Original Article

# Oxaliplatin treatment and peripheral nerve damage in cancer patients: A Polish cohort study

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## ABSTRACT

**Introduction:** Oxaliplatin-induced neurotoxicity is the single main dose-limiting factor in the treatment of colorectal cancer. The degree of neurotoxicity may be either acute and reversible or observed as cumulative and chronic peripheral nerve damage leading to peripheral neuropathy (PNP), walking difficulties, extremity hypersensitivity, tingling and numbness, and increased pain sensation.

**Aim:** The aim of this paper is to determine and compare the ratio of clinical versus subclinical PNP cases in colorectal patients who underwent oxaliplatin treatment.

**Materials and Methods:** Thirty-two colorectal cancer patients were enrolled in the study. Patients received chemotherapy either as folinic acid and 5-fluorouracil and oxaliplatin or capecitabine and oxaliplatin regimen. Electroneurophysiological tests were performed before the treatment and after the 4th cycle when the risk of peripheral nerve damage increases. All patients were subject to a standard neurological examination and a semi-structured questionnaire interview.

**Results and Discussion:** Following oxaliplatin treatment, 21 (66.6%) of all patients presented neurological symptoms and/or electrophysiologically measured signs of PNP; of those, 7 patients (33.4%) displayed only electrophysiological changes and the remaining 14 patients (66.6%) presented fully symptomatic PNP – 4 patients were new neuropathy cases while the other 10 patients were previously diagnosed with PNP and showed signs of further neuronal deterioration and progressing sensory and motor dysfunction.

**Conclusion:** Our study lays ground for further larger scale longitudinal studies on oxaliplatin neurotoxicity and its prevention. We believe that early diagnosis of oxaliplatin-induced neurotoxicity is essential in the prevention of irreversible nerve damage and should be prioritized when assessing and evaluating treatment so that adequate adjustment may be made.

**KEY WORDS:** Colorectal cancer, nerve conduction velocity, neurotoxicity, oxaliplatin, peripheral neuropathy

## INTRODUCTION

Oxaliplatin belongs to a group of platinum-based drugs and is one of the most common and effective medications used in colorectal cancer therapy.[1-4] Unfortunately, its anticancer action is often outweighed by its neurotoxic effects exerted on peripheral nerves, leading to irreversible nerve damage, motor disabilities, and neuropathic pain.[5,6] According to numerous studies, the prevalence of oxaliplatin-induced neurotoxic effects ranges from 60% to 100% in various populations.[7-11] Oxaliplatin-induced neurotoxicity is the single main dose-limiting factor in colorectal cancer treatment. Neurotoxicity may present in two distinct forms: a reversible, transient, and acute neurotoxicity described as face muscle tightening, eye pain, pseudo-laryngospasm, and increased sensitivity to cold or cumulative and chronic peripheral nerve damage leading to peripheral neuropathy (PNP), walking difficulty, extremity hypersensitivity, tingling and numbness, and increased pain sensation.[5,6,10,11] An estimated 30%–40% of all patients treated with neurotoxic cytostatics present clinical symptoms of neuropathy. The higher actual number of patients suffering from chemotherapy-induced neuropathies could be attributed to subclinical nerve conduction impairment, noticeable only during electrophysiological examination. These subtle, subclinical changes, if left untreated, might progress to neuronal dysfunction and irreversible



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nerve damage, developing into symptomatic neuropathy, affecting patients' mobility and sensory response, and decreasing patients' quality of life.[12]

To better understand the differences between the clinical and subclinical neuropathy, we carried out electrodiagnostic studies before and throughout multiple time points during oxaliplatin treatment.

Abnormalities of sensory nerve conduction are early features of oxaliplatin nerve damage and it is evident that such changes are the most common consistent indicators of subclinical neuropathy.

While it is well documented that patients who received infusions of oxaliplatin often develop short-term neurological symptoms, electrophysiological recordings reflecting prolonged neurotoxicity are relatively scare.[13,14] The main aim of the paper was to fill in the gap in current data on oxaliplatin-induced neurotoxicity by providing electrophysiological evidence of its deteriorating effects on the peripheral nervous system in patients undergoing oxaliplatin chemotherapy.

## MATERIALS AND METHODS

### Patients and treatment regimen

Thirty-two patients with colorectal cancer were either on folinic acid and 5-fluorouracil and oxaliplatin (FOLFOX4) or capecitabine and oxaliplatin (XELOX) regimen. Patients on FOLFOX4 received intravenous oxaliplatin at 85 mg/m$^2$ on day 1, leucovorin 200 mg/m$^2$ on day 1 and 2, and a bolus of 5Fu 400 mg/m$^2$ on day 1 and 2 and 5Fu 600 mg/m$^2$ in 22 h on day 1 and 2; the cycle was repeated every 2 weeks for a maximum of 12 cycles. Patients on XELOX received oxaliplatin 130 mg/m$^2$ on day 1 and oral capecitabine 1000 mg/m$^2$ twice daily on days 1 through 14 followed by a week of rest; the cycle was repeated every 3 weeks for a maximum of 8 cycles. All patients provided written informed consent to participate in the study. The study was performed in accordance with the Declaration of Helsinki ethical standards and approved by the institutional review board.

### Electrophysiological examination

Electroneurographic tests were performed before the first chemotherapy treatment and after the 4$^{th}$ cycle when the risk of peripheral nerve damage increases. All patients were subject to a standard neurological examination and a semi-structured questionnaire interview regarding history of neurological symptoms such as numbness, tingling, burning sensation, neuropathic pain, weakness in the extremities, functional limitations, and disturbances indicating thermoregulatory and autonomic dysfunction. The electrophysiological examination was carried out according to standard procedures using a Viking Quest electromyograph (Nicolet Biomedical Incorporated, Madison, USA) according to standard protocols.[15] All patients were subject to an electrophysiological examination of median, ulnar, axillary, peroneal, sural, and tibial nerves. For nerve stimulation, surface silver electrodes or ring finger electrodes were used; the duration of the stimuli was 0.2 ms at all sites. Sensory nerve action potentials (SNAP) and compound motor action potentials (CMAP) were recorded with two surface 8 mm cup electrodes situated 3 cm apart. For reference, previously established standards were used.

## RESULTS

All patients enrolled in the study completed neurological and electrophysiological evaluation before the treatment. Chemotherapy was interrupted or delayed in more than half of all patients mainly due to the occurrence of G3/G4 neutropenia. One-fifth of all patients had oxaliplatin dose reduced throughout the course of the treatment. All patients, but one, completed four full cycles of oxaliplatin treatment. One patient was removed from the study due to prolonged absence and no contact available.

A decline in SNAP and CMAP amplitudes of lower limbs was the most common finding in our study while sensory and/or motor nerve conduction velocity (NCV) remained within normal range in most cases. A complete lack of single nerve excitability was diagnosed in five patients, four of these patients lacked SNAP and one of them lacked both SNAP and CMAP. Conduction block was not observed in all enrolled patients.

Before the treatment, PNP was diagnosed in 10 (31.25%) of all enrolled patients; of those, 3 patients had diabetic neuropathy and the remaining 7 patients showed nerve damage due to prolonged alcohol abuse. Following the treatment, the number of patients with PNP increased significantly. Twenty-one of all enrolled patients (66.6%) were diagnosed with PNP, presenting neurological symptoms and/or electrophysiologically measured signs of nerve damage; of those, 7 patients (33.4%) displayed only subclinical changes at the electrophysiological level and the remaining 14 patients (66.6%) manifested fully symptomatic PNP – 4 patients were new clinical neuropathy cases while the other 10 patients were previously diagnosed with PNP and showed signs of further neuronal deterioration and progressing sensory and motor dysfunction. Detailed results of the electrophysiological evaluation and a summary of results are presented in Table 1.

Two years after completion of the chemotherapy, the signs and symptoms of PNP have been maintained in all of the living patients who developed neuropathy.

## DISCUSSION

Neurotoxicity and peripheral nerve damage are the most common side effects of oxaliplatin cancer treatment, affecting from 60% to 100% of all patients.[10,11,16-18] In our study, we determined and compared the ratio of clinical versus subclinical PNP in colorectal patients following

**Table 1: Dosage, treatment duration, age/gender, neuropathy symptoms, and results of electrophysiological examination pre- and postoxaliplatin treatment in patients with colorectal cancer**

| Age/sex | Oxaliplatin treatment (mg)/duration of treatment (months) | Neuropathy symptoms G0-G5 | Pretreatment | Posttreatment |
|---|---|---|---|---|
| 58/male | 2040/5.8 | G1 | Normal | Normal |
| 59/female | 1256/3.8 | G2 | Normal | Normal |
| 63/female | 1200/3.5 | G1 | Normal | Normal |
| 44/male | 662/2.6 | G0 | Normal | Normal |
| 78/male | 920/2.6 | G1 | Normal | Normal |
| 52/female | 844/3.3 | G3 | Normal | Normal |
| 59/male | 790/1.1 | G1 | Normal | Normal |
| 59/male | 828/1.7 | G0 | Normal | Normal |
| 39/female | 1920/5.8 | G3 | Normal | Normal |
| 52/male | 800/2.3 | G1 | Normal | Normal |
| 54/female | 1270/5.1 | G3 | Normal | Normal |
| 48/male | 1433/3.6 | G1 | Normal | Normal |
| 60/female | 606/2.0 | G1 | Normal | Normal |
| 53/male | 1865/5.5 | G3 | Normal | Sensory axonal polyneuropathy |
| 55/female | 1561/3.5 | G2 | Normal | Sensory axonal polyneuropathy |
| 64/female | 1700/6.2 | G1 | Normal | Sensory axonal polyneuropathy |
| 65/female | 1251/4.7 | G3 | Normal | Sensory axonal polyneuropathy |
| 64/male | 1075/1.6 | G1 | Normal | Sensory axonal polyneuropathy |
| 63/male | 1000/2.1 | G1 | Normal | Sensory axonal polyneuropathy |
| 57/female | 540/2.2 | G2 | Normal | Sensory axonal polyneuropathy |
| 56/male | 602/2.2 | G0 | Normal | Sensory and motor axonal polyneuropathy |
| 44/female | 1300/5 | G3 | Normal | Sensory and motor axonal polyneuropathy |
| 67/male | 960/2.9 | G2 | Sensory axonal polyneuropathy | Sensory axonal polyneuropathy |
| 72/female | 600/1.5 | G0 | Sensory axonal polyneuropathy | Sensory axonal polyneuropathy |
| 60/male | 680/2.1 | G1 | Sensory axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 70/male | 1600/4.9 | G0 | Sensory axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 63/male | 2040/5.1 | G1 | Sensory axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 60/male | 1856/5.1 | G3 | Sensory axonal polyneuropathy | Sensory axonal polyneuropathy |
| 54/male | 2040/5.4 | G2 | Sensory and motor axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 69/male | 1460/3 | G1 | Sensory and motor axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 71/male | 1000/2.3 | G2 | Sensory and motor axonal polyneuropathy | Sensory and motor axonal polyneuropathy |
| 68/male | 1738/4.7 | G2 | Sensory and motor axonal polyneuropathy | Sensory and motor axonal polyneuropathy |

oxaliplatin treatment. We showed that after four cycles of treatment, the number of patients manifesting neurological symptoms and/or electrophysiological signs of PNP significantly increased, demonstrating a link between oxaliplatin treatment and nerve damage. We demonstrated that 21 (66.6%) of all patients enrolled in the study presented clinical or subclinical symptoms of PNP. Of all the cases diagnosed, 7 patients manifested neuronal damage only during electrophysiological examination (subclinical neuropathy), 4 patients presented both electrophysiological changes and clinical symptoms, and finally, 10 previously diagnosed patients showed signs of further deterioration of existing conditions, i.e., impaired or lack of NCV, pronounced sensory and/or motor symptoms such as paresthesias or dysesthesias, walking difficulties, etc.

Our finding is consistent with previous reports showing that patients at risk of developing neuropathy or already with diagnosed peripheral nerve changes are the most affected by the treatment.[11,19-21] This observation provides key information on increased susceptibility to oxaliplatin-induced neuropathy in at-risk populations of colorectal patients and should be crucial in designing customized treatment plans for such patients.

The increased susceptibility to oxaliplatin-induced neuropathy might be triggered by underlying genetic predisposition. Indeed, studies show that the polymorphisms of genes belonging to families of ATP-binding cassettes, cytochrome P450, glutathione S-transferase, or voltage-gated sodium channel increase the risk of oxaliplatin-related peripheral nerve damage;[22-25] however, their exact mechanism of action of these genes in the development of oxaliplatin-induced neuropathy remains elusive and requires further studies.[22,24,26] Furthermore, running pharmacogenetic tests on an ongoing basis in the hospital setting is often impractical, cumbersome, and costly; hence, simpler and less expensive tests are indicated.

## CONCLUSION

The results of our study provide preliminary evidence on oxaliplatin effects in two different groups of patients with and without clinical neuropathy symptoms. We observed that oxaliplatin exacerbated preexisting nerve damage in both groups impairing NCV. These changes were more pronounced in patients with subclinical neuropathy and lead to the development of clinical, symptomatic neuropathy in half of these patients. Our study lays ground for further

larger scale longitudinal studies on oxaliplatin neurotoxicity and its prevention. We believe that early diagnosis of oxaliplatin-induced neurotoxicity is essential in the prevention of irreversible nerve damage and should be prioritized when assessing and evaluating treatment so that adequate adjustment may be made.

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**Conflicts of interest**
There are no conflicts of interest.

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