Peripheral neurotoxicity of oxaliplatin in combination with 5-fluorouracil (FOLFOX) or capecitabine (XELOX): a prospective evaluation of 150 colorectal cancer patients

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Background: To report our prospective experience on the incidence and pattern of oxaliplatin (OXA)-induced peripheral neuropathy (OXA-IPN) in patients with colorectal cancer (CRC) treated with either FOLFOX-4 or XELOda + OXaliplatin (XELOX).

Patients and methods: One hundred and fifty patients scheduled to be treated with either FOLFOX or XELOX for CRC were prospectively monitored at baseline and followed-up during chemotherapy. The incidence and severity of symptoms secondary to OXA-IPN were recorded using three different types of assessment, i.e. the motor and neurosensory National Cancer Institute common toxicity criteria, version 3.0 (NCI-CTCv3), the clinical version of the

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The OXA-induced peripheral neuropathy (OXA-IPN) is one among the principal dose-limiting toxic effects of OXA treatment plan [9] thus impairing their functional capacity and compromising the consent of OXA 85 mg/m² as a 2-h i.v. infusion (d1), the formal FOLFOX-4 regimen, repeated every 2 weeks, either the FOLFOX or the XELOda + OXaliplatin (XELOX). The incidence of acute neurotoxicity during FOLFOX-4 therapy is similar to XELOX. However, it seems that FOLFOX-4 is more neurotoxic than XELOX in terms of cumulative OXA-IPN, despite comparable OXA cumulative dose.

**Key words:** FOLFOX-4, incidence, oxaliplatin, peripheral neurotoxicity, XELOX

**introduction**

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the Western world [1]. Oxaliplatin (OXA), in combination with either 5-fluorouracil (5-FU) or capecitabine, is widely used in the treatment of CRC, both in the adjuvant and metastatic setting [2–5]. Peripheral neuropathy (PN) is one among the principal dose-limiting toxic effects of OXA [6]. The OXA-induced peripheral neuropathy (OXA-IPN) is manifested with the neuratomyotonia-like acute transient syndrome, which is mainly characterized by cold-induced hyperexcitability phenomena and the cumulative form that is mostly a sensory, axonal neuropathy [7].

The incidence of acute OXA-IPN ranges from 65% to 100%, and the symptoms are usually reversible within hours or days. On the other hand, the cumulative form may affect up to 80% of patients [8]. Severe grade 3 OXA-IPN occurs in up to 30% of patients treated with cumulative doses ranging from 765 to 1020 mg/m², and in 50% of patients treated with higher doses, thus impairing their functional capacity and compromising the treatment plan [9–11].

OXA-based chemotherapy usually used in CRC includes either the FOLFOX or the XELOda + OXaliplatin (XELOX). The formal FOLFOX-4 regimen, repeated every 2 weeks, consists of OXA 85 mg/m² as a 2-h i.v. infusion (d1), concurrent with leucovorin 200 mg/m² (d1&d2), followed by 5-FU 400 mg/m² (d1&d2) as an i.v. bolus and 5-FU 600 mg/m² administered afterwards as a 22-h infusion (d1&d2) [12]. XELOX, also known as CapOx, consists of i.v. OXA 130 mg/m² (d1) followed by oral capecitabine 1000 mg/m² twice daily every 3 weeks [13].

Little is known about which of FOLFOX or XELOX is safer in terms of neurotoxicity. Recently, a retrospective study assessed whether OXA-IPN was more common with CapOx than with FOLFOX-4. However, there were limitations in the study design and the need for prospective studies to evaluate the exact prevalence of OXA-IPN after OXA-based chemotherapy was highlighted [14]. We report our prospective experience on the incidence and features of OXA-IPN in CRC patients treated with FOLFOX-4 or XELOX.

**patients and methods**

**patients’ selection**

The study protocol was approved by the Institutional Review Boards of each site and a written informed consent was obtained from patients before study entry. One hundred and fifty consecutive patients with histologically confirmed CRC (90 men, 60 women; mean age 63.5 ± 8.9 years), scheduled to receive adjuvant or first-line treatment with either FOLFOX-4 or XELOX, were prospectively studied. The allocation to either treatment regimen was made according to treating oncologist’s discretion. Patients were recruited during an 18-month period at four sites in Greece, Italy and Spain. There were no significant differences in the contribution of sites concerning the number of patients treated with FOLFOX-4 or XELOX.

The following were the inclusion criteria: chemotherapy-naive adult patients, satisfactory liver and renal function, life expectancy of at least 9 months and the Karnofsky performance score ≥70. The exclusion criteria included history of PN, co-morbidities, such as diabetes, renal insufficiency, alcohol abuse (>5 IU/day), and any medication that would interfere or complicate the clinical assessments.

**outcome measures**

Aiming at ruling out any evidence of pre-existing neuropathy, all patients were clinically evaluated at baseline (visit 1), which occurred in the vast majority of patients (n = 145) at the time of the screening visit or up to 2 days (n = 5) after the administration of the first chemotherapy course. Despite the rapid induction of symptoms following OXA administration, this assessment window seemed suitable for this baseline assessment, because just one administration of chemotherapy could not change patients’ baseline nerve conduction characteristics and neuropathic chronic OXA-induced symptoms.

Chronic, cumulative OXA-IPN was defined as a clinical syndrome characterized by persistent (at least two subsequent cycles without a ‘symptoms free’ interval), symmetrical distal painful or non-painful paresthesia and dysesthesia; the severity of which was dose-related as it increased with the amount of delivered OXA [6, 7]. Its incidence and severity were graded using the National Cancer Institute common toxicity criteria, version 3.0 (NCI-CTCv3) [15] as also with the clinical version of the Total Neuropathy Score (TNSc). The TNSc is a seven-item composite clinical neuropathy scale that includes symptoms, signs and ability aspects (Table 1) [16–18]. According to the TNSc, OXA-IPN severity was classified as grade 1 (scores 1–7), grade 2 (scores 8–14), grade 3 (scores 15–21) and grade 4 (scores >21) [19].

A simple descriptive questionnaire (a yes/no response format) was used to quantify the frequency of the 11 most common hyperexcitability symptoms associated with the acute OXA-IPN [6], including cold-induced perioral paresthesias; cold-induced pharyngolaryngeal dysesthesia; shortness of breath; swallowing difficulty; laryngospasm; muscle cramps; jaw stiffness; visible fasciculations; voice changes; ptosis and visual field changes. The severity of acute OXA-IPN was scored based on the sum number of symptoms reported by the patients at each clinical assessment.

Neuropsychological examination was carried out unilaterally on the non-dominant side and the widely accepted criteria of the identification of abnormalities were employed to interpret results [20]. The...
elec trophysiological study included motor conduction of common peroneal nerve with measurements of peak-to-baseline amplitude of compound muscle action potential and motor conduction velocity. Sensory conduction of ulnar, radial (orthodromic technique) and sural nerves (antidromic technique and proximal segment) with measurements of peak-to-peak amplitude of sensory action potentials (a-SAPs) and sensory conduction velocities was also recorded.

All the aforementioned baseline evaluations were repeated after 3 and 6 months of therapy, corresponding to 6 and 12 cycles of FOLFOX-4 (OXA total dose, 510 and 1020 mg/m², respectively) and 4 and 8 cycles of XELOX (OXA total dose, 520 and 1040 mg/m², respectively). The last follow-up assessment was carried out within 1 month after the discontinuation of OXA-based chemotherapy. No further follow-ups were formally planned afterwards.

**chemotherapy regimen and dose modification**

Overall, toxic effects were graded using the NCI-CTC, with the exception of OXA-IPN which was also graded with the TNSc. The OXA dose was reduced by 30% for persistent or temporary (at least 14 days) painful paresthesia, dysesthesia or functional impairment. If in spite of the 30% OXA dose reduction the grade 3 neurotoxicity persisted, chemotherapy was omitted in subsequent cycles [21].

**results**

**demographics and baseline characteristics**

FOLFOX-4 was administered to 77 patients (51.3%) and XELOX to 73 patients (48.7%). The demographic and clinical characteristics of the sample size, according to groups, were well balanced. Despite the median single OXA dose being higher in XELOX than in FOLFOX-treated patients, the cumulative OXA doses were similar (Table 2).

**statistical analysis**

Descriptive statistics were generated for all variables. Comparison of categorical data between patients treated with XELOX versus FOLFOX-4 was carried out using the two-sided chi-square tests, while the independent samples t-test was used to reveal between-group differences in continuous data. For within-group comparisons, the changes in mean electrophysiological scores from baseline to subsequent scores were examined using the paired samples t-test. For between-group comparisons, the changes in mean clinical and electrophysiological scores were calculated by subtracting each patient’s baseline value from his/her last value, and were examined using independent samples t-tests. All tests were two-sided and the significance was set at P < 0.05. Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) for Windows (release 17.0; SPSS Inc., Chicago, IL).

**Table 1.** Items making up the clinical version of the total neuropathy score

<table>
<thead>
<tr>
<th>Sensory symptoms</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms</td>
<td>None</td>
<td>Limited to fingers</td>
<td>Extend to ankle or</td>
<td>Expand to knee or</td>
<td>Above knees/elbows</td>
</tr>
<tr>
<td>Autonomic symptoms (n)</td>
<td>0</td>
<td>1</td>
<td>Moderate difficulty</td>
<td>Require help/assistance</td>
<td>Disabled</td>
</tr>
<tr>
<td>Pin sensation</td>
<td>Normal</td>
<td>Reduced in fingers</td>
<td>Reduced up to wrist/ankle</td>
<td>Reduced up to elbow/knee</td>
<td>Reduced above elbow/knee</td>
</tr>
<tr>
<td>Vibration sensibility</td>
<td>Normal</td>
<td>Reduced in fingers</td>
<td>Reduced up to wrist/ankle</td>
<td>Reduced up to elbow/knee</td>
<td>Reduced above elbow/knee</td>
</tr>
<tr>
<td>Strength</td>
<td>Normal</td>
<td>Mild weakness</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Normal</td>
<td>AR reduced</td>
<td>AR absent</td>
<td>AR absent and others reduced</td>
<td>All reflexes absent</td>
</tr>
</tbody>
</table>

AR, ankle reflex; TNSc, total neuropathy score.

**Table 2.** Baseline demographic and disease data in colorectal cancer patients treated with FOLFOX-4 versus XELOX

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOLFOX-4 (n = 77)</th>
<th>XELOX (n = 73)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>34 (44.2%)</td>
<td>26 (35.7%)</td>
<td>0.320</td>
</tr>
<tr>
<td>Males</td>
<td>43 (55.8%)</td>
<td>47 (64.3%)</td>
<td></td>
</tr>
<tr>
<td>Age ± SD (range)</td>
<td>63.3 ± 9.1 (41–83)</td>
<td>63.7 ± 8.8 (38–79)</td>
<td>0.798</td>
</tr>
<tr>
<td>Disease setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>51 (66.3%)</td>
<td>47 (64.3%)</td>
<td>0.865</td>
</tr>
<tr>
<td>Metastatic</td>
<td>26 (33.7%)</td>
<td>26 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbidities related to increased risk of OXA neurotoxicity, e.g. diabetes</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>OXA (mg) single doses per patient</td>
<td>147 (80–190)</td>
<td>220 (138–260)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OXA (mg) cumulative doses per patient</td>
<td>1646 (900–2280)</td>
<td>1634 (848–2280)</td>
<td>0.815</td>
</tr>
</tbody>
</table>

OXA, oxaliplatin; SD, standard deviation.
comparison of OXA-IPN incidence between groups

No statistically significant difference was observed in the incidence of acute OXA-IPN, which was present in 65/77 of FOLFOX-4-treated patients (84.4%) and in 60/73 of patients treated with XELOX (79.5%; P = 0.525). In contrast, FOLFOX-4 was associated with increased incidence of cumulative neurotoxicity compared with XELOX-treated patients (n = 64/77 versus 44/73; chi-square P = 0.002). The OXA cumulative dose was significantly associated with the development of chronic OXA-PN in both the groups (r = 0.254; P = 0.026 for FOLFOX-4 and 0.252; P = 0.031 for XELOX), but it has not influenced the manifestation of acute neurotoxicity during treatment with either regimen.

comparison of OXA-IPN severity between groups

According to the evaluation of acute neurotoxicity intensity at the final follow-up, the median number of symptoms that patients reported was 3 (range 1–7) both in the FOLFOX-4 and in the XELOX group (P = 0.280), and the sum number of acute symptoms was also similar (Table 3). According to NCI-CTCv3, 19/77 patients treated with FOLFOX-4 experienced grade 1 chronic OXA-IPN (24.7%), 37/77 experienced grade 2 (48.1%), while grade 3 was revealed in eight cases (10.4%). Comparatively, XELOX-treated patients had less overall rates of OXA-IPN severities than the FOLFOX-4-treated patients (P < 0.001). The same observation emerged using the TNSc scale, with higher severity of cumulative OXA-IPN in patients treated with FOLFOX-4 than with XELOX. Accordingly, the TNSc mean values were statistically different between groups (7.3 ± 4.4 for FOLFOX versus 5.7 ± 5.4 for XELOX; P = 0.046). Similar results were obtained when only the sensory components of the TNSc (sum score of TNSc item 1 + 4 + 5) were considered (3.9 ± 2.7 for FOLFOX versus 3.0 ± 3.0 for XELOX; P = 0.048). Table 3 shows the incidence and severity of OXA-IPN, according to the study groups.

The severity of cumulative OXA-IPN, as graded with both the NCI-CTCv3 (r = 0.246; P = 0.031) and TNSc (r = 0.228; P = 0.046), strongly correlated with the cumulative OXA dose during FOLFOX-4 treatment. The same significant correlation emerged between the incidence (r = 0.252; P = 0.031) and severity (r = 0.308; P = 0.008) of cumulative OXA-IPN during XELOX treatment.

Concerning the impact of neurotoxicity on the capability of completing the chemotherapy as per protocol, severe acute OXA-IPN required prolongation of OXA infusion from 2 to 4–6 h in 13/77 patients (16.9%) treated with FOLFOX-4 and in 17/73 (23.2%) patients treated with XELOX (P = 0.482). However, none of the patients needed dose reduction or discontinued treatment due to persistent (over 2 weeks) grade 3 acute neurotoxicity. On the contrary, six and two patients in the FOLFOX-4 group needed dose reduction and early withdrawal, respectively, because of grade 3 chronic neurotoxicity. Similar rates of dose reduction or treatment discontinuation were observed in the XELOX group.

comparison of clinical neurological data between groups

Regardless of the type of chemotherapy, the vast majority of patients experiencing acute OXA-IPN manifested cold-induced perioral (98.4% versus 89.3%, respectively, for FOLFOX-4 and XELOX groups) or pharyngolaryngeal dysesthesias (98.3% versus 91.7%, respectively). Other less common symptoms were equally recorded in both the treatment groups.

The clinical characteristics of cumulative OXA-IPN were similar between groups, mostly with distal numbness and/or painful paresthesia limited to fingers/toes or in a stocking-and-glove distribution. Clinical examination disclosed proprioceptive sensory disturbances and ankle hyporeflexia or areflexia.

comparison of neurophysiological data both within and between groups

Within-group comparison revealed a significant longitudinal deterioration (baseline to subsequent scores) in the a-SAPs of all three sensory nerves tested. The comparison of motor and sensory conduction variables failed to reach significance in both the treatment groups. Between-group comparisons of a-SAP median changes at baseline versus at the end of treatment did not reveal significant differences, with the exception of radial nerve a-SAP, which however should be attributed to the significantly different baseline values between groups.

Electrophysiological data from baseline to subsequent scores within and between treatment groups are described in Table 4. Clinical variables such as treatment setting, age and gender did not influence the electrophysiological results. To demonstrate this, Figure 1 shows subgroup analysis of sural a-SAP median changes in relation to the treatment setting (adjuvant versus metastatic) in patients treated with either FOLFOX-4 or XELOX.
**discussion**

A temporary dysfunction of voltage-gated sodium channels in the nerve membrane through a pathway involving calcium ions is considered the pathogenic hallmark of the OXA-induced acute, transient cold-induced neurotoxicity [22, 23]. Temperature is considered a strong triggering factor of acute OXA-IPN. Specifically, cooling is able to significantly affect sodium channel kinetics, thus predisposing to ectopic activity and induction of cold-induced hyperexcitability phenomena [23, 24].

On the other hand, the cumulative sensory neuropathy is attributed to the direct neurotoxic damage of sensory neurons in the dorsal root ganglion from OXA accumulation [24–26]. Notwithstanding often reversible, this cumulative neurotoxicity may be extremely clinically relevant, in particular for those patients who are potentially cured from CRC and receive OXA as adjuvant treatment.

There are few published studies attempting to directly compare the potential of FOLFOX with XELOX to induce OXA-IPN [14, 27]. As such, a prospective study providing a detailed description of OXA-IPN incidence and features in a large, homogeneous cohort of patients treated with FOLFOX or XELOX is needed.

Our main result was that FOLFOX and XELOX did not differ in terms of incidence and severity of acute neurotoxicity. This finding compares well with those emerging from NO16966, where no difference was found in terms of neurotoxicity between the two regimens [28]. The rate of our patients manifesting acute OXA-IPN after the administration of either FOLFOX (84.4%) or XELOX (79.5%) is similar to that previously reported in large trials [13, 29]. Again, with the limitation of an inter-trial comparison, similar rates of neurotoxicity were reported in the adjuvant treatment trials MOSAIC (FOLFOX-4), NSABP C-08 (mFOLFOX-6) and NO16968 (XELOX) [2, 30, 31].

The cumulative OXA dose was strongly associated with an increased and more severe chronic neurotoxicity regardless of regimen, but it may be both more common and severe with FOLFOX than with XELOX, when it was assessed with the NCI-CTC and TNSc. This finding might suggest a role for the companion fluoropyrimidine, with a major involvement of 5-FU in the development of cumulative OXA-IPN. However, neurotoxicity is a very rare complication of both 5-FU and capecitabine therapy [32, 33], and it seems more plausible that the different neurotoxicity profile should be due to the different OXA schedule in the two combinations. Nevertheless, one could assume that XELOX might be more neurotoxic than FOLFOX, because of the higher, although less frequent OXA dose. However, based on our results, it seems that this is not the case and more frequent exposure to FOLFOX every two weeks, regardless of the dose, significantly increases both the development and severity of OXA-IPN. In fact, the efficacy of the ‘Stop-and-Go’ concept against OXA-IPN might support the latter hypothesis [34]. This intervention uses the predictability and reversibility of neurological symptoms, to aim at delivering intensified and repeated short courses of

**Table 4.** Changes in the mean electrophysiological scores from baseline to subsequent scores within and between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Intermediate follow-up</th>
<th>Last follow-up</th>
<th>p*</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ulnar a-SAP (μV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td>15.3 ± 7.6</td>
<td>13.4 ± 7.1</td>
<td>6.4 ± 4.9</td>
<td>&lt;0.001</td>
<td>0.202</td>
</tr>
<tr>
<td>XELOX</td>
<td>13.0 ± 7.4</td>
<td>9.9 ± 4.8</td>
<td>5.6 ± 4.3</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Radial a-SAP (μV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td>19.1 ± 9.4</td>
<td>15.6 ± 9.1</td>
<td>8.2 ± 6.1</td>
<td>&lt;0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>XELOX</td>
<td>13.6 ± 7.8</td>
<td>10.7 ± 5.4</td>
<td>6.2 ± 5.3</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Sural a-SAP (μV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td>13.0 ± 5.1</td>
<td>10.1 ± 3.9</td>
<td>6.1 ± 5.1</td>
<td>&lt;0.001</td>
<td>0.867</td>
</tr>
<tr>
<td>XELOX</td>
<td>13.7 ± 4.6</td>
<td>10.4 ± 4.3</td>
<td>6.9 ± 6.2</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Per/al a-CMAP (mV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td>6.4 ± 3.1</td>
<td>6.1 ± 3.0</td>
<td>6.3 ± 2.9</td>
<td>0.5</td>
<td>0.314</td>
</tr>
<tr>
<td>XELOX</td>
<td>5.0 ± 2.3</td>
<td>4.8 ± 2.4</td>
<td>4.8 ± 2.3</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td><strong>Per/al MCV (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td>47.7 ± 4.7</td>
<td>46.3 ± 3.5</td>
<td>46.8 ± 3.7</td>
<td>0.08</td>
<td>0.920</td>
</tr>
<tr>
<td>XELOX</td>
<td>48.1 ± 3.6</td>
<td>46.8 ± 2.5</td>
<td>47.9 ± 3.3</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

*a*-SAP, amplitude of sensory action potential; a-CMAP, amplitude of compound muscle action potential; MCV, motor conduction velocity; Per/al, peroneal.

*p* -value (paired samples *t*-test) refers to changes in the mean electrophysiological scores from baseline to subsequent scores occurring within groups.

**p** -value (independent samples *t*-test) refers to changes in the mean electrophysiological scores from baseline to subsequent scores occurring between groups.

![Figure 1](image-url) Within-group comparison revealed a significant longitudinal deterioration (baseline to subsequent scores) in the sural nerve amplitude of sensory action potential (a-SAP) median changes, which remained independent from the disease setting (adjuvant versus metastatic).
FOLFOX (lowering OXA dose intensity and increasing cumulative dose but prolonging intervals) as long as the therapy is still effective [35].

Our results contradict the conclusions made by Storey et al. on a recently published retrospective series of 188 CRC patients who received XELOX, whereas the incidence of acute PN with XELOX was comparable with that on FOLFOX (historical control), but chronic neurotoxicity appeared to be more common with XELOX [14]. By contrast, our results agree with those of a recent prospective non-randomized study of patients treated with either FOLFOX or XELOX where severe OXA-IPN, as assessed with NCI-CTCv3, was significantly higher in patients treated with FOLFOX than with XELOX [27]. Unfortunately, no data on chronic OXA-PN from randomized clinical trials are available, as even when a randomization between FOLFOX and XELOX was present (as in NO16966 and AVANT trial), a formal assessment of late neurotoxicity was not planned. Moreover, follow-up patient series focused on OXA-IPN evaluation are scarce. The long-term prospective assessment of chronic OXA-IPN after the chemotherapy discontinuation is ongoing in our patients in order to ascertain its course and reversibility in adjuvant patients years after treatment and in metastatic patients when second-line therapy is started.

We report that 83.1% of FOLFOX-treated patients experienced cumulative OXA-IPN, whereas a significantly lower rate (60.3%) was disclosed in XELOX-treated patients. Data on the incidence of cumulative OXA-IPN greatly vary, with reports ranging between 50% and 80% [8, 10, 29, 36]. As in several previous publications, the majority of patients treated with either FOLFOX or XELOX experienced grade 1 or 2 cumulative OXA-IPN [2, 12, 13]. In the current setting, the incidence of grade 1 neurotoxicity was higher with FOLFOX than with XELOX when it was assessed with NCI-CTCv3, but the incidence of grades 2 and 3 was almost similar. However, when the TNSc was also taken into account, grade 2 cumulative OXA-IPN was also more frequent in FOLFOX-treated patients.

In our study, grade 3 neurotoxicity, according to NCI-CTC, was observed in 10.4% and 12.3% of FOLFOX- and XELOX-treated patients, respectively, whereas similar rates were recorded when the TNSc had been considered. One could argue that the difference observed was mostly for low-grade OXA-IPN. However, even grade 1 and 2 neurotoxicities have an important impact on patients’ daily life activities and quality of life [6]. In any case, the reported rate of grade 3 neurotoxicity in our study is similar to that previously reported in the MOSAIC trial and elsewhere [2, 10]. However, worth mentioning is the great heterogeneity between different trials, with studies reporting either a much lower [9, 36] or higher neurotoxicity rate [13, 37].

To assure a reliable and objective interpretation of our results and to bypass the difficulties in distinguishing between NCI-CTC grade 2 and 3 cumulative OXA-IPN, we have applied the TNSc, already shown to be reliable for assessing the chemotherapy-induced peripheral neuropathy (CIPN) in comparison with NCI-CTCv2. Moreover, it has a much larger range of values (0–28) than the common oncology toxicity scales, and thus higher sensitivity to CIPN changes [16–18]. Still, one could argue that the use of the NCI-CTC and perhaps also the acute symptom scale might also have induced bias, because data on OXA-IPN are preferably reported by patients using Likert-type scales. We decided not to use a Likert-type scale, because of the several confounding factors present in patients with cancer, whereas the acute OXA toxicity scale, although not validated, could be interpreted as a patient-oriented questionnaire.

A limitation of this trial is that it was not randomized, thus introducing an element of bias. Nevertheless, we believe that our findings should be taken into account in the everyday clinical oncology practice. Our two groups of patients were well balanced with regard to risk factors for developing OXA-IPN, whereas our series is among the largest to be exclusively focused on prospectively determining the incidence, severity and characteristics of OXA-IPN in chemotherapy-naïve CRC patients treated with FOLFOX-4 or XELOX.

In summary, for the first time a large homogeneous CRC population had been prospectively studied during OXA-based chemotherapy, thus allowing us to closely monitor the incidence of phenomenon. We have shown that both regimens demonstrated equally acute neurotoxicity profiles. However, XELOX may be the preferable regimen to avoid a significant cumulative neurotoxicity associated with FOLFOX. Subsequent, more refined, studies are needed to further address the important clinical question of whether FOLFOX-4 or XELOX is safer in terms of neurotoxicity.

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**disclosure**

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**references**


