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Oxaliplatin Neurotoxicity

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Abstract Oxaliplatin (OXA) is a first-line agent in the systemic treatment of colorectal cancer (CRC). OXA-induced neuropathy is the most prominent adverse effect, both during and after the completion of chemotherapy. OXA neurotoxicity (OXA-NTX) is a dose-limiting, frequent, and long-lasting adverse event that may compromise therapeutic outcome and the quality-of-life of CRC patients. Increased knowledge of the pathophysiology and clinical profile of this neuropathy is being achieved. Two types of neuropathy are usually observed, and evidence suggests a link between the acute symptoms and the development of chronic NTX. In this paper we review the main advances and the outstanding issues concerning OXA-NTX, for example calcium/magnesium and other drugs in the prophylaxis and treatment of this neuropathy. Recently available and ongoing investigation of pharmacogenomics, clinical and neurophysiological risk factors, and early markers of OXA-NTX are of great value in clinical decision-making, contributing to minimizing the risk of severe neuropathy.

Keywords Oxaliplatin · Platinum compounds · Colorectal cancer · Neuropathy · Neurotoxicity · Chemotherapy-induced neuropathy · FOLFOX · CAPOX · XELOX · Oxalate · Voltage-gated sodium channel · Nerve conduction studies · Total neuropathy score · EORTC QLQ-CIPN20

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Introduction

Oxaliplatin (OXA) neurotoxicity (NTX) is of major concern to oncologists and OXA-treated patients [1, 2••]. Since the early published trials demonstrating the benefit of OXA in first-line treatment of colorectal cancer (CRC) patients [3, 4], growing interest in and increasing knowledge of this chemotherapy-related effect has been reflected in the literature. OXA-based regimens have become the standard therapy for CRC in both the adjuvant and palliative settings. At present, combination regimes of infusional OXA and 5-fluorouracil with leucovorin (FOLFOX) or oral capecitabine (XELOX) are standard options in the treatment of CRC [5]. Furthermore, OXA is increasingly administered against other malignancies [6, 7]. OXA has a good tolerability profile with side-effects (myelosuppression, nausea, and vomiting) that are usually easy to handle [8]. Conversely, the occurrence of sensory neuropathy is a significant unsolved problem because it is frequent, necessitates dose-adjustments, and leads to nearly half of patients not finishing their chemotherapy treatment as planned [9, 10]. Besides limiting treatment, and this is very important in a palliative setting, OXA-NTX is not fully reversible after stopping the OXA, and therefore compromises the quality of life of CRC patients.

OXA is a third-generation antitumor platinum agent. Although peripheral neuropathy is a fully recognized common adverse event secondary to all platinum-compounds [11], the neurotoxic profile among these drugs is not identical. Peripheral NTX secondary to OXA usually presents as two distinct clinical syndromes: acute and chronic neuropathy, with the former being exclusive to OXA. Both types of neuropathy may become particularly troublesome. In this paper we review the characteristics and related factors associated with their occurrence in addition to strategies for correctly assessing, promptly recognizing, and helping to prevent or even ameliorate them successfully.

Acute Neurotoxicity: the First Stage of Persistent Neuropathy

Acute neurotoxicity emerged as a distinctive type of toxicity in oncological practice, thereby widening the range of chemotherapy-induced neuropathies. Acute symptoms related with OXA administration are characterized by their early onset, appearing during or immediately after infusion of OXA. It usually resolves within a few hours or days for the vast majority of patients. Acute clinical complaints reported by patients can be classified into two groups: typical (sensory) and atypical (motor). The most frequent and characteristic syndrome associated with OXA administration is induced or exacerbated by cold. It is characterized by acral, perioral, or pharyngolaryngeal dysesthesias, reported for 99 %, 95.2 %, and 91.8 % of patients, respectively [12]. Conversely, the atypical presentation of acute NTX resembles a neuromyotonia-like syndrome, with hyperexcitability motor symptoms, for example shortness of breath (32 %), jaw spasm (26 %), fasciculations (29.5 %), cramps (20 %), and difficulty in swallowing (18 %). More infrequently, patients report such symptoms as voice changes (4 %) and visual changes (1 %), ptosis (1 %), and pseudolaryngospasm (1 %). Atypical acute NTX presentation is usually unrelated to cold exposure. These atypical symptoms, particularly jaw spasms and cramps, usually present as paroxysmal episodes and tend to recur several times a day. Loss of sensation of breathing is a very unpleasant and disturbing symptom but without any objective evidence of respiratory distress. The median number of different acute symptoms reported by patients, including typical and atypical, is 2–4 [12, 13••].

Acute neurotoxicity is an early manifestation of OXA toxicity, usually present after the first administration. Symptoms of acute neurotoxicity are more frequently reported by patients during the first half (61.7 %) rather than the second half of the schedule (38.4 %) [12]. No association between type of acute neurotoxicity and clinical or demographic patient characteristics has been demonstrated [12, 14]. Typical acute OXA syndrome does not require discontinuation of treatment or dose reduction, but prolonging the time of infusion from 2 h to 4 to 6 h must be considered when severe acute neurotoxicity (interfering with daily activities) or evidence of atypical presentation is present [14, 15].

Although less attention was initially paid to the acute form of OXA-induced peripheral neuropathy, increasing awareness of its importance emerged after the first evidence suggesting a link between acute NTX and the feared chronic form [10, 16, 17]. Several clinical and neurophysiologic studies have demonstrated this association, and the usefulness of acute syndrome assessment in predicting the severity of the development of the chronic form. In this way, patients with symptoms of acute NTX during the first half of OXA-based schedule are more likely to report severe chronic neuropathy at the end of the chemotherapy schedule [12, 13••, 18].

Clinical presentation of acute NTX syndrome depends on pharmacokinetic properties of OXA, with plasma OXA levels known to peak approximately 1 h after infusion followed by a prolonged terminal half-life of approximately 10 days [19]. In plasma, OXA rapidly undergoes non-enzymatic biotransformation into dach-platinum ($Pt(DACH)Cl_2$) the active metabolite, by losing the oxalate chain; this is believed to be responsible for the acute NTX [20, 21]. Oxalate is a known dianion metal chelator, and Ca and/or mg chelation has been suggested as a putative mechanism underlying acute NTX. Na^+ channel dysfunction is associated with acute NTX [16, 22, 23••, 24]. Physiologically, the binding of extracellular calcium within the pore of Na^+ channels is required for channels to close and their release from the pore may be necessary for the activation gates to open [25]. Therefore, oxalate interferes with channel deactivation rate, increasing neuronal hyperexcitability and predisposition to ectopic activity, a mechanism of paresthesia generation [16, 23••, 26].

Chronic Neurotoxicity: Disturbing and Long-lasting

The most feared neurologic consequence of OXA administration is known as persistent, chronic, or cumulative neuropathy. It is very frequent, being a complaint for up to 80 % of patients one month after finishing OXA [3, 4]. Reported incidence of neuropathy on completion of treatment, according to severity, is 14–40 % for grade 1, 15–45 % for grade 2, and 5–8 % for grade 3, depending on the approach to the neurological complication [3, 4, 10, 13••]. Persistent neuropathy resembles that observed after cisplatin administration, and it consists of paresthesia and/or dysesthesia in stocking-and-glove distribution and ataxic gait. Neurological examination usually reveals loss of peripheral deep tendon reflexes, with ankle reflex the most frequently abolished, and impairment of vibratory sensitivity in feet and legs. Pin, joint position, and light touch sensitivity are also affected. Positive Romberg sign is a characteristic, because of loss of proprioception. Motor nerves remain free from damage, although fine motor skills can be impaired because of sensory deficits. Lhermitte's phenomenon characterized by "electric-shock" sensations precipitated by neck flexion are also observed. This phenomenon is secondary to anterograde degeneration of dorsal column sensory fibers caused by the loss or impairment of dorsal root ganglia neurons [11, 27].

OXA chronic NTX reflects selective sensory neuron damage. As for other platinum compounds, the damage affects the nucleus of the sensory dorsal root ganglia neurons. Mechanisms explaining the physiopathology of platinum-induced neuropathy include the formation of DNA intrastrand adducts and interstrand crosslinks altering the tertiary structure of DNA, and oxidative stress as the main inducer of neuronal apoptosis [11].

Chronic neuropathy usually manifests during the last cycles or even just after finishing OXA-based treatment. Sometimes it can worsen during the first month after cessation of OXA in the setting of the so-called "coasting effect", which has been observed in approximately 10–15 % of patients [3, 11, 28–30]. Although overall evolution is usually favorable and OXA-NTX severity tends to improve, recovery usually takes years [4]. However, complete resolution of persistent NTX is not always achieved, especially for those patients affected by more severe forms. Long-term studies report persistence of symptoms and/or signs of neuropathy up to 10 years after cessation of OXA treatment, especially sensory symptoms in the lower extremities in up to one third of patients [31–33, 34••, 35]. In the MOSAIC trial, the incidence of grade 3 NTX at completion of treatment was estimated to be up to 18 % among those patients who received the full planned treatment. Although severe neuropathy decreased to 1 % one year after discontinuation of therapy, some NTX in the second post-treatment year was still affecting approximately one-third of patients [3, 4]. Retrospective studies based on patient-reported symptoms have described incidence of moderate (grade 2) or severe (grade 3) neuropathy in up to 40 % of patients two years after finishing chemotherapy [35]. Interestingly, transient exacerbation of symptoms among patients with chronic neuropathy has been described when they undergo surgery just after the completion of chemotherapy. This effect has been related to the release of clusters of inter-erythrocyte OXA in the plasma with the surgery-associated hemolysis [36].

OXA-NTX causes discomfort to patients, compromising the quality of the survival period [34••, 37–39]. Difficulty in writing and walking, buttoning clothes, and driving are reported by 40 %, 25 %, and 10 % of patients, respectively [39]. Even car crashes have been attributed to this impairment [32]. Moreover, those patients with many neuropathy symptoms reported significant and clinically worse health-related quality of life scores [34••, 37].

Assessment of OXA-induced Neurotoxicity

Assessment of acute and chronic neuropathy must be addressed differentially. Patients must be specifically interviewed about the presence and characteristics of the neuropathic symptoms, either transient or persistent.

The Clinical Evaluation

The severity of acute toxicity is difficult to quantify because neither cold-related symptoms nor other uncommon hyperexcitability phenomena are well addressed in common NTX scales, and no validated scale is available. Initially, an oxaliplatin-specific neurotoxicity scale was developed. This scale grades not only the severity but also the duration of symptoms, as follows: grade 1, dysesthesia or paresthesia that completely regresses before the next cycle of therapy (<7 days); grade 2, dysesthesia or paresthesia persisting between courses of therapy (>7 days); and grade 3, dysesthesia or paresthesia causing functional impairment [3, 8]. Recently, a score based on recording the sum of symptoms reported by patients has been proposed as useful for routine evaluation [12, 13••] (Table 1).

The presence and severity of chronic NTX induced by OXA is usually graded by using the widely known cancer toxicity scales (NCI.CTC), with which grade-2 and grade-3 symptoms affect patients' instrumental and personal activities of daily living, respectively [40]. However, there is growing consensus concerning the difficulty of measuring the extent of impairment of the peripheral nervous system by chemotherapy by use of these scales, because they are somewhat subjective and imprecise, with suboptimum inter-rater reliability and poor sensitivity in detecting subtle changes [28, 41–43]. In this way, the Total Neuropathy Score (TNS) [44] has been extensively validated as a useful instrument for measuring the severity of peripheral neuropathy caused by different drugs, including OXA during treatment [13••, 45] and at follow-up [46••]. However, TNS is not useful for detecting acute complaints related with OXA because neurological signs associated with the acute NTX are transient [47, 48].

Increasingly, many authors argue the need to incorporate patient "self-report" questionnaires or patient-reported outcomes (PRO) in daily practice [49]. Discrepancies between patients' and physicians' perceptions are fully recognized [49]. In one recent study only 10 % of patients were designated by clinicians as having severe OXA neurotoxicity, whereas, in contrast, patient interviews and self-report questionnaires described significant physical limitations because of neuropathic symptoms for 60 % of patients [39]. Among

Table 1 Acute neurotoxic symptoms scored among patients receiving oxaliplatin

Symptom	Absence	Presence
Cold-induced perioral paresthesias	0	1
Cold-induced pharyngolaryngeal dysesthesia	0	1
Shortness of breath	0	1
Difficulty swallowing	0	1
Laryngospasm	0	1
Muscle cramps	0	1
Jaw stiffness	0	1
Visible fasciculations	0	1
Voice changes	0	1
Ptosis	0	1
Ocular changes	0	1
TOTAL (sum):		

these, quality of life questionnaires are the most commonly used in clinical practice. Importantly, although FACT/GOG-oxaliplatin-specific Ntx-12 [50] evaluates acute and chronic symptoms related with OXA neurotoxicity, the EORTC-CIPN20 only measures discomfort from chronic neuropathy induced by OXA [34••, 46••, 51, 52]. More scales are being published [53, 54], and psychometric studies for better definition of the best PRO.

Neurophysiological Assessment

Nerve conduction studies (NCS) enable evaluation of acute and chronic neuropathy. NCS might be performed approximately one month after finishing chemotherapy treatment to confirm the diagnosis and assess the extent of axonal loss [55]. Characteristic findings typically reveal the presence of an exclusively axonal sensory neuropathy with a neuronopathy pattern caused by dorsal-root ganglia somatic neuron damage [13••, 35, 55]. In the acute phase of toxicity, repeated motor action potentials after a single electrical stimulus and neuromytonic discharges can be documented by use of NCS and needle electromyography studies, respectively [47, 48], although their performance in daily practice is not recommended. Other complementary electrodiagnostic tests have been evaluated in the setting of OXA-NTX. Thermal quantitative sensory testing (QST) is a noninvasive psychophysical test, based on thermal stimuli, that evaluates the small Aδ and C sensory nerve fibers, involved in thermal and pain sense. This technique can detect signs of OXA chronic NTX at an early stage when the clinical manifestations are absent [56] and after completing treatment [57]. Impairment of the vibration perception threshold (VPT) measured with the QST was reported to be an effective marker of neuropathy due to OXA at low cumulative doses [58]. In addition, Park et al. have reported several comprehensive studies based on nerve excitability techniques that have investigated the pathophysiology of OXA-NTX and demonstrated alterations in sensory axonal excitability throughout treatment [10, 17, 59].

Risk Factors and Early Neuropathy Makers: Avoidable or Predictable?

Demographic and Clinical Risk Factors

OXA-NTX is a well-recognized cumulative dose-related adverse event. Severe NTX (grades 3 and 4) may be present in up to 10 %, 30 %, and 50 % of patients receiving 510–765 mg, 765–1000 mg, and >1000 mg, respectively [11]. However, no threshold or cut-off value in the dose effect is actually known [13••, 18], and at the same dose severity of neuropathy with OXA treatment differs among patients. The frequency of exposure to OXA or dose-intensity has been suggested as another risk factor for the development of severe neurotoxicity. Concerning the neurotoxic profile of the combination of OXA with capecitabine or infusional 5FU, contradictory results have been reported in the literature [59–61]. A large meta-analysis comprising six prospective randomized trials did not find differences between the two regimens with regard to incidence and severity of neuropathy, although details of the type of neuropathy are missing [62].

Among patient characteristics, several studies have examined the effect of patient age on toxicity; this was found be important—CRC is a disease mainly of the elderly. Most evidence shows that elderly patients do not carry an increased risk of either acute or cumulative NTX [12, 13••, 59, 63–65]. Concerning gender, in contrast with evidence for increased leukopenia and mucositis among female patients treated with OXA [66], it seems not to be predictive of NTX [17, 18, 59, 63, 65]. The putative higher associated risk of neuropathy among patients with pre-existing neuropathy is difficult to evaluate, because most studies have routinely excluded these patients, although subclinical neuropathy occurs in a very high-proportion of CRC patients before chemotherapy [67]. Evidence based on retrospective analysis does not support preexisting neuropathy as a risk factor [18]. Finally, there are comorbidities such as diabetes mellitus (DM) and renal impairment that have been related with the risk of OXA-induced neuropathy. However, retrospective analysis of the three major randomized studies of FOLFOX regimens among patients with CRC showed that the presence of DM per se, without neuropathy, does not seem to carry a higher risk of neuropathy [68], similar to other studies published recently [65, 69]. Furthermore, the effect of diminished renal function on OXA-NTX is conflictingly addressed [18, 65, 70, 71]. Recently, the presence of pre-OXA treatment hypomagnesemia was associated with higher incidence and duration of chronic neuropathy, but calcium was not [65].

Pharmacogenetics

To investigate inter-subject variability in the occurrence of OXA-NTX, increasing attention has been placed on the involvement of individual genetic susceptibility in the neurotoxic effects of chemotherapy [72, 73]. Several single-nucleotide polymorphism (SNPs) variations in genes involved in OXA biotransformation and voltage-gated sodium channels (SCNAs) have been the most intensively investigated. Metabolic routes of OXA involve conjugation of the platinum-diaminocyclohexane metabolite by glutathione. Glutathione S transferase protein 1 (GSTP1) is an enzyme-mediating glutathione-related detoxification of OXA. The most studied polymorphism related with OXA-NTX is GSTP1 Ile105Val, with more than 20 studies published to date [2••]. It was speculated that GSTP1 Ile105Val polymorphism resulted in

substantially lower enzyme activity, leading to less effective capability of detoxification. Results are contradictory, with approximately half the studies supporting and the other half rejecting the hypothesis [2••, 74]. According to the results of a recently published meta-analysis, association between GSTP1 Ile105Val polymorphism and the occurrence of neurotoxicity among OXA-treated patients remains inconclusive [74].

Other relevant pharmacogenomic markers being investigated are genes coding for the enzymes involved in oxalate metabolism, especially glyoxylate aminotransferase (AGXT). These were found to be significant predictors of both acute and chronic neurotoxicity in one study [63] but not in another [75]. Mutations in voltage-gated sodium channels (SCNAs) also invite investigation, owing to their suggested involvement in the pathogenesis of acute OXA-NTX, specifically SCNA4A and SCNA10A. As far as we are aware, four studies evaluating several genes have been conducted, with promising results [29, 76–78]. Overall, available evidence is still inconsistent. Discrepancies among the studies may be related with differences in the population (interethnic), neurological definition of toxicity, size of the studies conducted, techniques of pharmacogenetic analysis [72], or even clinical setting (adjuvant vs metastatic) [79], and critically they lack further validation among other populations. Other genes evaluated include excision repair cross-complementing genes (ERCC1 and ERCC2), ATP-binding cassette gene subfamily C member 2 gene (ABCC2), and integrin B3 gene (ITGB3) [2••, 79–82].

In summary, despite greater knowledge of the genetic-neurotoxicity profile of CRC patients receiving OXA, no definite validated marker for genetic susceptibility to OXA-associated neuropathy is available. Therefore, the use of pharmacogenomics to individualize therapy cannot yet be implemented in clinical practice.

Neurological Monitoring

The early identification of patients at risk of high-grade neuropathy could be useful to enable prompt reductions of the dose of OXA before irreversible or severe nerve damage occurs. Accordingly, neurological monitoring may help to guide clinicians towards better counseling of patients about chemotherapy [83]. A prospective multicenter study, including patients under treatment with FOLFOX-4, 6, and XELOX, recently identified three variables at the midpoint of the planned schedule as independent risk factors for development of severe OXA-NTX: the number of acute symptoms and the >30 % decrease in sensory nerve action potential amplitude from the baseline value in radial and dorsal sural nerves. For these variables the sensitivity is 96.3 % and the specificity 79.1 %, with a positive and negative predictive values of 53 % and 98.9 %, respectively [13••]. Neurological monitoring with this score that combines clinical and neurophysiologic measures is a suitable tool for daily clinical practice and offers clinicians a practical means of identifying patients at the greatest risk of persistent neuropathy.

Other techniques have been used for prediction of OXA-NTX. Determination of sustained thermal hyperalgesia after the third OXA cycle has been shown to be an early predictor of persistent severe OXA-NTX [56]. Moreover, nerve excitability studies revealed a positive correlation between changes in axonal excitability at the time of OXA infusion and the risk of developing chronic neuropathy, and these techniques have a predictive value [17, 23••, 84]. However, although authors proclaim their feasibility in the clinical practice, these techniques are not accessible for most centers, which limits their implementation.

Special Situations

Rechallenge Oxaliplatin

In the management of advanced CRC patients after standard first-line regimen, improvement of survival has led to an increase in the prevalence of NTX among survivors, but also to consideration of several treatment options including FOLFOX rechallenge [85, 86]. Therefore, the issue of residual neuropathy in those patients is of major concern in clinical decision-making. As far as we are aware, published evidence of the incidence and severity of neuropathy among CRC patients for whom OXA was reintroduced is limited to one retrospective study. This study included 29 CRC patients, treated twice with a combination of FOLFOX schedules, and revealed a lower incidence of chronic grade 3 OXA-NTX among patients receiving OXA for the second time, even among patients who had experienced severe neuropathy during their first OXA-based treatment [87]. Five patients experienced an increase in NTX grade. However, this study is retrospective with a heterogeneous population treated with several FOLFOX schedules, and including diverse approaches to OXA reintroduction. Moreover, detailed information about acute neurotoxicity in this study is lacking. Therefore, neurological tolerance among patients previously exposed to OXA should be better investigated in studies with a comprehensive neurological approach.

Reintroduction of OXA (Stop and Go)

A more extensively evaluated strategy for avoiding neurotoxic adverse effects has been temporary withdrawal of OXA, to avoid cumulative toxicity and maintain a good quality of life and tumor sensitivity [86]. Commonly known as the stop and go approach, it is based on intensified and repeated short courses of FOLFOX. First studies (OPTIMOX) [88] showed

that interruption of OXA after six cycles, followed by leucovorin–5-FU alone, resulted in a significantly lower incidence of grade 3 neurotoxicity (13 % vs 19 %) with achieved response and survival equivalent to those of the traditional schedule [88]. More recently, in the setting of first-line treatment, the COIN trial reported grade ≥3 peripheral neuropathy was more frequent on continuous than on intermittent treatment (27 % vs 5 %). However, subgroup analysis revealed detriment in survival and quality of life with intermittent chemotherapy among those patients with elevated baseline platelet counts [89]. Conversely, results from the prematurely closed CONCEPT trial showed an increased time to treatment failure with an intermittent OXA treatment strategy [90]. In summary, although a treatment break seems feasible in terms of reducing cumulative NTX, more evidence is needed before making strong safety recommendations.

Finally, aggravation of previous residual OXA-NTX when administering other chemotherapy has been reported. Cetuximab-induced hypomagnesemia has been associated with exacerbation of previous OXA-induced neurotoxicity [91]. Moreover, treatment with 5FU concurrent with bevacizumab has also been reported to increase the risk of persistent severe neuropathy in a study comparing FOLFOX vs FOLFOX + bevacizumab for treatment of advanced CRC [92], although these results were not confirmed in first-line treatment (TREE trial) [93].

Therapeutic Strategies Against OXA-NTX

Neuroprotection

To prevent the development of OXA-NTX many neuroprotective agents have been tested. According to the rationale presented above, several authors support the usefulness of infusing 1 g gluconate calcium and 1 g magnesium sulfate concurrently with OXA administration, to prevent acute and chronic OXA-NTX. Favorable evidence sustaining this practice contrasts with preliminary studies not supporting their use because of lack of efficacy [94–97], and with a recent randomized phase III, placebo-controlled, double-blind trial [52] which revealed no benefit of Ca and/or Mg. Several meta-analysis studies have tried to resolve the problem of the efficacy of this therapeutic approach [94–97]. However, all these studies except two [94, 95] include in the analysis randomized and nonrandomized clinical trials with the high risk of biased conclusions; this may partially explain the differences encountered. Although favorable efficacy for acute but not chronic neuropathy was reported by Wen et al. [94], it is important to take into account that these meta-analyses did not include the latest published negative randomized trial [52]. Importantly, concerns regarding reduced chemotherapy efficacy secondary to Ca and/or Mg vanished after the latest evidence supporting the safety of their use [94–97]. Besides chelating agents, several other drugs have been tested as neuroprotectors during OXA treatment, including antiepileptics, antioxidants, antinflammatories, and trophic factors [2••, 28, 29]. However, these studies have small sample sizes or are not randomized and/or controlled. Although results from a study of the effect of vitamin E on cisplatin-induced neuropathy development were promising [98], there was no significant decrease in the incidence of acute OXA-induced peripheral neuropathy in phase II and III randomized studies compared with placebo [99, 100]. Efficacy and safety data are currently insufficient for recommending any neuroprotective agent. Currently, a phase II trial testing a novel mechanism with a selective sigma1 receptor antagonist (E-52862) and a regulator of Ca flow is ongoing in Europe (EudraCT Code:2012-000398-21).

Other strategies for preventing persistent neuropathy in clinical practice rely on close neurological monitoring [13••] and adjustments to dose–time of treatment infusion. Amelioration of acute neuropathy symptoms is based solely on patient education, avoiding cold stimuli, and wearing gloves.

Treatment of Persistent OXA-NTX

The purpose of treatment of established OXA-NTX is to relieve disturbing symptoms, for example neuropathic pain, numbness, and tingling. The types of drugs usually recommended by physicians include topical analgesics, antidepressants, and anticonvulsants. Evidence of their effectiveness is scarce or negative. Only venlafaxine has been demonstrated to be useful in relief of OXA-induced acute NTX in a small double-blind trial [101]. Recently, duloxetine, a selective serotonin and norepinephrin reuptake inhibitor used to treat depression and diabetic neuropathy, was demonstrated to be more effective than placebo for treatment of chemotherapy-induced peripheral neuropathic pain [102••]. Subanalysis of the platinum-treated patients (n=106) in this large randomized, double-blind, placebo-controlled phase III trial showed maintenance of the benefit of duloxetine administration. However, according to IMMPACT recommendations [103] the results obtained by use of duloxetine in this trial were of minimal clinical importance.

One recently published study evaluating the most common treatments taken by patients for management of OXA-NTX reported that nearly 30 % use nutritional supplements including B-vitamins, alphalipoic acid, acetyl-L-carnitine, L-glutamine, Bing Ling Herbals, omega-3 fatty acids, oral calcium, and magnesium, for a mean period of three years after OXA treatment, even though there is no empirical evidence in support of their use for treatment of existing neuropathy

among cancer survivors. Opioids, anti-inflammatories, anticonvulsivants, and antidepressants were being taken by 10 %, 15 %, 10 %, and 12 % of patients, respectively [39].

Conclusions

OXA-NTX is a growing problem because of the widespread use of oxaliplatin for treatment of CRC and its increasing use to treat other malignancies. The long-term nature of this side effect makes it especially problematic, and it is becoming a major issue both during CRC survival and in a palliative setting. Hence identification of those patients at higher risk of developing OXA-NTX is clinically relevant, and might help to avoid significant cost, toxicity, and patient discomfort. Adjusting treatment on the basis of genetic toxicity markers is being suggested and, although promising, further study is still needed. Currently, no agents can be recommended for prevention of OXA-NTX. Persistent painful NTX may be ameliorated by use of duloxetine. Supervised neurological treatment seems crucial, and NCS contributes not only to diagnosis but also to early identification of high-risk patients. Finally, trials addressing the possibility of reducing the duration of adjuvant chemotherapy from 6 to 3 months are being conducted with accrual almost complete [104]. Evidence of reduced incidence and/or severity of neurotoxicity without impaired antineoplastic effect will be welcome.

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Compliance with Ethics Guidelines

Conflict of Interest Roser Velasco and Jordi Bruna have received compensation from Esteve Laboratories for services as consultants.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by either of the authors.

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