

Electroneurography in the evaluation of oxaliplatin-induced neuropathy in colorectal cancer patients

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Cold-induced neuropathy is the most observed side effect of oxaliplatin. Presence of neuropathy is routinely assessed by electroneurographical examination. The use of electroneurography has not been a part of typical oncological monitoring and treatment protocols, leading to untreated, irreversible damage to patients' peripheral nerves, undiagnosed for long periods of time. 36 colorectal cancer patients followed FOLFOX4 with/without bevacizumab or XELOX were enrolled between February 2013 and January 2015 in the study at the University Hospital Oncological Department, Krakow, Poland. Electroneurography was performed prior to the first cycle of chemotherapy and after the 4th cycle. 32 out of 36 enrolled patients completed neurological evaluation. Pre-treatment neurographic examination revealed presence of peripheral neuropathy in 10 (31.25%) patients; 6 (18.75%) had sensory neuropathy and 4 (12.5%) had mixed, sensorimotor neuropathy. After treatment examination revealed significant increase in the number of neuropathic patients; presence of peripheral neuropathy was observed in 19 patients (59%), sensory polyneuropathy was diagnosed in 10 patients (31.25%) and mixed neuropathy was diagnosed in 9 patients (28.13%). Early electrophysiological monitoring followed by a symptom dependent oxaliplatin regimen would be highly beneficial for patients undergoing oxaliplatin treatment, improving their well-being and positively affecting their life quality.

Key words: oxaliplatin, neuropathy, colorectal cancer, electroneurography

Oxaliplatin is a common cytotoxic agent in the treatment of colorectal cancer, used either as an adjuvant or palliative system therapy [1]. It belongs to the platinum class of drugs and, along with cisplatin and carboplatin, aside from treating affected tissue, exerts certain neurotoxic effects on peripheral nerves. Chemotherapy-induced neurotoxicity is often presented as a cold hypersensitivity of hands and feet, prolonged tingling and numbness and increased pain sensation, difficulties with walking leading, if not treated, to peripheral neuropathy [2, 3]. Oxaliplatin-induced neuropathy might be diagnosed as reversible, acute paresthesia and dysesthesia in the extremities triggered or enhanced by exposure to cold. 82% of patients experience their neuropathy regress within 4 to 6 months. 41% of patients have complete recovery within 6 to 8 months [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Accumulative, often irreversible, chronic polyneuropathy induced by oxaliplatin in 13% to 20% of the patients and usually has a predictable clinical course [6, 8, 9, 13, 14, 15,

16]. In this kind of polyneuropathy occur paresthesias and dysesthesias of gradually prolonged duration (between cycles), and increase in intensity with the cumulative dose and that eventually causes functional impairment and in consequence – the quality of life [8, 9]. Moreover, exacerbation of oxaliplatin-induced neurotoxicity with the functional impairment following surgery are observed. It could be the result of peroperative hemolysis [17, 18].

The factors contributing to the development of long-term irreversible neuropathy remain unclear, however a growing number of studies indicate that certain forms of channelopathies and disturbance of normal axonal membrane potential might be responsible for neuropathy development [3, 19, 20, 21, 22, 23]. Despite the prevalence of neurotoxicity symptoms in oxaliplatin treated patients, neurological examination has not been a part of standard cancer treatment protocol. Here in this paper we report high prevalence of neuropathy in oxaliplatin treated patients and underscore the benefits of

early diagnosis and treatment of the peripheral nerve changes in colorectal cancer survivors.

Material and methods

A total of 36 colorectal cancer patients were enrolled between February 2013 and January 2015 for the study. Patients followed FOLFOX4 (folinic acid and 5-fluorouracil and oxaliplatin) with/without bevacizumab or XELOX (capecitabine and oxaliplatin) chemotherapy regimen at the University Hospital Oncological Department, Krakow, Poland. FOLFOX4 consisted of intravenous oxaliplatin 85 mg/m² on day 1, leucovorin 200 mg/m² on day 1,2 and 5Fu 400 mg/m² in bolus on day 1,2 and 5Fu 600 mg/m² in 22 hours on day 1,2. Treatment courses were repeated every 2 weeks for a maximum of 12 cycles. Bevacizumab 10 mg/kg was administered intravenously on day 1 of each cycle. Chemotherapy regimen XELOX consisted of intravenous oxaliplatin 130 mg/m² on day 1 and oral capecitabine 1000 mg/m² twice daily on days 1-14 followed by a 7-day rest. Treatment courses were repeated every 3 weeks for a maximum of 8 cycles. Electroneurography was performed prior to the first cycle of chemotherapy and after the 4th cycle (when peripheral neuropathy risk increases). All patients underwent a complete neurological examination and a semi-structured questionnaire interview. The neurographic examination was carried out according to standard procedures using Viking Quest (Nicolet Biomedical Incorporated, Madison, WI, USA) following manufacturer guidelines. In all patients, neurographic examination of motor and sensory fibres of the following nerves: median, ulnar, peroneal, sural and tibial, was performed using standard stimulating sites [24]. The results of the examinations were compared with standard reference ranges established in our department and standard adopted from literature [24]. The study was approved by a local institutional ethical committee. Prior to the initiation of the study, written informed consent was obtained from all individual participants included in the study. Four patients did not complete the study due to collateral health issues or treatment discontinuation. Patient characteristics are presented in table 1.

Statistical analysis. Statistical analysis carried out using STATISTICA 10.PL. Comparison between groups were carried out using chi-squared test. The multiple logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (95%CI). The results were considered statistically significant at P values of = 0.05.

Results

Thirty two out of thirty six enrolled patients completed neurological evaluation. Four patients had only one examination; of those, in three cases, premature completion was due to the progression of the primary disease and in one case, the patient resigned from treatment continuation.

More than a half of all enrolled patients had a treatment delay. Neutropenia G3/G4 was the most common reason of chemotherapy interruption. Oxaliplatin dose was reduced for one fifth of all patients throughout the course of the treatment.

Adverse events were assessed at each cycle according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 4.03). Advanced symptoms of neuropathy (G3/G4) were observed in 5 cases (15.6%). Despite oxaliplatin dose reduction, symptoms of neuropathy persisted. In 4 out of 5 cases, oxaliplatin was omitted in the last few chemotherapy cycles. In 1 case the oxaliplatin dose was reduced. Premature treatment completion was necessary in 18 patients (56.25%). Half of the patients (28.1%) had progression of disease confirmed in the CT scans. Advanced symptoms of neuropathy G3/G4 in 4 patients (12.5%), neutropenia G3/G4 (despite of neutropenia treatment) in 3 patients (9.4%) and thrombocytopenia (despite of thrombocytopenia treatment) in 1 patient (3.1%) were other reasons of premature treatment completion. Chemotherapy was completed at patient's request in 1 case (3.1%). Delayed treatment was observed in 19 patients (59.4%). Neutropenia G3/G4 (in 7 patients) and infection (in 4 patients) were the main reasons of the delay.

Thrombocytopenia G3 and neutropenia G3/G4 were observed in 1 (3.1%) and 7 (21.9%) of treated patients, respectively. The median cumulative dose was 686 mg/m² and varied between 508 and 1000 mg/m².

Electrophysiological examination. The diminution of amplitude of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs) in lower limbs were most common and more advanced than the generally normal or moderate slowing of sensory and motor fibre conduction velocity. Lack of excitability in single nerves was diagnosed in 5 patients. We ascertained a lack of SNAPs: in the peroneal nerve (3 patients), in the ulnar nerve (1 patient) and lack of SNAP and CMAP in the peroneal nerve (1 patient). None of the patients showed signs of a conduction block.

Pre-treatment neurographic examination revealed presence of peripheral neuropathy in 10 (31.25%) patients; 6 (18.75%) had sensory neuropathy and 4 (12.5%) had mixed, sensorimotor neuropathy. After treatment examination revealed significant increase in the number of neuropathic patients; presence of peripheral neuropathy was observed in 19 patients (59.4%), sensory polyneuropathy was diagnosed in 10 patient (31.25 %) and sensorimotor neuropathy was diagnosed in 9 patients (28.13%). None of the patients showed electrophysiological features of demyelination. In the remaining patients (40.63 %) neurographic examination remained within normal range. Results of the examination and the summary of neurographic findings are presented in table 2 and 3.

Discussion

Our study reports a high prevalence (59.4%) of electrophysiological changes in the peripheral nerves of

oxaliplatin treated patients. The results are consistent with earlier reports and emphasize the value of expanding cancer treatment monitoring protocols in cancer survivors by supplementing them with a routine neurological examination in order to prevent and/or alleviate oxaliplatin induced neurotoxicity and peripheral neuropathies [2, 3, 25, 26]. Dorsal root ganglia sensory neurons, satellite cells, Schwann cells, neuronal and glial cells in the spinal cord are the most probably sites where occur neurotoxicity-induced chemotherapy [19]. The underlying mechanisms behind oxaliplatin toxicity remain unclear. However, DNA damage, alterations in cellular system repairs, mitochondria changes, increased intracellular reactive oxygen species, glutamate signalling, MAP-kinases and nociceptors ectopic activation are known as the most important reasons of the onset of oxaliplatin-induced peripheral neurotoxicity [19]. The organic cation transporter 2 expressed on dorsal root ganglia cells is responsible for multiple increasing of oxaliplatin uptake in cells. This phenomenon correlates with acute oxaliplatin-induced neurotoxicity [27]. Recently, it emphasizes that an alterations on human motor and sensory axonal membrane Na(+) channels cause oxaliplatin-induced neurotoxicity [3, 19, 21, 22, 23]. On the basis of excitability studies performed before and immediately after oxaliplatin infusion show significant increases in refractoriness and relative refractory period postinfusion in all patients, consistent with an effect of oxaliplatin on axonal Na(+) channels. The patients with chronic neuropathy have greater changes. Following cessation of oxaliplatin treatment, 41% of patients have persistent symptoms and nerve conduction abnormalities consistent with the development of chronic neuropathy [23]. In our study premature treatment completion was in 4 patients (12.5%) due to advanced symptoms of neuropathy. On the other hand, following oxaliplatin infusion, developing abnormalities are observed in the recovery cycle with refractoriness markedly increased. Continuing oxaliplatin infusions, changes developed consistent with axonal hyperpolarization, with proportional changes pre- and post-oxaliplatin in normalized threshold [20].

Establish early clinical and neurophysiological markers of oxaliplatin-induced peripheral neuropathy is the aim of Velasco's et al. study. The patients presented a decrease in all nerve conduction studies, reported more acute neuropathic symptoms and received higher oxaliplatin cumulative dose. Neurological assessment and acute neuropathy symptoms meaning the over 30% decrease in sensory nerve action potential amplitude from the baseline in radial and dorsal sural nerves in nerve conduction studies at mid-treatment can indicate patients with risk of high-grade oxaliplatin-induced neurotoxicity [28]. Sensory axonal excitability techniques may be useful in monitoring for early signs of oxaliplatin-induced neurotoxicity. Patients with severe neurotoxicity at the treatment completion demonstrated greater excitability changes than those left with mild or moderate neurotoxicity, suggesting that assessment of sensory excitability parameters

may provide a sensitive biomarker of severity for oxaliplatin-induced neurotoxicity [3, 29].

On databases PubMed and Cochrane established a relation between long term oxaliplatin-induced peripheral neuropathy (at least 12 months after completion of chemotherapy), severity of symptoms and higher cumulative dose of oxaliplatin [4, 29, 30]. On the basis of neurological assessment, clinical neuropathy score and nerve conduction studies performed at baseline, the end of chemotherapy and two years after chemotherapy completion established that chronic oxaliplatin-induced neuropathy two years after discontinuing chemotherapy occurs very often. Almost 80% of patients have residual neuropathic symptoms, with distal loss of pin-prick sensibility and loss of vibration sensibility. There is observed correlation between severity of oxaliplatin-induced neuropathy two years and high severity of neuropathy at the end of chemotherapy [30,31]. Cumulative dose and infusion duration are critically associated with the incidence of this kind of neurotoxicity [4, 8, 9, 12, 22, 32]. Factors such as anemia, diabetes mellitus, high BMI (body mass index), hypomagnesemia are predisposing to the neuropathy from oxaliplatin [33, 34]. On the other hand, the advanced age (69 years and more) of colorectal patients without any other significant co-morbidities receiving oxaliplatin does not influence the acute and cumulative oxaliplatin-induced neuropathy [35]. In our study alcohol abuse and the advanced age increase risk of neuropathy but these results are not statistically significant.

Pharmacogenomic methods are one of the methods to identify reasons in differences in oxaliplatin-induced neurotoxicity escalation within and/or after chemotherapy completion. The results of prospective, multicenter Argyriou's et al. study shows that nucleotide polymorphism of voltage-gated sodium channels gene (SCN4A-rs2302237) is predictive factor of the severity of acute and the occurrence of chronic oxaliplatin-induced neuropathy. Furthermore, two single nucleotide polymorphisms (SCN4A-rs2302237 and SCN10A-rs1263292) are significantly associated with an increased incidence of acute oxaliplatin-induced neuropathy [36]. In the other study identifies single-nucleotide polymorphisms in genes (involved in among others oxaliplatin metabolism) to predict oxaliplatin-induced peripheral neuropathy among patients treated with oxaliplatin based chemotherapy. The rs2230641 cyclin H (CCNH) rs2230641 C/C and the ATP-binding cassette subfamily G, member 2 (ABCG2) rs3114018 A/A genotypes are associated with a higher risk of severe oxaliplatin-induced peripheral neuropathy. Moreover, the combination of CCNH C/C and/or the ABCG2 rs3114018 A/A genotypes results in a higher risk of grade 2-3 oxaliplatin-induced peripheral neuropathy than those with the CCNH any T and ABCG2 any C genotypes. These findings of single-nucleotide polymorphisms allows to foresee higher probability of severe oxaliplatin-induced peripheral neuropathy [1]. Other two trials estimating of polymorphisms in different genes as determinants of chronic oxaliplatin-induced peripheral neurotoxicity are negative [37, 38].

Besides sensory peripheral neuropathy hematologic and gastrointestinal toxicities are frequent and moderate [5,6]. Neutropenia and thrombocytopenia are the major hematologic toxicities [12, 39]. Neutropenic febrile complications are rare [5]. The occurrence of side effects did not increase when oxaliplatin was added to fluorouracil-based regimens in our patients what is consistent with the literature data [5]. Gastrointestinal toxicities such as diarrhea, nausea, vomiting, stomatitis, abdominal pain are common, but controllable and rare long-lasting [5, 6, 7, 10, 39, 40]. Older patients may have been more susceptible to dehydration, diarrhea, hypokalemia [39]. Hepatic failure with perisinusoidal fibrosis, peliosis or nodular regeneration hiperplasia with a progressive increase in gammaglutamyl transpeptidase and alkaline phosphatase is rare and severe side effect. In general liver function tests improve after oxaliplatin withdrawal. In some cases hepatic failure is lethal [41]. Hypersensitivity reactions related to oxaliplatin may manifest as facial flushing, rash/hives, tachycardia, dyspnoea, erythema, pruritus, fever, tongue swelling, headache, chills, weakness, vomiting, burning sensations, dizziness and oedema. These reactions are observed in approximately 12% of patients. In 1 – 2% of patients develop symptoms grade 3 or 4 [40, 42]. Furthermore, severe thrombocytopenia with immediate onset as a hypersensitivity reaction has been reported in literature [43]. All of the symptoms are reversible. Ocular toxicity included tunnel vision, visual loss with postural changes, altered color vision are rare and reversible [44, 45]. Dysphonia with acute onset is other rare symptom after the administration of oxaliplatin [46]. Both ocular toxicity and dysphonia impair transiently the quality of life. Rare, isolated cases of pulmonary fibrosis and fatal diffuse alveolar damage induced by oxaliplatin are reported in literature [47, 48, 49]. Reversible urinary retention and Lhermitte sign after the higher than 1000 mg cumulative dose of oxaliplatin [32]. Toxicity was mild and generally acceptable in presented group of the patients. Hematological toxicity G3/G4 occurred in 8 patients. Gastrointestinal toxicities (nausea, diarrhea, vomiting) G1/G2 were reported in 14 patients. Advanced symptoms of neuropathy G3/G4 with the quality of life impairment was observed in 5 cases. None of the patients did not report any other side effects.

Early diagnosis of the neurotoxicity and reductions in oxaliplatin dose or alteration of chemotherapy schedule can prevent against chronic symptoms which in consequence can be persisted and effect on the quality of life [50, 51]. Despite this procedure efficacy of oxaliplatin therapy is safely maintained. Effective medicaments against oxaliplatin-induced neurotoxicity are topical pain relievers, such as baclofen/amitriptyline/ ketamine gel, and serotonin and norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine [52, 53]. Amifostine is a radioprotective drug that has oto- and neuroprotector effects to cisplatin injury and protect against cyclophosphamide-induced taste loss [54]. In preclinical study showed neuroprotection effect of amifostine. Further clinical trials are necessary to evaluate in patients treated with oxaliplatin regimens [55]. On the other hand, there are

disappointed results from the current trial where observed a lack of benefit for Vitamin E in prophylaxis oxaliplatin-induced peripheral neuropathy [56]. A nonpharmacological therapy cutaneous electrostimulation seems to be potentially effective in the treatment of oxaliplatin-induced neurotoxicity [52]. The earlier recommendations for the management of the acute and chronic neuropathy induced oxaliplatin include use of neuromodulatory agents, such as intravenous calcium and magnesium infusions [52, 57]. In more recent Han's et al. double blind crossover study revealed that oxaliplatin given with Ca/Mg or placebo has the same plasma pharmacokinetics of intact anticancer drug and free platinum. Moreover, electromyography motor nerve hyperexcitability scores is similar with Ca/Mg or placebo. In addition, frequency of acute neurotoxicity symptoms are not differ between Ca/Mg and placebo [58].

Summarizing, oxaliplatin-induced neuropathy is a common side effect of oxaliplatin therapy in colorectal cancer patients. Early electrophysiological monitoring followed by a symptom dependent oxaliplatin regimen adjustment and early introduction of anti-neuropathy preventive measures would be highly beneficial for patients undergoing oxaliplatin treatment, improving their well-being and positively affecting their life quality. Based on the results of our and other's studies, we postulate that the routine neurographical examination should be a part of a standard colorectal cancer therapy protocol.

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