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REVIEW ARTICLE

A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration

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Abstract
Purpose The aim of this study was to systematically review the literature on the influence of oxaliplatin administration (e.g. cumulative dose, dose intensity, number of cycles and combination regimen) on the long-term prevalence of oxaliplatin-induced peripheral neuropathy (O-IPN) at least 12 months after termination of chemotherapy.
Methods A computerized search of literature on databases PubMed and Cochrane was performed. Published original articles were included if they reported about long-term O-IPN and gave concomitant information about oxaliplatin therapy given to the patients. All articles were assessed for quality.
Results We included 14 articles (n=3,869 patients), and the majority of these studies were of high quality. All included patients who were treated for colorectal cancer, mainly with oxaliplatin in combination with 5-fluorouracil/leucovorin. Median cumulative doses and dose intensity varied between 676 and 1,449 mg/m^2 and 30.8 and 42.6 mg/m^2/week, respectively. Neuropathy assessment differed between studies, and the National Cancer Institute-Common Terminology Criteria (NCI-CTC) was used most often. The degree of neuropathy ranged from grade 0 to 3. Only six studies directly assessed the relationship between oxaliplatin administration and neuropathy. Of these studies, five did find a relation between neuropathy and higher cumulative dose, while one study did not find a relation.
Conclusions O-IPN is still present in a great amount of patients in ≥12 months after termination of therapy. A higher cumulative dose is likely to have an influence on the development of long-term O-IPN. More studies are needed that assess long-term neuropathy and oxaliplatin administration by means of validated neuropathy assessments.

Keywords Cancer · Chronic · Chemotherapy · Neurotoxicity · Oxaliplatin · Peripheral neuropathy

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Introduction

The platinum compound oxaliplatin is a widely used cytostatic agent which has proven to be effective in various solid tumours, mainly among colorectal cancer (CRC). Oxaliplatin, first successfully used for the management of advanced CRC, is nowadays also the regimen of choice for adjuvant treatment of patients with curative resected node-positive colon cancer [1–5]. Unlike cisplatin, it causes no nephrotoxicity and only mild haematological toxicity, but oxaliplatin-induced peripheral neuropathy (O-IPN) on the contrary is the most common dose-limiting side effect of oxaliplatin [1, 2, 5–8]. The mechanism by which neuropathy is induced is unclear. Several trials have suggested that oxaliplatin accumulates in the dorsal root ganglia and produces axonal hyperexcitability and repetitive discharges due to changes in voltage-dependent Na^+ channels [8–11].

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Oxaliplatin is known to cause two different types of neuropathy: acute and chronic neuropathy. Acute neuropathy (e.g. distal paresthesias, dysaesthesias and mild muscle contractions of hands, feet and perioral region) is mainly cold triggered, occurs in approximately 90 % of patients and reverses characteristically within a week [12, 13]. In addition, chronic cumulative O-IPN persists between and after treatment, and severe O-IPN resolves in approximately 13 weeks after treatment in the majority of patients [13]. However, a significant proportion of patients still experience chronic neuropathy after more than a year which may have a negative influence on patients' quality of life (QOL) [6, 14–17]. For instance, a population-based study among CRC survivors (n=1,643) showed that long-term chemotherapy-induced peripheral neuropathy (CIPN) was negatively associated with QOL 2–11 years after diagnosis [16]. Furthermore, a well-conducted recent study also demonstrated that O-IPN impacts emotional and physical well-being and QOL years after treatment [17]. In addition, a recently conducted systematic review concerning CIPN and QOL states that CIPN may negatively influence QOL.

It is acknowledged that the degree of O-IPN is dependent on cumulative dose, duration of administration and dose intensity [6, 8, 18, 19]. Nonetheless, this knowledge is mainly based on studies concerning the development of acute neuropathy [1, 2, 5] instead of studies reporting about chronic neuropathy more than a year after treatment. Therefore, the influence of oxaliplatin administration on the development of chronic neuropathy remains unclear. Although a recent study by Vatandoust et al. advocated that persistent grades 2 and 3 O-IPN was more common in patients who received a cumulative dose of more than 900 mg/m^2, suggesting influence of oxaliplatin administration on long-term O-IPN [20]. This interesting study correctly states that there is an increasing need to understand this long-term side effect.

Oxaliplatin is commonly regarded as the standard therapy in adjuvant and palliative chemotherapy regimens, and since the survival of CRC increases, the management of long-term side effects is becoming more important. Because there is no well-accepted proven therapy or neuroprotective strategy for O-IPN, it is very important to determine the influence of oxaliplatin administration on the development of this chronic neuropathy as it may have consequences in clinical decision making. Therefore, our aim is to review studies that report about the influence of oxaliplatin administration (e.g. cumulative dose, dose intensity, number of cycles and combination regimen) on the prevalence and course of O-IPN at least 12 months after cessation of oxaliplatin.

Methods

Search strategy

A computerized search of the literature through the search engines PubMed and Cochrane was performed using the terms 'oxaliplatin' AND 'chemotherapy' AND 'neuropathy' OR 'neurotoxicity' OR 'oxaliplatin-induced neuropathy' AND 'long term' OR 'prospective' OR 'retrospective' OR 'follow up'. References of all identified articles were checked for other relevant publications, which had not been identified through the computerized search.

Selection criteria

Studies that met the following criteria were included: (1) if O-IPN was assessed among cancer patients treated with oxaliplatin after a follow-up time of at least 12 months, (2) if information about oxaliplatin administration was available (e.g. treatment schedule, total cumulative dose and dose intensity), (3) if the publication was an original study (e.g. no review, poster abstracts, editorials, letters to the editor, etc.), (4) if they were published in peer-reviewed journals and (5) if they were written in English. Studies were excluded for the following reason: (1) if they investigated a therapeutic option or preventive strategy for O-IPN.

The described inclusion and exclusion criteria were applied to our initial 244 hits. These studies were conducted between 2003 and 2012. After careful review, 14 articles fulfilled our selection criteria and were included in this review [3, 6, 7, 21–31]. A flowchart of this selection procedure is shown in Fig. 1.

Quality assessment

All included articles were assessed for methodological quality with a 12-item checklist of predefined criteria by two

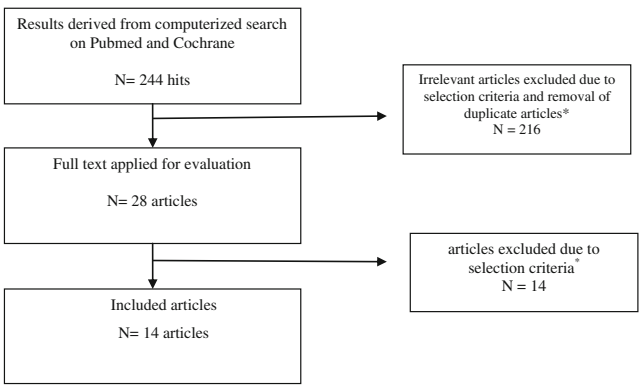

Fig. 1 Flowchart of the selection procedure. *Asterisk* indicates that the selection criteria are described in the "Methods" section

investigators (TB and FM). The checklist was based on items of recognized criteria lists for systematic reviews [32, 33] and on items which were considered to be relevant for the aim of our study. The checklist is presented in Table 1.

Each item of a selected study that matched our criteria received one point. If an item did not correspond to our criteria or was mentioned insufficiently, no points were assigned. Studies of 'high quality' were arbitrarily considered to score 75 % or more of the maximum achievable score (≥9). Studies of 'adequate quality' were considered to achieve a score between 50 and 75 % (six to eight points), and studies with a score of less than six points were classified as 'low quality'. Therefore, the highest achievable score was 12 points. Disagreements between the two reviewers were solved through discussion in a consensus meeting.

Table 1 List of criteria for assessing the methodological quality of studies concerning the prevalence of long-term oxaliplatin-induced peripheral neuropathy and relation to oxaliplatin administration

Positive if with respect to
Outcomes
1. Oxaliplatin-induced neuropathy is assessed according to the NCI-CTC criteria or by a neuropathy questionnaire
2. A neuropathy exam (e.g. neurophysiological assessment) is performed (at time of follow-up >12 months)
3. A description of at least two variables of oxaliplatin administration is given (e.g. oxaliplatin regime, cumulative doses, dose intensity, median number of cycles)
Study population
4. A description is included of at least two baseline variables (e.g. cancer, stage, age, sex) of participants
5. Inclusion and/or exclusion criteria are described
6. Insight in time of CIPN measurement and number of patients assessed at those time points
7. Information is given about the degree of selection of sample (e.g. information is given about the ratio respondents versus non-respondents after at least 12 months)
Study design
8. The study size consists of at least 50 participants (arbitrarily chosen)
9. The data is prospectively gathered
10. The process of data collection is described (no points were assigned if it was only report that NCI-CTC was recorded without mentioning by whom and how)
Results
11. The results are compared between two groups or more (e.g. different chemotherapy treatment, different cumulative doses, different time of assessment, etc.)
12. Relationship between long-term neuropathy and oxaliplatin administration is described

CIPN chemotherapy-induced peripheral neuropathy, *NCI-CTC* National Cancer Institute-Common Terminology Criteria

Results

Study characteristics

The 14 studies included were conducted between 2003 and 2012 (Table 2). The included number of oxaliplatin-treated patients (n=3,869) varied from 16 patients [6] to 2,710 patients [21]. Patients in all studies were treated with oxaliplatin for stage II or III [3, 21, 23–25, 27, 28, 30, 31] or stage IV [6, 7, 25, 26, 29, 31] CRC. However, an Italian study also included 15 patients with gastric cancer [30]. Generally, oxaliplatin was administered in combination with 5-fluorouracil/leucovorin (5-FU/LV) [3, 6, 7, 21, 23–30]. Furthermore, combination therapy with capecitabine was given in two studies [25, 31], oxaliplatin monotherapy was administered in one study [26], and the exact oxaliplatin regimen was not clear in one study [22]. Available median cumulative doses varied between 676 mg/m^2 [23, 24, 27] and 1,449 mg/m^2 [6], and dose intensity varied between 30.8 mg/m^2/week [23, 24, 27] and 42.6 mg/m^2/week [30]. Predominantly, neuropathy was assessed according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) [3, 6, 21, 24, 25, 27–31], but it was also assessed with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity (FACT/GOG-Ntx) questionnaire [23, 24], a neuropathic symptom questionnaire [22], or neurophysiological examination (e.g. nerve conduction studies) [6, 7, 22, 25]. Time of neuropathy assessment varied between 12 months [6, 21, 28, 31] and 8 years [27].

Quality assessment

The quality scores ranged from 5 to 11 points (Table 2). Ten studies were of high quality, three studies were of adequate quality, and one study was considered to be of low quality according the checklist.

Long-term neurotoxicity and oxaliplatin administration in phase III trials

Two phase III trials, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, comparing 5-FU/LV with or without oxaliplatin (FOLFOX) in patients with CRC stage II or III, reported about the development of chronic O-IPN and oxaliplatin doses and dose intensity. The high-quality MOSAIC trial (n=976 oxaliplatin-treated patients) showed neuropathy symptoms of any grade among 24.1 % and grade 3 neuropathy symptoms in 0.7 % of the oxaliplatin-treated patients after 18 months [3]. In addition, after 48 months, grades 1, 2 and

Table 2 Characteristics of the included studies (n=14) and assessed study quality

Author	Patients with oxaliplatin[a] (n)	Design	Oxaliplatin schedule	Dose intensity (mg/m^2/week)	Cumulative doses (mg/m^2) (mean; range)	Study quality
Allegra [21]	2,710	Prospective	FOLFOX (85 mg/m^2 once every 2 weeks for 12 doses with or without bevacizumab)	41.6–40.5	850–880	9
André [3]	1,108	Prospective	FOLFOX (85 mg/m^2 every 2 weeks)	34.2	810	9
Brouwers [22]	25	Cross-sectional	NR (however, in combination with calcium and magnesium)	NR	878 (585–1,170)	8
Kidwell [23]	353/92	Cross-sectional/ longitudinal	FOLFOX (85 mg/m^2 every 2 weeks)	30.8	676 (320–763)	10
Krishnan [6]	16	Prospective	FOLFOX (100 mg/m^2 every 2 weeks, median 8 cycles)	NR	1,449 (380–2,989)	9
Land [24]	189	Cross-sectional	FOLFOX (85 mg/m^2 every 2 weeks)	30.8	676 (320–763)	10
Lee [28]	159	Prospective	FOLFOX (85 mg/m^2 every 2 weeks, for 12 cycles)	35.7	NR (median 12 cycles)	9
Matsumoto [29]	112	Retrospective	FOLFOX (85 mg/m^2 once every 2 weeks)	34.5	NR (median 8 cycles)	9
Park [25]	24	Prospective	85 mg/m^2 FOLFOX4 regime, 100 mg/m^2 (with the FOLFOX6 regimen) or 130 mg/m^2 XELOX regime	NR	800 (574–1,160)	11
Petrioli [30]	64	Prospective	FOLFOX (85 mg/m^2 with arm A infusion in 6 h and arm B infusion in 2 h)	42.6–40.2	NR	9
Pietrangeli [7]	31	Prospective	FOLFOX (25 mg/m^2 5 days every 3 weeks or 4 days every 2 weeks for 12 courses)	37.5	1,222 (1,000–1,340)	8
Storey [31]	188	Retrospective	XELOX (130 mg/m^2 on day 1 every 3 weeks for 8 or 6 cycles)	NR	702 (130–1,040)	8
Rothenberg [26]	308	Prospective	Single-arm oxaliplatin (85 mg/m^2 once in 2 weeks), FOLFOX4 (85 mg/m^2 every 2 weeks)	42.3–37.3	Median number of 3 cycles (1–18)	8
Yothers [27]	1,200	Cross-sectional	FOLFOX (85 mg/m^2 every 2 weeks)	30.8	676 (320–763)	5

FOLFOX fluorouracil/leucovorin/oxaliplatin, *NR* not reported, *XELOX* capecitabine/oxaliplatin

[a] Number of patients treated with oxaliplatin within the studies

3 neuropathy was observed in 11.9, 2.8 and 0.7 %, respectively. The median cumulative dose received in this trial was 810 mg/m^2 (9.5 cycles), and dose intensity was 34.2 mg/m^2/week. Furthermore, the NSABP C-07 trial, in which oxaliplatin-treated patients (n=1,200) received a median cumulative dose of 676 mg/m^2 (dose intensity 30.8 mg/m^2/week) [34], showed that 8 years after oxaliplatin treatment, overall 30.4 % of the patients experienced ≥grade 2 neurosensory toxicity. However, the time of O-IPN assessment was unclear, and the study was considered to be of low quality according to our checklist [27]. Furthermore, a high-quality sub-study of the NSABP C-07 trial [24] (n=189 oxaliplatin-treated patients) showed a mean clinical difference with worse scores on the FACT/GOG-Ntx in 31 % of the patients (p=0.016), and 13.9 % of oxaliplatin-treated patients still experienced numbness and tingling in their feet after 18 months. Besides, 10 % of the oxaliplatin-treated patients still had unresolved neurotoxicity at 27 months of follow-up. Moreover, a high-quality long-term survivorship study (LTS-01), designed by the NSABP, reported that oxaliplatin-treated patients (n=92) did not have significant greater total neurotoxicity scores than 5-FU/LV-treated patients after 7 years [23]. Another high-quality NSABP C-08 trial (n=2,710), FOLFOX with or without bevacizumab in stage II or III CRC patients with a median cumulative dose of oxaliplatin of 850–880 mg/m^2, demonstrated grade ≥2 sensory neuropathy in 26.1 vs. 32.4 % (p<0.01) in the FOLFOX and FOLFOX/bevacizumab arm, respectively, after 12 months [21]. Moreover, interim 5-year data from an American trial of adequate quality showed grades 3 and 4 cumulative peripheral neuropathy in 2 and 3 % of metastatic CRC patients treated with oxaliplatin monotherapy (n=153, dose intensity of 99.6 %) or oxaliplatin in combination with 5-FU/LV (n=150, dose intensity of 87.8 %). However, it is not clear when this cumulative neuropathy was assessed [26].

Long-term neurotoxicity and oxaliplatin administration in other studies

Although the other eight studies were not based on phase III trials, they described long-term O-IPN in combination with information about oxaliplatin administration. Two were retrospective, five of them had a prospective design, and one had a cross-sectional design. Of these studies, six [6, 7, 22, 25, 29, 31] did directly assess the association of oxaliplatin administration on O-IPN (Table 3).

The largest non-phase III studies which directly assessed the influence of oxaliplatin administration on the development of O-IPN were of retrospective design. Firstly, a retrospective high-quality Asian study showed persistent neuropathy after 12, 15 and 18 months among patients with advanced CRC (n=112). Also, grade 2 neuropathy was more often experienced in patients who had received more than 10 cycles of FOLFOX (cumulative dose of >850 mg/m^2) without a break in comparison with cumulative dose of >850 mg/m^2 with a break between cycles [29]. The other retrospective study of adequate quality [31] (n=188) showed that 28 % of patients had persistent neuropathy with impaired function in 7 % of patients after 12 months. Besides, neuropathy was associated with a higher median cumulative doses of 834 mg/m^2 in symptomatic vs. 702 mg/m^2 in the asymptomatic patients [31].

Two prospective studies of high quality and one prospective study of adequate quality reported the association between oxaliplatin administration and long-term O-IPN. An Australian prospective study reported persistent neuropathic symptoms in 79.2 % of oxaliplatin-treated patients (n=24) and loss of sensory amplitude in both upper and lower limbs at a median follow-up of 25 months after treatment with median cumulative oxaliplatin doses of 800 mg/m^2 [25]. Cumulative dose was a significant predictor of the development of neuropathy [25]. Another Australian high-quality prospective study, with a small sample size (n=16), showed that eight of the 16 patients developed chronic neuropathy after cessation of oxaliplatin and that all symptomatic patients received a cumulative dose of more than 1,200 mg/m^2 [6]. Only two patients developed symptomatic grades 1 and 2 neuropathy after 12 months. Additionally, a small prospective study (n=31) of adequate quality demonstrated persistent neuropathy with alteration in neurophysiological tests after receiving a cumulative dose of more than 1,000 mg/m^2 [7]. Finally, a Dutch cross-sectional study (n=25) assessed neuropathy using questionnaires, neurological tests and vibration threshold measurements after a median follow-up of 18 months and

Table 3 Studies investigating the association between oxaliplatin-induced peripheral neuropathy and cumulative doses

Study	Cumulative dose in symptomatic patients (mg/m^2)	Neuropathy and cumulative dose (mg/m^2)	p value
Matsumoto [29]	>850	Grade 2 neuropathy was more often experienced in patients who had received more than 10 cycles of FOLFOX (cumulative dose of >850 mg/m^2) without a break in comparison with cumulative dose of >850 mg/m^2 with a break between cycles	NR
Storey[31]	≥834	Symptomatic patients received 834 mg/m^2 Asymptomatic patients received 702 mg/m^2	0.001
Park [25]	NR	Cumulative dose was an important predictor of the development of neuropathy, and symptom severity scores were significantly correlated with cumulative oxaliplatin dose at follow-up–correlation coefficients:	0.001
		TNSc, 0.658	0.0005
		TNSr, 0.704	0.002
		NCI grade, 0.603	0.03
		NSS, 0.453	
Pietrangeli [7]	≥1,000	All 5 patients with a long follow-up and alteration in neurophysiological tests receiving a cumulative dose of ≥1,000 mg/m^2	NR
Krishnan [6]	1,787±219 (mg)	Symptomatic patients (1,787±219 mg) Asymptomatic patient group (1,110±446 mg)	0.03
		A stronger inverse correlation was noted between cumulative dose and radial SNAP amplitude compared with sural SNAP amplitude (radial, r=0.51; sural, r=0.45)	
Brouwers [22]	NA	No relationship between oxaliplatin dose and neuropathy could be observed	NR

NA not applicable, *NR* not reported, *NSS* neuropathy symptom score, *TNSc* total neuropathy scale clinical version, *TNSr* total neuropathy scale reduced version with neurophysiological measures, *SNAP* sensory nerve action potential

reported persistent neuropathy in the majority of patients. However, no relationship between oxaliplatin dose and neuropathy could be observed [22].

The remaining two, non-phase III, studies did not directly address the influence of oxaliplatin administration on long-term O-IPN. A study with 159 patients receiving 12 cycles with oxaliplatin (median dose intensity of 35.7 mg/m^2/week) reported that no patients experienced grade ≥3 neuropathy, and only one patient had complaints of long-term neuropathy after 12 months [28]. Another high-quality study with 64 patients, who were randomized between FOLFOX infusion in 2 or 6 h with dose intensity of 42.6 and 40.2, respectively, showed that only one patient still experienced grade 2 neuropathy after 12 months [30].

Influence of follow-up, setting and combination therapy on the development of O-IPN

Not only oxaliplatin administration (e.g. cumulative doses and dose intensity) is considered important for the development of neuropathy. The time of neuropathy assessment, indication of therapy and type of combination therapy might also influence the degree of neuropathy. The time of neuropathy assessment varied between 12 months and 8 years in the studies. The degree of neuropathy after 12 months or longer, in studies using the NCI-CTC for neuropathy assessment, was compared in Table 4. After 12 months, incidence of O-IPN grades 1 and 2 neuropathy varies between 0.6 % [28] and 46 % [29] of patients, and after 15 months or longer, the overall experienced neuropathy differs between 13 % [29] and 79.2 % [25] of patients. Furthermore, oxaliplatin has been given as adjuvant and palliative treatment. However, only one study compared O-IPN between patients with adjuvant vs. palliative treatment which are very different populations with different symptom burdens [31]. They reported that adjuvant-treated patients were more affected with O-IPN (35 %) than palliative-treated patients (16 %) after 12 months [31]. In addition, the majority of the adjuvant-treated patients received 7 or 8 cycles of oxaliplatin vs. 6 cycles in palliative treatment. Moreover, comparison between the other studies including stages II and III vs. stage IV CRC patients receiving adjuvant or palliative treatment, respectively, does not show differences in degree of O-IPN. However, comparison is difficult as time, oxaliplatin administration and way of assessment are different. Therefore, no conclusions concerning different prevalences of O-IPN in patients receiving adjuvant vs. palliative treatment can be drawn. Further, oxaliplatin was administered in the majority of the studies in combination with 5-FU/LV [3, 6, 7, 21, 23–30], combination therapy with capecitabine was only given in the majority of patients in one study [31], and oxaliplatin monotherapy was administered in one study of adequate quality [26]. In addition, one study also included few (4 %) patients treated with capecitabine and oxaliplatin; however, no comparison on neuropathy was made between combination therapies with 5-FU/LV and capecitabine [25]. The Australian study, including patients treated with oxaliplatin and capecitabine, reports that O-IPN still occurred in 28 % of patients after 12 months [31]. On the other hand, the largest study with 5-FU/LV and oxaliplatin-treated patients reports grade ≥2 sensory neuropathy in 26.1 % [21].

Discussion

In the 14 articles included, any degree ranging from grades 1 to 3 of O-IPN is still present in a large number of patients after at least 12 months of follow-up. However, in the majority of patients, symptoms are mild to moderate (grade 1 or 2). Although all studies reported about the oxaliplatin regimen (e.g. cumulative doses and/or dose intensity), only six studies [6, 7, 22, 25, 29, 31], of which four have a rather small sample size [6, 22, 24, 25], directly assessed the influence of cumulative dose on the development of long-term O-IPN. Of these six studies, five did find an association between cumulative dose and the development of chronic O-IPN. Two retrospective studies of high and adequate quality found that neuropathy was associated with higher median cumulative doses (≥834 and 850 mg/m^2) [29, 31], and three small high-quality prospective studies found similar results [6, 14, 25]. However, another small prospective study from the Netherlands did not find a relationship between oxaliplatin dose and observed neuropathy [22]. The other eight studies reported long-term O-IPN and information about oxaliplatin administration separately.

Although time of follow-up, indication of therapy and type of combination regimen might also influence the degree of neuropathy, only few studies investigated these associations. Only one adequate-quality study reported about the difference in O-IPN in patients treated in adjuvant vs. palliative setting [31]. Furthermore, oxaliplatin given in combination regimen with 5-FU/LV or capecitabine might influence the degree of O-IPN [5, 35, 36]. The only study with oxaliplatin- and capecitabine-treated patients reports that O-IPN still occurred in 28 % of patients after 12 months [31], compared to 26.1 % of patients in the largest study with treatment with 5-FU/LV [21]. However, comparison between studies remains difficult.

Studies resemble in the fact that they all included patients treated for stages II–IV CRC, and oxaliplatin regimen was mainly given in a combination of oxaliplatin with 5-FU/LV. However, the studies differed enormously in neuropathy assessment and presentation of results, study design, follow-up time and the included sample size. For example, the time of the neuropathy assessment differed between 12 months and 8 years after cessation of treatment with oxaliplatin and sample size varied between 16 and 2,710 patients. Furthermore, O-IPN was assessed both in patients treated in the adjuvant

Table 4 Comparison of the degree of oxaliplatin-induced peripheral neuropathy between studies using the NCI-CTC after ≥12 months of follow-up

Author	Time of O-IPN assessment	Neuropathy incidence (grade according the NCI-CTC)
Studies with O-IPN assessment after 12 months of follow-up		
Allegra [21]	12 months	Grade ≥2 sensory neuropathy in 26.1 vs. 32.4 % in the FOLFOX and FOLFOX/bevacizumab arm, respectively
Krishnan [6]	12 months	Grades 1 and 2, 2/16 (12.5 %) patients
Land [24]	12 months	Grades 0 and 1, 95 %
		Grade 2, 4.7 %
		Grade 3, 0.5 %
Lee [28]	12 months	Grade 0, 99.4 % of patients
		Grade ≤3, 1 patient (0.6 %)
		Grade ≥3, 0 % of patients
Matsumoto [29]	12 months	Grades 1 and 2, 51/112 (46 %) patients
Petrioli [30]	12 months	Grade 2, 1/64 (1.6 %) patients
		Grade 3, 0 %
Storey [31]	12 months	Overall, 28/101 patients (28 %) had persistent O-IPN
		Grade not clear, 18/101 (18 %) patients
		Grade 1, 3/101 (3 %) patients
		Grade 2, 2/101 (2 %) patients
		Grade 3, 5/101 (5 %) patients
Studies with O-IPN assessment after >12 months of follow-up		
André [3]	18 months	Grade 1, 195/976 (20 %) patients
		Grade 2, 34/976 (3.5 %) patients
		Grade 3, 7/976 (0.7 %) patients
	48 months	Grade 1, 11.9 %
		Grade 2, 2.8 %
		Grade 3, 0.7 %
Matsumoto [29]	15 months	Grades 1 and 2, 27/112 (24 %) patients
	18 months	Grades 1 and 2, 15/112 (13 %) patients
	24 months	Grades 1 and 2, 1/112 (0.8 %) patients
Park [25]	25 months	Any grade, 19/24 (79.2 %) patients
		Grade 1, 9/24(37.5 %) patients
		Grade 2, 7/24 (29.2 %) patients
		Grade 3, 3/24 (12.5 %) patients
Yothers [27]	8 years	Grade 2+, 30.4 % of patients
		Time of assessment was not quite clear

NCI-CTC National Cancer Institute-Common Terminology Criteria

and palliative setting. In addition, O-IPN was mainly assessed according to the NCI-CTC; however, other questionnaires and nerve conduction examinations were also used. Different questionnaires were used, and a recent study in supportive care in cancer correctly reported that a lack of standardized questionnaires for O-IPN make it difficult to compare results between studies [20]. Nonetheless, besides that the studies used different assessment tools of O-IPN, even comparison of studies using the NCI-CTC is difficult as interobserver agreement has shown to be inadequate [37]. In addition, there is no consensus on which factors (e.g. subjective or objective measurements) are most important in determining clinical severity of neuropathy. In spite of the fact that the methodological quality of the majority of the 14 studies was high and all these differences and lack of consensus in determining the severity of O-IPN, it remains difficult to forecast the development of O-IPN in patients.

As there is no well-accepted proven therapy for O-IPN, it is important to identify patients at risk of developing O-IPN. In our study, only two studies [6, 22] reported the influence of pre-existing risk factors, e.g. pre-existing neuropathy, alcoholism and diabetes mellitus, which are supposed to be risk factors for O-IPN, and three studies excluded patients with pre-existing neuropathy or diabetes mellitus [25, 28, 30]. As

the majority of studies did not mention these risk factors, this is also a limitation of the studies included in the review. Furthermore, it is suggested that certain single nucleotide polymorphisms of voltage-gated sodium channels genes are involved in the development of oxaliplatin-induced neurotoxicity [10, 11, 38]. As certain patients might be more at risk of developing O-IPN, it is important to identify the role of oxaliplatin administration on the development of severe O-IPN. In that way, the risk of developing severe O-IPN can be minimized by applying dose modification on time or by restraining oxaliplatin therapy in certain patients.

In summary, no firm conclusions can be drawn regarding oxaliplatin administration and the emergence of long-term O-IPN. However, a higher cumulative dose is likely to be a predicting factor for the development of long-term O-IPN. Given the heterogeneous definitions and tools utilized in the studies of O-IPN, we believe that a formal framework for the definition, classification and measurements of O-IPN is necessary. Moreover, as there is no currently well-accepted proven therapy for O-IPN, it is very important to try to prevent O-IPN and to identify patients who are prone to develop severe forms of this side effect as it has a negative influence on patients' quality of life. Therefore, more and larger prospective studies are needed to assess the development of long-term O-IPN in relation to these risk factors and oxaliplatin administration. Consequently, in the future, cancer treatment might become more personalized as clinicians might decide to restrain oxaliplatin treatment for certain patients who are at risk of developing long-term severe neuropathy.

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Conflict of interest None

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