0.18

Significantly different values of both groups (*p*-values) and pathological values to normative data (Z-scores >/<2) are shown in bold numbers. In the P-group the cold pain (CPT) and mechanical pain thresholds (MPT) were decreased indicating cold hyperalgesia and pin-prick hyperalgesia in comparison to normative data. Comparison of the QST parameters of both groups showed a significant decrease of the CPT, MPT, HPT and increase of the WDT, indicating cold, pin-prick and heat hyperalgesia and warm hypoesthesia in the P-group. All QST data except PHS, CPT, HPT and VDT were transformed logarithmically before statistical analysis[16]. To identify pathological values and determine the somatosensory profile, mean values of QST parameters were calculated and transformed into a common z-value. Using the *U*-test $p < 0.05$ was considered to be significant. P, pain symptoms; non-P, no pain symptoms. °C, degrees Celsius, mN, mille-Newton, NRS, numeric rating scale (0, 'no pain', 10, 'maximum pain that can be imagined'), kPa, kilo Pascal. Mean values ± single standard deviation and range (in parentheses).

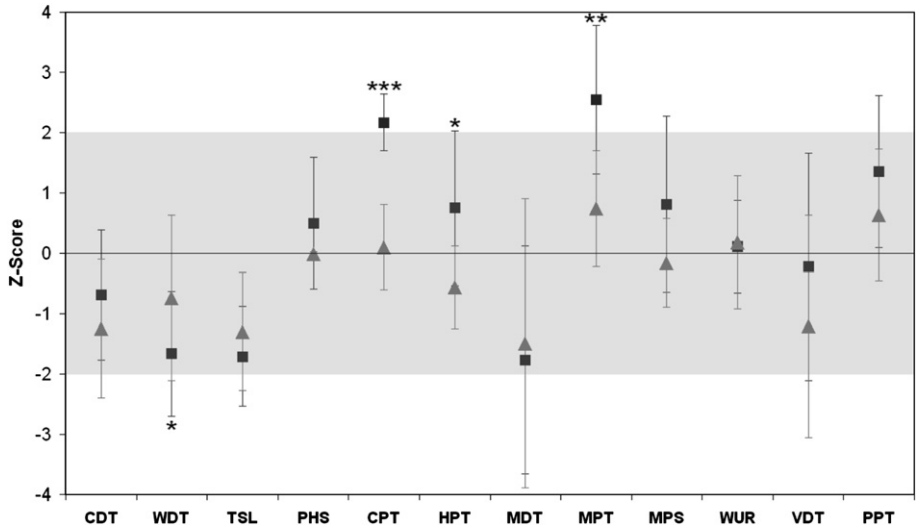

Fig. 1 – Z-score sensory profiles of patients suffering (P-group) and not suffering from pain symptoms (non-P-group) following oxaliplatin therapy. The figure shows the QST profile of 9 patients with (P-group; ■) and 7 patients without pain symptoms (non-P-group; ▲). The profile of patients with pain symptoms shows in comparison to normative data pathologically decreased cold pain (CPT) and mechanical pain thresholds (MPT) indicating cold hyperalgesia and pin-prick hyperalgesia (values outside the 95% confidence interval of the distribution of healthy subjects: outside grey zone; z-score > +2 shows gain of fibre function, z-score < -2 shows loss of fibre function). Comparison of the QST parameters of both groups showed a significant decrease of the CPT, MPT, HPT and increase of the WDT, indicating cold, pin-prick and heat hyperalgesia and warm hypoesthesia (* = <0.05, ** = <0.01, * = <0.001; U-test of Z-scores) in the P-group. Z-score: Numbers of standard deviations between patient data and group-specific mean value. Vertical bars show single standard deviation.**

el of cold (heat and mechanical) hyperalgesia.[26] The underlying mechanism herein is binding of menthol to TRPM8 and TRPA1 receptors on nociceptive cold specific-C-fibres causing acute peripheral and central sensitisation.[24] Thus, it can be speculated whether oxaliplatin modulates or binds to TRP receptors and induces pain.[27] Due to the 'tingling' character of the pain reported it remains unclear to what extent large fibre involvement contributes to symptoms of acute neuropathy.

Predictors of acute oxaliplatin-induced neuropathy are not known besides infusion speed and dosage dependency.[5] Conversely, already developed neuropathy may explain the lack of pain in the non-Pain group, since this group received a (non-significant) higher number of treatment cycles and cumulative dose. Recently, a genetic polymorphism affecting detoxification and predicting chronic oxaliplatin neuropathy[14] has been reported. One may speculate whether genetic polymorphism of sodium channels or TRP receptors can be the reason for developing pain.[28–30] Moreover, low detoxification rates causing relative oxaliplatin accumulation may cause nerve sensitisation.

Summarizing, our study provides evidence that acute oxaliplatin-induced neuropathy with pain symptoms shows a characteristic somatosensory profile consisting of cold, heat and mechanical hyperalgesia indicating sensitisation in the peripheral and central nociceptive system. This strengthens the rationale for treatment of acute oxaliplatin-induced neuropathy with anticonvulsants and antidepressants and foster further research on possible predictors and preventive strategies for pain in cancer therapy.

Conflict of interest statement

The authors disclose any financial interest, relationships or commercial considerations. The sponsors had no influence on the design and conduct of the study, the collection, management, analysis, interpretation of the data or preparation, review or approval of the manuscript.

Acknowledgements

This study was financially supported by DFG (Ba1921), BMBF (01EM0504), the Alexander-von-Humboldt-Foundation, an unrestricted Grant from Pfizer Germany. We thank M. Freyer for her technical assistance.

REFERENCES

1. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *New Engl J Med* 2004;**350**:2343–51.
2. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;**18**:2938–47.
3. Cassidy J, Misset JL. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol* 2002;**29**:11–20.
4. Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol* 1998;**25**:13–22.
5. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. *Ann Pharmacother* 2005;**39**:128–35.

6. Culy CR, Clemett D, Wiseman LR. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000;**60**:895–924.
7. Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F, Lersch C. The chemotherapeutic oxaliplatin alters voltage-gated Na(+) channel kinetics on rat sensory neurons. *Eur J Pharmacol* 2000;**406**:25–32.
8. Grolleau F, Gamelin L, Boisdron-Celle M, Lapied B, Pelhate M, Gamelin E. A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. *J Neurophysiol* 2001;**85**:2293–7.
9. Webster RG, Brain KL, Wilson RH, Grem JL, Vincent A. Oxaliplatin induces hyperexcitability at motor and autonomic neuromuscular junctions through effects on voltage-gated sodium channels. *Br J Pharmacol* 2005;**146**:1027–39.
10. Wilson RH, Lehky T, Thomas RR, Quinn MG, Floeter MK, Grem JL. Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002;**20**:1767–74.
11. Holmes J, Stanko J, Varchenko M, et al. Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. *Toxicol Sci* 1998;**46**:342–51.
12. Cavaletti G, Tredici G, Petruccioli MG, et al. Effects of different schedules of oxaliplatin treatment on the peripheral nervous system of the rat. *Eur J Cancer* 2001;**37**:2457–63.
13. Jamieson SM, Liu J, Connor B, McKeage MJ. Oxaliplatin causes selective atrophy of a subpopulation of dorsal root ganglion neurons without inducing cell loss. *Cancer Chemother Pharmacol* 2005;**56**:391–9.
14. Lecomte T, Landi B, Beaune P, Laurent-Puig P, Loriot MA. Glutathione S-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. *Clin Cancer Res* 2006;**12**:3050–6.
15. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol* 2002;**249**:9–17.
16. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standarized protocol and reference values. *Pain* 2006;**125**:231–43.
17. Baron R. Mechanisms of disease: neuropathic pain – a clinical perspective. *Nat Clin Pract Neurol* 2006;**2**:95–106.
18. Stein C, Mendl G. The German counterpart to McGill Pain Questionnaire. *Pain* 1988;**32**:251–5.
19. Leonard GD, Wright MA, Quinn MG, et al. Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. *BMC Cancer* 2005;**5**:116.
20. Ling B, Authier N, Balayssac D, Eschalier A, Coudore F. Behavioral and pharmacological description of oxaliplatin-induced painful neuropathy in rat. *Pain* 2006;**128**: 225–34.
21. Krishnan AV, Goldstein D, Friedlander M, Kiernan MC. Oxaliplatin-induced neurotoxicity and the development of neuropathy. *Muscle Nerve* 2005;**32**:51–60.
22. Lehky TJ, Leonard GD, Wilson RH, Grem JL, Floeter MK. Oxaliplatin-induced neurotoxicity: acute hyperexcitability and chronic neuropathy. *Muscle Nerve* 2004;**29**: 387–92.
23. Durand JP, Alexandre J, Guillevin L, Goldwasser F. Clinical activity of venlafaxine and topiramate against oxaliplatin-induced disabling permanent neuropathy. *Anticancer Drugs* 2005;**16**:587–91.
24. von Delius S, Eckel F, Wagenpfeil S, et al. Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: final results of a randomised, controlled, multicenter phase II study. *Invest New Drugs* 2007;**25**:173–80.
25. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;**118**:289–305.
26. Wasner G, Schattschneider J, Binder A, Baron R. Topical menthol – a human model for cold pain by activation and sensitization of C nociceptors. *Brain* 2004;**27**:1159–71.
27. Tominaga M, Caterina MJ. Thermosensation and pain. *J Neurobiol* 2004;**61**:3–12.
28. Waxman SG, Dib-Hajj S. Erythermalgia: molecular basis for an inherited pain syndrome. *Trends Mol Med* 2005;**11**:555–62.
29. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006;**444**:894–8.
30. Kim H, Mittal DP, Iadarola MJ, Dionne RA. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *J Med Genet* 2006;**43**:e40.