Is quantitative sensory testing helpful in the management of oxaliplatin neuropathy? a two-year clinical study

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Abbreviations:
ADL
Activity of daily living
CDT
Cold Detection Threshold
NCI-CTCAE
Common Terminology Criteria For Adverse Events From The National Cancer Institute
NPSI
Neuropathic Pain Symptoms Inventory
QST
Quantitative sensory testing
OIPN
Oxaliplatin-induced peripheral neuropathy
WDT
Warm Detection Threshold
MDT
Mechanical Detection Threshold

ABSTRACT

Purpose: To better understand how quantitative sensory testing could help the clinician in the management of oxaliplatin-induced peripheral neuropathy in terms of earlier and more reliable detection, we conducted a two-year prospective study.

Methods: Thermal sensory assessment, tactile sensory assessment, neuropathic pain assessment and adverse events gradation (NCI-CTC) were performed during treatment and 6 months after treatment completion.

Results: 35 patients were enrolled and followed-up during one year. Cold and Warm Detection Thresholds were higher 6 months after treatment completion than at enrollment. Mechanical detection thresholds didn’t change significantly. Neurotoxicity was mostly grade-1, only 18% grade-2 and no grade-3. Grade-2 patients received lower oxaliplatin cumulative dose than grade-1, which reveals effective dose adaptation and grade-2 patients were more likely to develop painful neuropathy.

Conclusion: Thermal thresholds impairment emerges too late to help the clinician in the prophylaxis of neuropathy. Management of OXA-treatment based on NCI-CTC, as currently recommended, remains the best way to detect neuropathy and ensure treatment adaptation.

Introduction

Oxaliplatin is an effective platinum-based cytotoxic drug widely used in oncology since the early 2000s [1,2]. Its effectiveness is recognized in first-line chemotherapy regimens in metastatic colorectal cancer and in adjuvant therapy of several gastrointestinal cancers [3–6]. However, its use is limited by a development of a disabling sensitive neuropathy [7]. Oxaliplatin-induced peripheral neuropathy (OIPN) has a negative association with quality of life and this consideration is a major issue in the case of palliative care cancer [8,9]. It constitutes the second most common cause of dose limitation after hematological adverse effects [7,10]. Detection and characterization of OIPN during treatment remains a critical concern for the oncologist who has to continually evaluate the risk benefit ratio of the treatment. Recommendations for the management of this neuropathy include dose adaptation, use of neuromodulatory agents like duloxetine and patient education [7,11,12]. Evaluation of OIPN is based on the Common Terminology Criteria for Adverse Events from the National Cancer Institute (NCI-CTAE) which is a five-grade severity scale for adverse event grading [12,13].
were applied using a Peltier probe applied to the skin (25 mm wide and (SOMEDIC AB, Hörby, Sweden) and (3) global neuropathic pain as-

Neurological assessment can also include other tests like quantitative sensory testing (QST) such as thermal thresholds assessment, mechanical thresholds assessment or neuropathic pain assessment [14,15]. To better understand how QST could help the clinician in the management of OIPN in terms of earlier and more reliable detection, we conducted LIPIDOXA, a small prospective and monocentric clinical trial.

Methods

Study design: patients, chemotherapy regimen, study time course

LIPIDOXA study, is a prospective, open-label, single group assignment and monocentric clinical trial which was standing at the Department of Oncology at Paris Saint Joseph Hospital (F-75014). This study was prospectively registered at clinicaltrials.gov (NCT02169908) and all data regarding study design are available online. Patients included suffered from cancer at any stages and were treated with oxaliplatin-based regimen. All inclusion criteria are listed in Table 1 and all oxaliplatin-based regimen characteristics are available in supplementary material. The study was conducted according to the Declaration of Helsinki II and obtained approval from the ethics committee of Île-de-France II (CPP Île-de-France II) in May 2014. Written informed consent was provided to the patients before enrollment. Patients were recruited between May 2014 and June 2015 and were assessed before the beginning of the treatment, once a month in the course of oxaliplatin cure which lasted 3 or 6 months and finally 6 months after completion of the treatment; i.e. at 9th or 12th months follow-up.

Clinical assessment of neuropathy

Oxaliplatin-induced peripheral neuropathy was assessed using three complementary tests. These tests were (1) thermal sensory assessment using the MSA Thermal Stimulator (SOMEDIC AB, Hörby, Sweden) [16] (2) tactile sensory assessment using von Frey hairs aesthesiometer [17] (SOMEDIC AB, Hörby, Sweden) and (3) global neuropathic pain assessment using the Neuropathic Pain Symptom Inventory scale (NPSI) [15].

Thermal sensory assessment

Thermal sensory assessment consisted in measuring two parameters using the MSA Thermal Stimulator: Cold Detection Threshold (CDT) and Warm Detection Threshold (WDT) in the thenar. Thermal stimuli were applied using a Peltier probe applied to the skin (25 mm wide and 50 mm high). The probe was set at a baseline temperature of 32 °C and stimulus was delivered at 1 °C/s in both directions to a defined and stable value. Thresholds measurement was based on the method of limits [16]. For Warm and Cold Detection Thresholds, patients were instructed to indicate by clicking on a mouse as soon as they felt a change in temperature. Mean thresholds were calculated using three consecutive measurements, spaced by a random period of 4–10 s.

### Mechanical sensory assessment

Mechanical Detection Threshold (MDT) was measured with a standardized set of seven von Frey hairs that exert forces between 0.63 and 235.4 mN. The contact area of the von Frey hairs with the skin was of uniform shape and size. The calibrated rounded tip avoids sharp edges that would facilitate nociceptor activation (rounded tip, 0.5 mm in diameter) [18,19]. The hairs were repetitively applied perpendicularly to the skin surface on the dorsum of the hand. The threshold value was calculated using the geometric mean of five series of stimuli [20].

### Neuropathic pain assessment

Neuropathic pain symptoms were recorded, and their severity was scored using the Neuropathic Pain Symptom Inventory (NPSI scale), a 11-point (0–10) numerical scale of ten neuropathic symptoms (burning, squeezing, pressure, electric shocks, stabbing, pain evoked by a brush, by pressure or by cold, tingling, pins and needles). The total NPSI score i.e. the sum of individual sub-scores out of 100 was calculated [15].

The severity of neurotoxicity was graded with the National Cancer Institute - Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE) scale. Grade-1 corresponds to paresthesia or loss of deep tendon reflexes; grade-2 corresponds to moderate symptoms, limiting activity of daily living (ADL); grade-3 corresponds to severe symptoms, limiting self-care of ADL [13].

### Statistical analysis

Results were presented as mean ± standard deviation (SD) or standard error of the mean (SEM). Mechanical Detection threshold was transformed logarithmically before analysis. Comparisons were made using Kruskall-Wallis and Wilcoxon test on R software, v.64 bits 3.4.1. p < .05 was considered to be significant.

### Outcomes

The outcomes were the thermal thresholds (CDT, WDT), the mechanical threshold (MDT), the NPSI score and the grade of neurotoxicity (according to the NCI-CTCAE v4.0).

### Results

#### Patients

Between May 2014 and June 2015, 35 patients, 16 women and 19 men, were enrolled in LIPIDOXA study. Patient characteristics are presented in Table 2. The average age was 66.3 ± 10.7 years; ranging from 46 to 89 years. Most patients suffered from colorectal cancer (n = 19, 54%) and were at a metastatic stage (stage IV) (n = 20, 57%). At 6-month follow-up, three patients had been lost, one deceased and two left the clinical trial. The follow-up visits, i.e. 6 months following treatment completion, were performed only in 19 patients. This corresponds to the patients who consulted their practitioner six months after treatment completion as part of their personal medical care.

Thermal detection thresholds and clinical scales were reported for three visits. The baseline visit was stated as a reference since patients were naive from oxaliplatin based treatment. The end of treatment visit corresponded to the last infusion of oxaliplatin and coincided with the onset of the highest acute neuropathy crisis. Finally, the follow-up visit took place approximately six months after treatment completion.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Eligibility criteria of LIPIDOXA study.</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>Patient from the Department of Oncology at Paris Saint Joseph Hospital, male or female, aged over 18.</td>
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<td>Patient suffering from any type of cancer, at any stages (estimated according to the TNM classification)</td>
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<td>Patients treated with oxaliplatin based regimen: FOLFOX, FOLFIRINOX, GEMOX, XELOX, EOX.</td>
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</table>

**Non inclusion criteria**

| Patient with brain or leptomeningeal metastases |  |
| Patient previously treated with cisplatin |  |
| Patient addicted to alcohol |  |
| Diabetic patient with peripheral neurological disorders clinically objectified |  |
| Patient receiving calcium or magnesium salts intravenously |  |
| Patient suffering from peripheral neuropathy clinically objectified |  |
| Patient suffering from psychiatric disorders |  |
| Patient treated with at least one of the following drug (active in neuropathic pain relieve): venlafaxin, carbamazepin, gabapentin, pregabalin, clomipramin, amitriptylin, imipramin, duloxetine. |  |
Data were analyzable. Most patients had grade-1 neurotoxicity 6 months after the beginning of the treatment, which corresponds to the Terminology Criteria for Adverse Events (NCI-CTCAE) scale Evaluation of neurotoxicity with the National Cancer Institute - Common Mean = 4.4/10).

44% reported tingling and prickling pain (questions 11 and 12, gered by contact with a cold object (question 10, mean = 4.3/10), and Among the patients with painful neuropathy, 39% reported pain trig-

Mechanical sensory assessment

Thermal detection thresholds (mean ± SEM)

*Fig. 1. Cold and Warm Detection Thresholds measured at baseline, at the end of treatment and at 6-month follow-up. Values represent mean ± SEM of temperature differences between detection and basal temperatures after a cold (Cold Detection Threshold, CDT) or a warm stimulation (Warm Detection Threshold, WDT) using the MSA Thermal Stimulator device (SOMEDIC AB, Hörby, Sweden) in oxaliplatin-treated patients at baseline (i.e. before treatment) (n = 32), at the end of treatment (n = 24) and at follow-up (i.e. six months after treatment completion) (n = 14). The dark gray bar histogram represents the CDT measured on the thenar. The light gray slanting hatched bar histogram represents the WDT measured on the thenar. The 0-degree line corresponds to the basal temperature of the thermode (i.e. 32 °C).

Cold Detection Thresholds measured at the follow-up visit were higher than CDT measured at the first visit (−3.7 °C vs −2.1 °C, p = .022). Similarly, WDT measured at the follow-up visit were higher than WDT measured at the first visit (3.6 °C vs 2.0 °C, p = .005).

Statistical analysis use Wilcoxon test. * p < .05; ** p < .01.

Table 3
Thermal Detection Thresholds, Mechanical Detection Thresholds and Neuropathic Pain Symptoms Inventory score at baseline, end of treatment and 6 months after treatment completion.

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>End</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>CDT (Δ °C, mean ± SD)</td>
<td>−2.1 ± 1.2</td>
<td>−2.8 ± 2.0</td>
<td>−3.7 ± 2.2</td>
</tr>
<tr>
<td>WDT (Δ °C, mean ± SD)</td>
<td>2.0 ± 1.1</td>
<td>2.9 ± 2.6</td>
<td>3.6 ± 2.5</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>MDT (log mg, mean ± SD)</td>
<td>2.32 ± 0.62</td>
<td>2.22 ± 0.48</td>
<td>2.05 ± 0.21</td>
</tr>
<tr>
<td>NPSI score (mean ± SD)</td>
<td>0</td>
<td>44 ± 19</td>
<td>26 ± 20</td>
</tr>
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</table>

Values represent mean ± SEM of Cold Detection Threshold (CDT), Warm Detection Threshold (WDT) and Mechanical Detection Threshold (MDT) using the Thermotest device and Von Frey Hairs (SOMEDIC AB, Hörby, Sweden). Proportions of neuropathic patients are presented as percentage ± 95%IC and score of the Neuropathic Pain Symptoms Inventory scale (NPSI) is presented as mean ± SD. The effects of the studied population are n = 32 oxaliplatin-treated patients at baseline (i.e. before treatment), n = 24 at the end of treatment and n = 14 at follow-up (i.e. six months after treatment completion).

patients exhibited no neurotoxicity (Grade 0). Patients with grade-2 neurotoxicity received a mean cumulative oxaliplatin dose of 950 mg, patients with grade-1 neurotoxicity received a mean cumulative oxaliplatin dose of 1350 mg and patient with no sign of neurotoxicity received a mean cumulative oxaliplatin dose of 485 mg. Patients with grade-2 neurotoxicity received a dose of oxaliplatin lower than those with grade-1 neurotoxicity (p = .03) and similarly, all three patients

Mechanical sensory assessment

No change in MDT was observed regardless visit: 2.32 ± 0.62; 2.22 ± 0.48; 2.05 ± 0.21; p > .05 at baseline, end of the treatment and follow-up, respectively (Table 3 and supplementary material).

Evaluation of pain with the Neuropathic Pain Symptom Inventory (NPSI) scale

At baseline, no patient presented neuropathic pain. At the end of the treatment, 44% (12/27) of patients had painful neuropathy (positive NPSI score) while at follow-up, they were only 26% (5/19) (Table 3).

Among the patients with painful neuropathy, 39% reported pain trig-

Evaluation of neurotoxicity with the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale

The grade of neurotoxicity (NCI-CTCAE scale) was assessed six months after the beginning of the treatment, which corresponds to the longer follow-up with minimum patient’s loss. At this point, 32 patients’ data were analyzable. Most patients had grade-1 neurotoxicity (n = 23), while 6 patients experienced a grade-2 neurotoxicity and 3

Table 2 Patient demographics (n = 35).

<table>
<thead>
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<th>n (%)</th>
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<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>&lt; 60</td>
<td>8 (23)</td>
</tr>
<tr>
<td>[60–66]</td>
<td>8 (23)</td>
</tr>
<tr>
<td>[67–73]</td>
<td>10 (28)</td>
</tr>
<tr>
<td>≥73</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Primary site of cancer</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Stomach</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Rectum</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Tumor Node Metastasis (TNM) stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (9)</td>
</tr>
<tr>
<td>II</td>
<td>5 (14)</td>
</tr>
<tr>
<td>III</td>
<td>7 (20)</td>
</tr>
<tr>
<td>IV</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Oxaliplatin based regimen</td>
<td></td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>3 (9)</td>
</tr>
<tr>
<td>EOX</td>
<td>1 (3)</td>
</tr>
<tr>
<td>XELOX</td>
<td>1 (3)</td>
</tr>
<tr>
<td>GEMOX</td>
<td>1 (3)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>29 (82)</td>
</tr>
<tr>
<td>IV</td>
<td>20 (57)</td>
</tr>
</tbody>
</table>

No change in MDT was observed regardless visit: 2.32 ± 0.62; 2.22 ± 0.48; 2.05 ± 0.21; p > .05 at baseline, end of the treatment and follow-up, respectively (Table 3 and supplementary material).
with grade-0 neurotoxicity received a lower dose of oxaliplatin than those with grade-1 neurotoxicity ($p = .001$). Results are presented in Fig. 4.

Subset analyzes

In subset analyzes, the patients were retrospectively divided into three subgroups:

1. According to the grade of neurotoxicity (NCI-CTCAE): grade-0, $n = 3$; grade-1, $n = 23$; grade-2, $n = 6$.
2. According to the dose adjustment time: modification of the dose within the three first months ($n = 9$); modification within the three last months, $n = 9$; no modification of the dose ($n = 14$) (Figs. 2 and 3).

(1) Thermal and Mechanical Detection Thresholds didn’t show any difference according to the grade of neurotoxicity ($p > .05$). Regarding NPSI scale results, among patients who developed grade-1 neurotoxicity, 47% (9/19) were painful at the end of the treatment, whereas only 8% (1/12) were painful at follow-up. For grade-2, 60% (3/5) of patients were painful both at the end of treatment and at follow-up. Grade 2 neuropathic patients were more likely to develop painful neuropathy ($p = .05$).

(2) Thermal and Mechanical Detection Thresholds as far as neuropathic pain occurrence didn’t show any relationship with the dose adjustment time ($p > .05$).

Discussion

The present study attempts to assess whether quantitative sensory testing can help the clinician in oxaliplatin-induced peripheral neuropathy management. In this field, thermal sensory assessment, tactile sensory assessment, neuropathic pain assessment and adverse events gradation (NCI-CTC), were performed during treatment and 6 months after treatment completion.

Regarding thermal sensory assessment, Cold and Warm Detection Thresholds were higher six months after completion of the treatment, revealing a hypoesthesia to thermal stimuli [21]. At this visit, chronic neuropathy was clinically present while acute neuropathy was very unlikely to be observed [14]. The few studies dealing with long term follow-up of oxaliplatin treated patients report a delayed onset of chronic OIPN, confirming our results [22]. Brouwers et al. estimated a long half-life recovery of neuropathy in the hands to 6.8 (± 3.1) years [21]. Park et al. highlighted persistence of hypoesthesia two years after the end of the treatment [23]. In the subset analyses, evolution of cold and warm detection thresholds didn’t differ according to the dose adjustment time. But, interestingly, the CDT measured at baseline appeared to be lower in the patients whose treatment was modified earlier than the patients who didn’t experiment change in treatment. This could suggest a greater thermal sensitivity of patients whose treatment was modified earlier because of early neurotoxicity. However, these differences were not significant and there was no relationship between the Cold Detection Threshold measured at the start of treatment and the dose adjustment time (logistic regression performed).

Regarding mechanical sensory assessment, no difference was found between the different visits. The mean MDT values measured during treatment were consistent with those published in previous studies [14]. Interestingly and in the same way as previously, the MDT measured at baseline appeared to be lower in the patients whose treatment was modified earlier than the patients who didn’t experiment change in treatment. Of the same, this could also suggest a greater mechanical sensitivity of patients whose treatment was modified earlier because of early neurotoxicity. But, these differences were not significant and there was no relationship with the dose adjustment time.

For both Cold and Mechanical Detection Threshold, we cannot
The light gray bar histogram represents the CDT measured in the group. Statistical analysis use Wilcoxon test. The medium gray bar histogram represents the CDT measured in the group. The dark gray bar histogram represents the CDT measured in the group. The right slanting hatched bar histogram represents the WDT measured in the group. The horizontal hatched bar histogram represents the WDT measured in the group.

The authors declare no conflicts of interest.

**Conclusion**

Hypoesthesia to thermal stimuli forms a marker of chronic oxaliplatin-induced neuropathy of late onset. This sensory loss worsens even after treatment completion and QST seems to remain useless for the management of oxaliplatin-induced peripheral neuropathy. Management of OIPN based on NCI-CTCAE remains the best way to detect neuropathy and ensure treatment adaptation.

**Conflicts of interest**

The authors declare no conflict of interest.
Mechanical detection thresholds according to dose adjustment (mean ± SEM)

Fig. 3. Mechanical Detection Thresholds measured at baseline, at the end of treatment and at 6-month follow-up according to kinetics of dose adjustment. Values represent mean ± SEM of Mechanical Detection Thresholds (MDT) expressed in log(threshold in milligram). A standardized set of seven von Frey hairs (SOMEDIC AB, Hörby, Sweden) was used. At the end of the study, three groups of patients were established according to the eventual change of dosage at mid-treatment (Change before mid-treatment, Change after mid-treatment and No change). Of the 32 analyzed patients, 9 patients experienced change in treatment before mid-treatment (n = 8 at the end of treatment and n = 5 at follow-up); 9 patients experienced change in treatment after mid-treatment (n = 7 at the end of treatment and n = 6 at follow-up); 14 patients experienced no change in treatment (n = 12 at the end of treatment and n = 6 at follow-up).

Retrospective analysis

The light gray bar histogram represents the MDT measured in the group Change before mid-treatment. The medium gray bar histogram represents the MDT measured in the group Change after mid-treatment. The dark gray bar histogram represents the MDT measured in the group No change.

No differences were found for MDT (Statistical analysis use Wilcoxon test).

which the study LIPIDOXA.

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Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.ctarc.2018.10.002.

References


