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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Rechallenge with oxaliplatin and peripheral neuropathy in colorectal cancer patients

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Abstract

Background Oxaliplatin (OXA) is a cornerstone in the treatment of colorectal cancer (CRC). Retreatment with OXA is frequently considered as salvage treatment. OXA-induced neuropathy (OIN) is the most frequent and feared long-term side effect.

Patients and methods CRC patients receiving at least twice OXA-based chemotherapy lines at our institution between June 2000 and July 2016 were reviewed. The aim of this study was to investigate whether retreatment with OXA increases the risk of developing new or worsening previous neuropathy. OIN was assessed by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI), Total Neuropathy Score© (TNS) and nerve-conduction studies.

Results 106 patients were included in the analysis. Median age at OXA-based retreatment was 61.5 (20–83) years. After the first OXA-based chemotherapy treatment, 63.4% of patients developed OIN, 30.7 and 8.9% grades 2 and 3, respectively, after a median of 11 (1–17) cycles. After 30 (11–90) months of median to retreatment with a median of 8 (1–14) OXA cycles, 39.6, 22.6, and 0% of patients developed grade 1, 2, and 3 OIN, respectively. Worsening of the previous OIN was observed in one-third (31.1%) of all patients. OXA-cumulative dose was independently associated with greater risk of worsening OIN ($p < 0.001$). Non-significant trend towards higher TNSc© scores after retreatment was observed [5 (0–11) vs 6 (3–13), $p = 0.083$].

Conclusion Retreatment with OXA in CRC patients is a feasible option even in patients who previously developed moderate or severe OIN. One-third of patients' OIN was worsened by retreatment. Neurological monitoring should be considered.

Keywords Oxaliplatin · FOLFOX · Retreatment · Oxaliplatin-induced neuropathy · Neurotoxicity

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Abbreviations

OXA	Oxaliplatin
CRC	Colorectal cancer
OIN	Oxaliplatin-induced neuropathy
PN	Peripheral neuropathy
NCI	National Cancer Institute-common toxicity criteria for adverse events
TNS	Total Neuropathy Score©
5-FU	5-fluorouracil
FOLFOX	OXA and 5-FU with leucovorin
XELOX	OXA and oral capecitabine
EGFR	Epidermal growth factor receptor
NCS	Nerve-conduction studies
SNAP	Sensory nerve action potentials
CMAP	Compound muscle action potential
DM	Diabetes mellitus

Introduction

Oxaliplatin (OXA), a platinum analogue, is widely used in the treatment of patients with colorectal cancer (CRC) in both the adjuvant and in the metastatic setting. At present, combination schedules of infusional OXA and 5-fluorouracil (5-FU) with leucovorin (FOLFOX) or oral capecitabine (XELOX) represent standard options in the treatment of CRC (Cassidy et al. 2008; Rothenberg et al. 2003). OXA has a good tolerability profile with most common side effects like myelosuppression, nausea or vomiting that are usually easy to handle and reversible (Cassidy et al. 2002). However, OXA-induced peripheral neuropathy (OIN) is a highly frequent and not always reversible adverse event which can result in dose reduction or premature cessation of treatment, representing a dose-limiting side effect, that negatively impacts in the patients' quality of life (Argyriou et al. 2008; Mols et al. 2013; Raphael et al. 2017).

OIN can present as two different clinical syndromes: the acute and the chronic form. The incidence of acute syndrome is very high, ranging from 65 to 100%. The most frequent and typical syndrome is characterized by cold-induced distal or perioral paresthesias and pharyngolaryngeal dysesthesias. Acute symptoms related to OXA administration are characterized by their early onset, appearing during or immediately after infusion of OXA. These symptoms are usually reversible within hours or few days in most of patients. On the other hand, the chronic form is a cumulative neuropathy that can affect up to 80% of patients (Velasco and Bruna 2014; Velasco et al. 2014; André et al. 2004, 2009). Chronic OIN is characterized by distal paresthesias and numbness in the extremities in stocking-and-glove distribution, resulting in sensory ataxia and functional impairment. Motor nerves remain free from damage, although fine motor skills can be impaired because of sensory deficits (Velasco and Bruna 2014). Chronic OIN is dose-limiting and usually manifests during the last cycles or even just after finishing OXA-based treatment (Velasco et al. 2010). Despite overall evolution is usually favorable and OIN tends to improve, recovery usually takes years and is frequently incomplete (Kokotis et al. 2016), especially for those patients affected by more severe forms (Briani et al. 2014).

Retreatment with OXA-based chemotherapy is an emerging option in many patients with CRC tumor progression and initial sensitivity to OXA, widely proven to be clinically beneficial (Tournigand et al. 2006; Chibaudel et al. 2009; de Gramont et al. 2007, 2009; Costa et al. 2017). However, information regarding safety in terms of neurotoxicity with this approach is very scarce. Up to our knowledge, evidence is limited to only one retrospective study including 29 advanced CRC patients treated with different schedules including OXA (Maindrault-Goebel et al. 2004), and one phase II clinical trial including 33 patients (Suenaga et al. 2015). In both, OIN was exclusively assessed by oncological toxicity scales and the lack of specific neurological assessment is highlighted.

The aim of this single-center retrospective clinical study was to investigate whether retreatment with OXA increases the risk of developing or worsening previous OIN in a large cohort of CRC patients. Data from detailed neurological and neurophysiological monitoring in a subgroup of retreated patients are first reported.

Patients and methods

All CRC patients who had received OXA-based chemotherapy treatment between June 2000 and July 2016 at Hospital Universitari de Bellvitge-Institut Català d´Oncologia were reviewed. The registry of patients was provided by the pharmacy service of our hospital. The whole patients who had received at least one cycle of OXA after one previous line with OXA-based chemotherapy schedule finished at least 6 months before were reviewed. Only patients in whom OIN before and after retreatment had been recorded, were included in the analysis. In all selected patients demographic data, type of OXA schedule, number of OXA cycles, dates of first and last cycle, cumulative OXA dose, dose reductions or discontinuation of OXA treatment due to the neurotoxicity and evidence of OIN were obtained from medical records, such as in the first line as in OXA retreatment. Schedules of treatment were defined as follows (Cassidy et al. 2004; de Gramont et al. 2002): FOLFOX-4 or 6 modified, consisting in OXA 85 mg/m^2 infusion in day 1 combined with leucovorin and 5-FU, in a 2-week cycle; XELOX, consisting in intravenous OXA 130 mg/m^2 on day 1 followed by oral capecitabine twice daily every 3 weeks or raltitrexed plus oxaliplatin. Concurrent treatment with bevacizumab or anti-epidermal growth factor receptor (EGFR) as cetuximab or panitumumab was recorded.

OIN was graded according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI) (Velasco et al. 2014). The worst grades of peripheral neuropathy (PN) reached after finishing first line, before and after OXA retreatment were considered. Neurological examination was registered according to the clinical version of the Total Neuropathy Score© (TNSc©) which is a seven-item composite clinical neuropathy scale that includes symptoms, signs and ability aspects validated as a useful instrument for measuring the severity of the chemotherapy-induced neurotoxicity during (Velasco et al. 2014; Cavaletti et al. 2007) and after (Cavaletti et al. 2013) treatment. The worst TNSc© after first line with OXA and before OXA retreatment was recorded. Conventional motor and sensory

nerve-conduction studies (NCS) were registered whenever performed. All electrophysiological studies were carried out on a Synergy (Carefusion, San Diego, California) electromyography machine, as standard practice at our institution. Sensory conduction was evaluated in ulnar, radial and sural nerves (antidromic technique) by measuring the amplitude of sensory nerve action potentials (SNAP) and sensory conduction velocity. Motor conduction was tested in median and peroneal nerves with measurements of amplitude of compound muscle action potential (CMAP) and motor conduction velocity. Electrodiagnostic tests were performed at constant temperature. NCS results were compared with normative age-matched reference data from each laboratory (Velasco et al. 2014).

Written informed consent was considered not necessary for the study, as it was a retrospective analysis of our daily routine practice. The data of the patients were anonymized for the purposes of this analysis. The confidential information of the patients was protected according to the national normative. This manuscript has been revised for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital.

Statistical analysis

Descriptive data analysis presented categorical variables as observed counts and weighted percentages, and continuous variables as mean or median with the corresponding standard deviation or range, depending on the nature of the variable. Chi square test was used for identifying differences among OIN severity groups. Wilcoxon test was used to compare TNSc, NCI scores and NCS before and after finishing OXA retreatment. To identify the independent variables associated to the risk of worsening (including new development) OIN, a multivariate logistic binary regression analysis introducing in a backward stepwise method the following variables (sex, age, DM, and OXA-cumulative dose) were performed. All calculations were performed using SPSS software package version 18.0 (SPSS Inc., Chicago, III) and p values < 0.05 were considered significant.

Results

Baseline

From June 2000 to July 2016, 1622 CRC patients received at least one cycle of OXA-based chemotherapy at our institution. Rechallenge with OXA was considered in 125 (7.7%) out of all CRC patients, mostly (77.6%) within the period between 2010 and 2016. Demographic and clinical data were available from 106 patients, which have been summarized in Table 1.

Table 1 Demographic and clinical characteristics before oxaliplatin retreatment ($n = 106$)

Variable	*n* (%)
Gender	
Male	75 (70.8)
Female	31 (29.2)
Age, years	61.5 [20–83]
DM	26 (24.5)
Schedule	
FOLFOX4	53 (50)
FOLFOX6	40 (37.7)
XELOX	10 (9.4)
TOMOX	3 (2.8)
Neuropathy according to NCI	
Absent neuropathy	62 (58.5)
Grade 1	35 (33)
Grade 2	9 (8.5)
Grade 3	0 (0)
TNSc ($n = 30$)	5 [0–11]
Number of cycles OXA	11 [1–17]
OXA-cumulative dose, mg[a]	1487.08 ± 444.04
OXA-free interval, months	30 [11–90]

Results are expressed as median [range]

DM diabetes mellitus, *OXA* oxaliplatin, *FOLFOX* 5-fluorouracil, leucovorin and oxaliplatin, *FOLFOX 6* FOLFOX 6 modified, *XELOX* capecitabine and oxaliplatin, *TOMOX* raltitrexed and oxaliplatin NCI, grade of neuropathy according to National Cancer Institute-Common Toxicity Criteria for Adverse Events [range 0–4], *TNSc* total neuropathy score, clinical version [range 0–28]

[a]Mean (SD)

First OXA-based chemotherapy treatment

At first-line OXA-based chemotherapy, most of patients were men (70.8%) and median age was 61.50 [range 20–83] years. One quarter (24.5%) of patients had diabetes mellitus (DM). According NCI, the great majority (63.4%) of patients developed some degree of OIN. Severities of PN are summarized in Table 2. Before rechallenge with OXA, frequencies of OIN according NCI were grade 1 and grade 2 in 33 and 8.5%, respectively. Some degree of improvement of OIN after first-line OXA treatment was observed in half of patients. One-third of patients who developed OIN had experienced complete recovery of PN according NCI. Most of patients (58.5%) were considered not having OIN at this time point by treating oncologist (Table 1). No differences in the severity ($<$ or $\geq$ grade 2 PN) in regard to concurrent treatment with bevacizumab or cetuximab or panitumumab was observed.

Table 2 Oxaliplatin-induced neuropathy after first, second and third line

	First		Second		Third	
	n (*n* = 106)	%	*n* (*n* = 106)	%	*n* (*n* = 14)	%
Schedule						
FOLFOX4	53	50	2	1.9	0	0
FOLFOX6	40	37.7	87	82.1	12	85.7
XELOX	10	9.4	12	11.3	1	7.1
TOMOX	3	2.8	5	4.7	1	7.1
OXA cycles	11 [1–17]		8 [1–14]		5.5 [2–12]	
Cumulative dose OXA (mg)*	1487.08 ± 444.04		1105.16 ± 545.76		950 ± 558.96	
Neuropathy						
None	37	36.6	40	37.7	6	54.5
Grade 1	24	23.8	42	39.6	4	36.4
Grade 2	31	30.7	24	22.6	1	9.1
Grade 3	9	8.9	0	0	0	0
Unknown	5				3	

Results are expressed as median [range]

OXA oxaliplatin, *FOLFOX* 5-fluorouracil, leucovorin and oxaliplatin, *FOLFOX 6* FOLFOX 6 modified, *XELOX* capecitabine and oxaliplatin, *TOMOX* raltitrexed and oxaliplatin, *NCI* grade of neuropathy according to National Cancer Institute-Common Toxicity Criteria for Adverse Events, range 0–4

*Mean (SD)

Retreatment

Most of retreated patients ($n = 55$, 51.9%) received OXA at least 2 years after finishing first-line OXA-based chemotherapy treatment. After OXA rechallenge, more than one-third of patients (37.7%) did not develop PN, whereas 39.6 and 22.6% had grade 1 and 2 OIN, respectively. No patient developed severe or grade 3 PN. At rechallenge, patients received a less number of cycles [8 (1–14) vs 11 (1–17), $p < 0.001$] and less OXA-cumulative dose (1105.16 ± 545.76 vs 1487.08 ± 444.04 mg, $p < 0.001$). Twenty-six patients (24.53%) received lower dose of OXA from the beginning of retreatment, whereas in the majority, therapy was initiated at standard doses. Overall, incidence of moderate–severe PN (≥ grade 2) was significantly lower after OXA retreatment than after first line OXA-based chemotherapy treatment (22.6 vs 39.6%, $p = 0.006$). Worsening of preexisting PN after OXA retreatment was observed in one-third (31.1%) of patients, whereas the majority (68.9%) of patients remained within the same grade of PN than before retreatment. Among those patients without PN after first-line OXA-based chemotherapy ($n = 37$), nine (24.3%) and six (16.2%) patients developed grade 1 and 2 OIN, respectively, after a median of 7 [1–13] OXA cycles. When comparing patients who presented or not worsening of PN, we observed a higher rate of worsening among those patients without/grade 1 PN compared to those who developed grade 2/3 after first-line OXA treatment (39.3 vs 20%, $p = 0.041$). No patient with grade 2 PN at initiating rechallenge presented worsening of PN during retreatment. In multivariate analysis, age, gender, and DM, were not associated with the risk to worsening previous OIN at rechallenge. However, the cumulated dose of OXA was the only factor with a significant independent influence on worsening OIN (odds ratio: 1.003; confidence interval 95%:1.001–1.005; $p = 0.004$). During the course of OXA retreatment, the main reason for stopping treatment was disease progression ($n = 33$, 31.1%). No differences in the rate of suspension of OXA due to OIN between the first-line and retreatment were observed (19.8 vs 15.2%, $p = 0.317$). In the group of patients who received at least 11 OXA cycles at retreatment ($n = 34$), at comparable OXA-cumulative dose (1515.79 ± 466.46 mg vs 1709.36 ± 275.57 mg, $p = 0.108$) between first and OXA retreatment, we did not observe differences in the rates of PN after first and OXA retreatment. Among the nine patients who developed grade 3 neuropathy after the first treatment, three received 12 cycles of OXA without worsening preexisting OIN in two.

Fourteen (13.2%) CRC patients of our series received at least three lines with OXA-based chemotherapy treatment. The median OXA-free interval between second and third line of OXA-based chemotherapy was 17 [range 6–40] months. Rates of PN, median cycles and cumulative dose are detailed in Table 2. No significant differences in the rates of PN according NCI after second and after third OXA-based treatment were observed. The reason for stopping prematurely OXA was OIN in one patient, whereas in five, it was because of progression of the disease. In other patients, the reason was hematotoxicity ($n = 1$), allergic reaction ($n = 1$),

decision of patient ($n=1$) or previous to palliative surgery ($n=1$). Three (2.8%) patients received 4 lines of OXA-based treatment. In 2 of them, treatment was stopped because of persistent grade 2 OIN. Noteworthy, one patient received four lines of OXA-based chemotherapy (40 cycles and 5718 mg of cumulative dose) without developing chronic OIN.

Neurological monitoring

In a subgroup of patients ($n=30$), who received 9 [2–13] cycles of OXA and 1192 ± 536.3 cumulated OXA at rechallenge, a detailed neurological assessment by TNSc© and NCS, whenever possible, before and after OXA retreatment was performed (Table 3). TNSc after retreatment was not available in six patients: two died and four patients were lost follow-up during retreatment. We observed a non-significant trend towards higher TNSc© scores after retreatment [5 (0–11) vs 6 (3–13), $p=0.083$]. We did not observed differences in the amplitude of SNAP of sural or radial, and CMAP of peroneal nerves when comparing before and after retreatment with OXA (Fig. 1).

Discussion

Chronic OIN is known to be a toxic cumulative neuropathy (Velasco and Bruna 2014; Velasco et al. 2014), so one would expect that additional cycles of OXA-based chemotherapy would entail a greater risk of PN. In the present study, we observed that most of patients who were retreated with OXA (68.9%) did not worsen of previous OIN, and even that some patients (37.7%) remained free of PN after receiving a second line of treatment with OXA-based chemotherapy up to a median of eight OXA cycles. To our knowledge, our data represent the larger study and the first including detailed neurological assessment which would further support previous evidences (Maindrault-Goebel et al. 2004; Suenaga et al. 2015) about the safety of administering additional OXA schedules in terms of neurotoxicity in CRC population. Importantly, our study illustrates a more heavily retreated population than previously reported studies that included a median of six (Maindrault-Goebel et al. 2004) or five (Suenaga et al. 2015) cycles and lesser cumulated doses (Maindrault-Goebel et al. 2014; Suenaga et al. 2015).

Prevalence of OIN after first-line treatment in our series was similar and in line with that published in the literature (Velasco et al. 2014; André et al. 2004, 2009; Park et al. 2009). Rate of recovery of PN after first OXA-based chemotherapy treatment was also in line with the literature (Briani et al. 2014). Incidences of moderate–severe (grades 2 and 3) PN after OXA rechallenge were significantly lower than after first-line OXA treatment. Noteworthy, no severe (grade 3) PN was observed after OXA rechallenge. The lesser incidence of moderate–severe PN observed in our study is related to the lower total cumulated dose and less number of OXA cycles that CRC patients received at retreatment. OIN is well known a dose-related peripheral neurotoxicity (Cassidy et al. 2002; Argyriou et al. 2008; Velasco and Bruna 2014). According to multivariate analysis in our study patients receiving higher dose of OXA had greater risk of worsening previous PN. However and intriguingly, the group of patients more heavily retreated, those who received at least 11 cycles at retreatment, did not present higher severity of PN, what could be related to the small size of the sample or in differences in the rate of recovery from PN before retreatment. Overall, it should be highlighted that at rechallenge patients received a median of cycles and a cumulative dose of OXA enough to develop PN, which is known to be present even after completing half of FOLFOX or XELOX schedules (Velasco et al. 2014) what one could expect adding to the previous damage.

Why patients displaying previous PN did not worsen more noticeably despite receiving additional OXA remains speculative. One could hypothesize that this fact could be related to the limited ability of oncologic scales for capturing the ongoing neuropathy in those patients affected from previous moderate–severe PN. Certainly, all patients who worsened of PN had absent or grade 1 PN after first-line OXA treatment. In this line, the specific neurological objective assessment addressed in a subgroup of patients by the TNSc© showing a trend in worsening TNS scores along OXA retreatment could suggest an increasing underlying neurotoxicity and be statistically limited by the small size of the monitored sample.

Nevertheless and importantly, in one-third of patients worsening of preexisting neuropathy after OXA retreatment was observed. According to this, neurological monitoring with TNS should be considered in CRC patients candidates to OXA retreatment to ensure the safety of this approach. As indicated above, the TNS is a composite scale that includes symptoms, clinical signs and neurophysiologic parameters and several studies have demonstrated to give a more accurate assessment of the extent, severity and longitudinal neurological impairment (Velasco et al. 2014; Cornblath et al. 1999; Frigeni et al. 2011), becoming the recommended tool for chemotherapy-induced peripheral neuropathy (CIPN) (Terpos et al. 2015). The TNS "clinical" version (TNSc), based exclusively on the clinical items, revealed similar accuracy in CIPN scoring in longitudinal studies to the original TNS (Cavaletti et al. 2006) with the advantage that TNSc assessment can be completed in about five minutes without requiring any instrumental.

The main limitation of our study is its retrospective nature, what does not allow us to exclude that some patients with grade 1 PN could have been misclassified as absent

Table 3 Clinical and neurophysiological characteristics of patients neurologically monitored

Pt	Sex/age	First OXA				Second OXA				Before retreatment					After retreatment				
		Schedule	Cycles (n)	OXA (mg)	NCI	Interval (m)	Schedule	Cycles (n)	OXA (mg)	NCI	TNSc	Sural (μV)	Radial (μV)	CPE (mV)	NCI	TNSc	Sural (μV)	Radial (μV)	CPE (mV)
1	M/64	FOX 4	12	1756	2	23	FOX 6	12	1860	1	5	1.10	5.10	2.20	2	7	3.8	3.9	6.9
2	M/64	FOX 4	11	1632	2	32	FOX 6-B	3	363	1	7	–	–	–	1	4	–	–	–
3	F/53	FOX 4-C	12	1380	2	28	FOX 6-B	9	777	2	7	–	19.9	2.4	2	–	–	–	–
4	F/28	FOX 6	12	1632	2	23	FOX 6-B	8	1128	1	6	–	–	–	1	8	–	–	–
5	M/60	FOX 4	11	1684	3	57	FOX 6-B	12	1557	2	7	7.40	8.9	8.60	1	–	–	–	–
6	M/55	FOX 6	12	1884	2	37	FOX 6	12	1884	1	4	4.70	5.50	7.80	1	5	6.00	15.10	8.20
7	F/57	FOX 4	11	1518	3	60	FOX 6-B	5	759	2	11	0.63	6.30	2.90	2	–	–	–	–
8	M/45	FOX 4	12	1994	3	50	FOX 6	12	2004	1	7	0.66	3.60	9.30	1	6			
9	M/60	FOX 6	12	1770	2	12	FOX 6	6	1020	2	6	–	–	–	2	6	–	–	–
10	F/56	FOX 4	12	–	2	23	FOX 6	12	–	1	5	–	–	–	2	7	–	–	–
11	M/33	FOX 4	11	1612	2	22	FOX 6	8	1416	2	9	0.46	2.80	4.60	2	–	–	–	–
12	F/69	FOX 6	8	1101	1	45	FOX 6	6	924	1	3	–	–	–	0	–	–	–	–
13	M/50	FOX 4	11	1859	2	85	FOX 6	2	366	1	7	1.80	4.80	2.00	1	9	–	–	–
14	M/71	FOX 4	11	1705	2	41	FOX 6	5	600	1	5	0.05	9.50	5.40	1	5	–	–	–
15	F/54	FOX 6-B	7	1166	1	10	FOX 6	5	782	1	5	1.10	20.10	1.50	1	3	1.90	20.10	1.30
16	M/58	FOX 4	12	1653	2	25	FOX 6	3	474	2	10	8.60	15.50	9.40	2	10	–	–	–
17	M/57	XELOX	5	870	2	29	FOX 6	4	576	2	8	–	–	–	2	9	–	–	–
18	M/56	FOX 6	8	1256	2	10	FOX 6	5	825	1	6	5.50	12.60	5.90	1	4	3.80	9.10	5.90
19	F/67	FOX 6	8	976	3	43	FOX 6	12	1445	1	4	3.80	25.80	1.80	2	5	–	–	–
20	M/46	FOX 4	11	1793	1	19	FOX 6	5	815	1	4	3.00	5.80	3.80	1	3	–	–	–
21	M/49	FOX 4	8	1352	2	44	FOX 6	10	1134	1	3	–	–	–	1	5	–	–	–
22	F/41	FOX 6	8	1216	1	19	FOX 6	12	1464	1	3	6.00	29.40	4.30	1	5	–	23.40	5.10
23	M/63	FOX 6	11	1200	2	39	FOX 6	8	904	1	4	6.50	–	7.10	1	5	–	–	–
24	M/34	FOX 6	9	1188	0	15	FOX6-B	9	1192	1	2	6.10	14.40	7.50	2	7	2.8	4.6	5.7
25	M/66	FOX 4	12	1740	1	27	FOX 6	7	1099	2	11	0	2.00	1.90	2	7	–	–	–
26	M/59	FOX 4	8	1272	0	29	FOX 6	12	1901	0	0				2	13	1.50	12.20	4.20
27	M/40	FOX 4	11	1707	2	39	FOX 6	9	1170	1	4	3.50	9.30	6.00	2	12	1.60	7.50	6.90
28	M/49	FOX 4	8	1432	0	16	FOX 6	12	2196	1	4	0.99	28.30	4.60	2	9	0	7.90	3.90
29	M/53	FOX 6	12	2076	2	28	FOX 6	10	986	1	4	8.20	12.00	12.40	1	4	–	–	–
30	F/59	FOX 4	11	1612	1	46	FOX 6	12	1788	0	0	–	–	–	1	–	–	–	–

M male, *F* female, Age in years, *m* months, *OXA* oxaliplatin, *FOX* FOLFOX (5-fluorouracil, leucovorin and oxaliplatin), *FOX6* FOLFOX 6 modified, *XELOX* capecitabine and oxaliplatin, *C* cetuximab, *B* bevacizumab, *NCI* grade of neuropathy according to National Cancer Institute-Common Toxicity Criteria for Adverse Events, range 1–4 (0: absent neuropathy), *TNSc* total neuropathy score, clinical versiona, range 0–28, *Sural* amplitude of sensory nerve action potential (μV), *Radial* amplitude of sensory nerve action potential (μV), *CPE, common peroneal nerve* amplitude of compound muscle action potential over extensor digitorum brevis (mV)

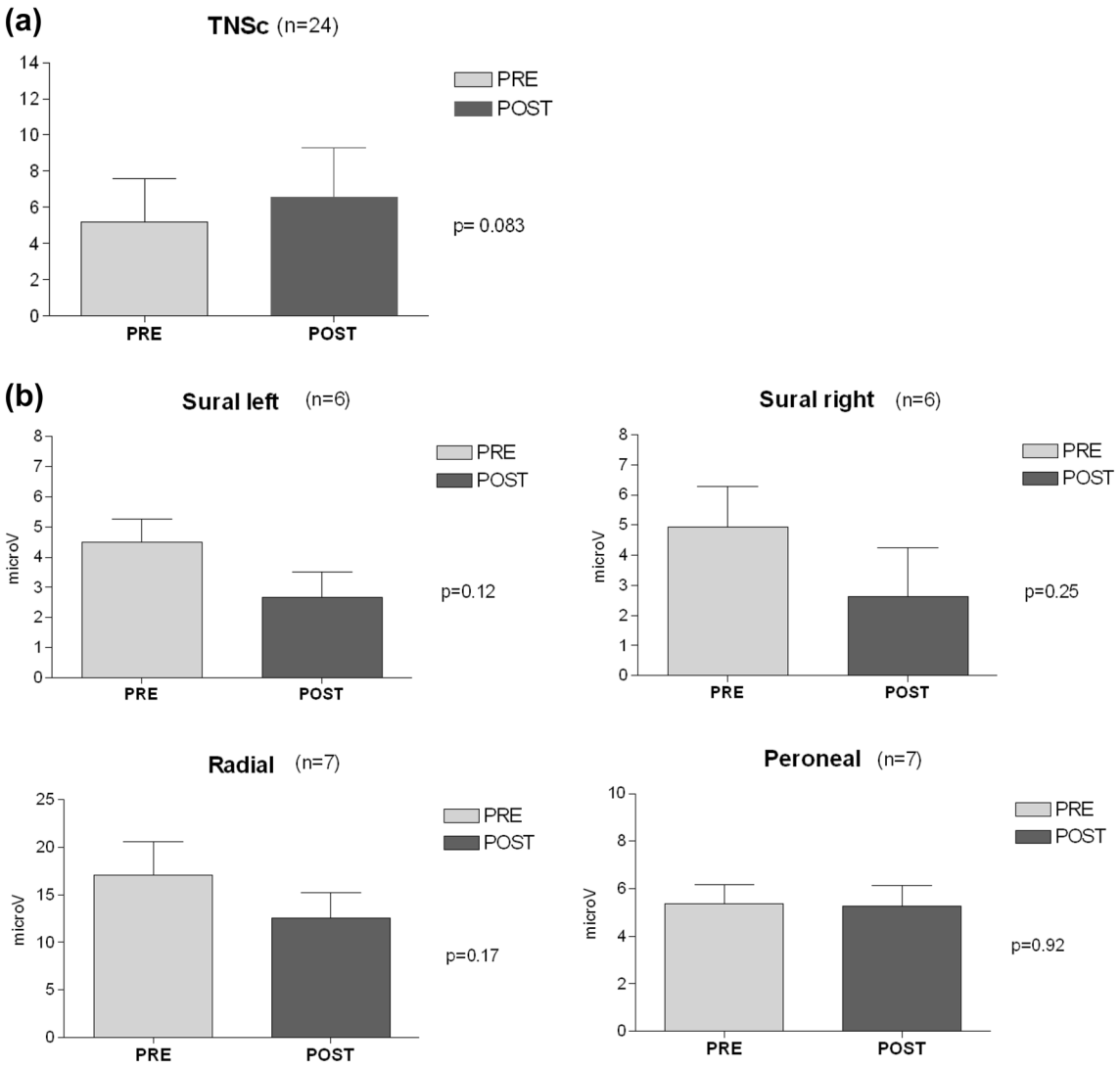

Fig. 1 Neurological scores (TNSc (**a**)) and nerve-conduction studies results (NCS (**b**)) obtained before (PRE) and after (POST) finishing retreatment with oxaliplatin. Results are expressed as mean ± SD

neuropathy, mainly because its asymptomatic nature. However, nearly, one-third of the whole patients had a detailed prospective neurological assessment performed. Unfortunately, a limited number of patients of our study had NCS performed, what would have been desirable to better explore the evolution of PN on this setting and could be underlying the lack of observed differences along treatment. Nevertheless, the disturbing nature of this test and the palliative nature of this treatment explain why NCS were occasionally done in our study. In addition, a selection bias could not be excluded. All patients monitored by neurologist during OXA retreatment were probably representing the most affected population, who were referred because of oncologist's fear about the risk of neurotoxicity. However, this potential a priori "negative" bias selection would represent the best evidence for considering treating patients with OXA again despite their previous negative experience with the agent due to PN. Further larger prospective studies including specific neurological assessment are needed to clarify the issues mentioned above.

Conclusion

Retreatment with OXA in CRC patients is a feasible option to be considered even in patients who developed moderate or severe OXA-induced neuropathy previously. Despite lack of worsening of previous PN is observed in many patients at retreatment, the OXA cumulated dose remains a significant independent risk factor for OIN development in this setting. Therefore, neurological monitoring of patients candidates to retreatment with OXA should be recommended.

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Compliance with ethical standards

Conflict of interest Sarah Besora declares that she has no conflict of interest. Cristina Santos declares that she has no conflict of interest. Cristina Izquierdo declares that she has no conflict of interest. Maria Mercedes Martinez-Villacampa declares that she has no conflict of interest. Jordi Bruna declares that he has no conflict of interest. Roser Velasco declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was considered not necessary for the study, as it was a retrospective analysis of our daily routine practice.

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