Role of Alpha Lipoic Acid in Prevention of Oxaliplatin Neurological Toxicity

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Background: Oxaliplatin, an effective antineoplastic agent against colorectal tumors, can cause severe peripheral neurotoxicity, which seriously limits its clinical application. To date, there is no effective treatment for this complication. Alpha lipoic acid (ALA) been shown to be an effective in the treatment of diabetic distal sensory-motor neuropathy. The aim of this study was to evaluate the effects of ALA on preventing oxaliplatin-induced neurotoxicity in patients with colorectal tumors. **Methods**: In this study, Forty-nine patients with colorectal cancer were treated with Oxaliplatin, Leucovorin and Fluorouracil Regimen (FOLFOX4 protocol). The patients were randomly divided into two groups, the experimental group (24 patients) and control group (25 patients). The experimental group received ALA, while no neuroprotective agents were applied in the control group. The incidence rates and classification of neurotoxicity in the two groups were evaluated and the differences between the two groups were examined. Furthermore, the effect of ALA on neuronal electrophysiological parameters was also examined. **Results**: The grade of neurotoxicity in the experimental group was significantly lower than in the control group (P<0.05, Mann-Whitney U test) after two, four and six cycles of chemotherapy. Interference of daily activity was significantly lower in the ALA group than in the control group. In addition, the evaluation of motor and sensory nerve conductions showed significantly improvement in ALA group compared to the control group. The rate of increment of conduction velocity in ALA group is greater in the sensory nerve than in the motor nerve compared to the control group (p<0.001). **Conclusion**: The data suggested that ALA could reduce the grade of oxaliplatin-induced neurotoxicity and was an effective neuroprotective agent against oxaliplatin-induced high-grade neurotoxicity in patients with colorectal tumors.

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1. Introduction:

Neurotoxicity is a common adverse effect associated with antineoplastic agents. Of these agents, oxaliplatin has been commonly used in clinical practice to treat various gastrointestinal tract cancers. A common toxic effect of oxaliplatin is peripheral neurotoxicity (PN), which is known to be cumulative [1]. At cumulative doses that reach 800 mg/m^2, the occurrence of neurotoxicity is highly likely. A total neuropathy score ≥ grade 3 PN occurs in 15% of cases after cumulative doses of 750-850 mg/m2 and in 50% of cases after a total dose of 1170 mg/m^2 [2].

Oxaliplatin treatment induces an acute neurotoxicity, characterized by a rapid onset of cold-induced distal dysesthesia and a chronic sensory peripheral neuropathy [1]. The clinical similarity between the acute oxaliplatin induced PN symptoms, such as transient paresthesia and dysesthesia in the perioral area, and conditions caused by impairment of neuronal ion channels suggests that oxaliplatin interacts with ion channels located in the cellular membrane [3] or induces alteration in voltage gated sodium (Na+) channel function [4]. On the other hand, the chronic, sensory, oxaliplatin-induced PN may be induced by decreased cellular metabolism and axo-plasmatic transport secondary to the accumulation of platinum compounds in dorsal root ganglia (DRG) cells [5], by the impairment of cellular mitochondrial oxygen consumption [6], or by the prolonged activation of voltage-gated Na+ channels, which induce cellular stress in sensory nerve cells via excess Ca2+ influx [7]. Antineoplastic agents are known to produce oxidative stress, reduce the total radical-trapping capacity of blood plasma, and decrease plasma levels of antioxidants [8]. Reactive oxygen species modulate Na+ channel activity [9], a class of ion channels that has been suggested to enhance nociceptor activity in patients with acute oxaliplatin-induced PN [10]. Moreover, the evidence that dorsal root ganglion oxidative stress may be an important pathogenic mechanism for chronic toxicity is increasing [11].

Dose-limiting neuropathies may require clinicians to adjust chemotherapeutic doses. An ideal approach is to prevent or minimize neuropathy symptoms and not to reduce the efficacy of chemotherapeutic agents against tumors. Though an effective treatment of established chemotherapy-induced PN has not been

found, many prevention and treatment strategies have been suggested, including amifostine, acetyl-L-carnitine, and antioxidants, such as vitamin E, vitamin C, β-carotene, and glutathione [12].

Alpha lipoic acid (ALA) is a strong antioxidant with anti-inflammatory effects. [13] In several studies, ALA has been demonstrated to inhibit free radicals that cause oxidative damage. [14, 15] In animal studies, alpha lipoic acid (ALA) has been shown to prevent or even reverse hyperglycemia- induced nerve dysfunction by reducing free-radical-mediated oxidative stress.[16] It has also been demonstrated that ALA improves nerve blood flow and peripheral nerve fiber conduction and increases endoneurial glucose uptake and energy metabolism in experimental diabetic peripheral neuropathy.[17] Two meta-analyses of randomized, placebo-controlled trials using ALA infusions of 600 mg intravenously/orally per day for 3 weeks in diabetic patients with positive symptoms of peripheral neuropathy have been published [18, 19] and suggest that this treatment produces clinically significant improvements in neuropathic symptoms and deficits. When given intravenously, ALA leads to a significant and clinically relevant reduction in neuropathic pain. Improvements with oral administration are less described but strongly marked after just 2 weeks of treatment. [20]

Platinum antineoplastic agents have been shown to induce a fall in plasma antioxidant levels, due to oxidative stress in human studies, and supplementation with antioxidants has shown a protective effect against cisplatin-induced renal toxicity and ototoxicity in animal studies [21]. Thus, based on the above, we conducted a pilot study in patients with colorectal cancer to assess the efficacy of ALA in preventing oxaliplatin induced neurotoxicity.

2.Methods

Design and Patients

We performed a randomized interventional study of colorectal cancer patients who were submitted to chemotherapy treatment. The study was carried out with 49 patients (24 females, 25 males) who had undergone complete resection of their colorectal cancer, which was of histologically scored as stage IIB, III, or IV, and who were going to begin adjuvant/palliative chemotherapy with Oxaliplatin, Leucovorin, and Fluorouracil Regimen (FOLFOX4 protocol) [22] at Clinical Oncology department, Tanta University Hospital, Tanta, Egypt.

The patients were randomly divided into two groups, the experimental group (ALA group, n =24) and control group(n=25). The ALA group was treated with FOLFOX4 plus ALA, and the control group received only FOLFOX4. Patients remained on study during 6 chemotherapy cycles, of 15 days each. The doses of medication in ALA group were as follows: **oxaliplatin** 85 mg/m² IV in 500mL D5W over 120 minutes Day 1, **leucovorin**200 mg/m² IV diluted in D5W over 120 minutes concurrently with oxaliplatin on day 1 Days 1 and 2 alone, **Fluorouracil** 400 mg/m² IV bolus, after leucovorin Days 1 and 2 ***THEN***, **Fluorouracil** 600 mg/m² IV continuous infusion over 22 hours Daily, on Days 1 and 2 and ALA , 600 mg oral daily from day 3 to day 15 (Alpha Lipoic Acid 600 mg, GNC live well Co, Kuala Lumpur, Malaysia). The dose of ALA is similar to that used in previous study of Bertolotto *et al.,*2012 [23].No changes in food intake pattern had occurred during the supplementation. The calculation for estimating the sample size required for a randomized clinical trial was according to Greenberg *et al.,*[24], with constant level of significance (α) of 5%.

Exclusion criteria:

Patients with pre-existing neuropathy, alcoholic disease, diabetes mellitus or central nervous system metastasis, and patients on therapy of vitamin supplement were excluded from this study. An institutional review board had reviewed the treatment protocol and all patients provided written, informed consent before initiation of study-related procedures. To avoid the possible effect on interpretation of neurotoxicity, calcium or magnesium infusion was not allowed during oxaliplatin administration.

Neurotoxicity grading scales

Neurological toxicities were assessed at baseline, and after 2, 4, and 6 cycles of treatment according to the National Cancer Institute Sanofi Criteria (Table 1) [25, 26].

Table 1. Neurotoxicity grading scales

Standard setting unit	Grade 1	Grade 2	Grade 3	Grade 4
NCI-Sanofi criteria	Paresthesias or dysesthesias of short duration that resolve and do not interfere with function	Paresthesias or dysesthesias interfering with function but not activities of daily living	Paresthesias or dysesthesias with pain or functional impairment that also interfere with activities of daily living	Persistent paresthesias or dysesthesias that are disabling or life-threatening

NCI, National Cancer Institute. [25]

General Clinical Assessment:

Interference with activities of daily living (ADL) such as bathing, personal hygiene, self feeding, dressing, and getting around inside the home were recorded. The oxaliplatin dose was reduced to 75 mg/m2 until recovery in patients with grade 3-4 neurological toxicity. Treatment was delayed until recovery if grade 3-4 non-neurological toxicity occurred. In patients with intolerable neurotoxicity or persistent functional impairment, oxaliplatin was omitted from the regimen

Electroneurography parameters:

Electroneurography parameters were assessed by a Dantec (Dantec, Skovlunde, Denmark) keypoint device to collect the signal and for the recording of the responses. The subjects were seated in a comfortable chair and instructed to be as relaxed as possible. Electroneurography parameters included motor nerve (peroneal) conduction and sensory (sural) nerve conduction.[23] Differences between baseline on the start of the study and post-treatment values after six chemotherapeutic cycles were recorded for all measured variables.

Statistical analysis

All data in this study were processed using SPSS 20 software (IBM, Armonk, NY, USA). For group comparisons, unordered categorical variables were compared using chi-square ($\chi 2$) test or Fisher's exact test, measurement data were compared using Student's t-test, and ordinal variables of multi-classification were compared using *Mann–WhitneyU* test. Logistic ordinal regression was used to determine correlations in classification of neurotoxicity between the experimental group and control group. A *P* value <0.05 was considered statistically significant.

3. Results

Patient's characteristics:

Forty-nine patients enrolled in this study were divided into 2 groups, the ALA group (24 patients) and the control group (25 patients). The distribution of patient's characteristics between the 2 groups was showed in Table (2) and they were balanced with no statistically differences between the treated groups as regard the age, gender, performance status, pathological grade, serum Carcino embryonic antigen (CEA) level and nodal status (N).

Neurotoxicity evaluation:

After chemotherapy, the incidence rates and classification of neurotoxicity in the two groups were comprehensively evaluated using the neurotoxicity grading scales, and the differences between the two groups were examined. All patients exhibited grade 0 to 3 neurotoxicity, and no patients exhibited grade 4 neurotoxicity. In our study, the incidence of neurotoxicity (Grades 1, 2 and 3) in the ALA group was 58%; while that in the control group was 92%. (*P* <0.05, *Mann–Whitney U* test, Table 3). After two cycles of chemotherapy, twenty five percentage of ALA group suffering from grade 1-2 neurological toxicity compared to fifty six percentage of control group (*P* <0.05) (Fig 1). No patient showed grade 3-4 neurological toxicity in both groups. After four cycles, ALA group showed a significantly lower incidence of neurological toxicity, Grade 1-2 neurological toxicity presented in 34% vs. 68% for the control group and grade 3 neurological toxicity presented in 8% vs. 12% respectively (p<0.05) (Fig 2). After six cycles, ALA group maintained a significantly lower incidence of neurological toxicity, Grade 1-2 neurological toxicity presented in 55% vs. 76% for the control group and grade 3 neurological toxicity presented in 4% vs. 16% respectively (p <0.05) (Fig 3).

Nerve conductions tests:

Table (4) shows the incidence of Nerve conductions tests in both groups. The motor and sensory nerve conductions studies improved in ALA group compared to the control group. The rate of increment of conduction velocity in ALA group is greater in the sensory nerve (11.9 %) than in the motor nerve (6.25 %) compared to the control group (p<0.001). These changes are considered as a good improvement particularly in sensory nerve conduction.

General Clinical Assessment:

The impact of ALA administration on oxaliplatin dose reduction, daily activity Interference and non neurological toxicity like severe leukopenia was recorded in Table (3). The need for oxaliplatin dose reduction was insignificantly lower in the ALA group 4.3% vs. 20% in the control group (p=0.2). Interference of daily activity was significantly lower in the ALA group than the control group (13% vs. 52% respectively; p=0.005). There was no significant difference, as regard the non-neurological toxicity, between the 2 groups.

4.**Discussion**

Oxaliplatin-induced neurotoxicity is a common, potentially severe and dose-limiting adverse effect of cancer treatment [27]. The characteristics of oxaliplatin-induced neurotoxicity are related to dose intensity and cumulative dose. Neurotoxicity can profoundly affect the quality of life, often compelling clinicians to lower the chemotherapy regimen, consequently limiting therapeutic efficacy [28]. Oxaliplatin-induced neurotoxicity is of two types: acute and chronic. Acute neurotoxicity was believed to reflect a state of peripheral nerve hyper-excitability that likely represents a transient oxaliplatin-induced impairment of ion channels, while the chronic treatment induces an axonal neuropathy similar to the other platinum-based drugs [29].

Table (2): Patients Characteristics

	ALA group	Control patients	Total	*P value*
	24 patients (49%)	25 patients (51%)	49 patients (100)	
Age-				0.889[a]
≥ 55	12(50%)	12(48%)	24(49%)	
< 55	12(50%)	13(52%)	25(51%)	
Gender				0.889 [a]
M	12(50%)	13(52%)	25(51%)	
F	12(50%)	12(48%)	24(49%)	
PS				0.869 [a]
0	10(48%)	11(44%)	21(43%)	
1	14(52%)	14(56%)	28(57%)	
CEA				0.917 [a]
Normal	9(37%)	8(32%)	17(44%)	
High	15(63%)	17(68%)	22(56%)	
N				0.666 [a]
0	9(37%)	10(40%)	19(39%)	
1	11(46%)	12(48%)	23(47%)	
2	4(17%)	3(12%)	7(14%)	

Median=55 years (range 41-71); ALA, Alpha lipoic acid; PS, Performance status;
CEA, Carcinoembryonic antigen; N, Nodal status.[a] Comparisons performed using χ^2 test

Table 3. Comparison of the grade of neurotoxicity between the two groups

	ALA group 24 patients (49%)		**Control patients** 25 patients (51%)		**Total**		***P* value**
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	0.029
Grade 0	10	42%	2	8%	12	24.5%	
Grade 1	4	16%	8	32%	12	24.5%	
Grade 2	9	38%	11	44%	20	41%	
Grade 3	1	4%	4	16%	5	10%	

[a]Comparisons performed using Mann–Whitney *U* test.

Table 4. Motor and sensory nerve conduction among oxaplatin and alpha lipoic acid treated patients

Motor nerve conduction (m/sec)			
	Pre-treatment **Mean ± SD**	Pre-treatment **Mean ± SD**	*P* value
ALA group	37.46 ± 2.76	39.8 ± 3.42	< 0.001
Control group	34.81 ± 1.9	34.90 ± 1.8	>0.05
Sensory nerve conduction (m/sec)			
	Pre-treatment **Mean ± SD**	Pre-treatment **Mean ± SD**	*P* value
ALA group	34.44 ± 3.98	38.53 ± 3.54	< 0.001
Control group	32.58 ± 2.99	32.61 ± 3.2	>0.05

Data expressed as mean ± SD standard derivation

Table 5: The impact of alpha lipoic acid supplementation

	ALA group	**Control patients**	***P value***[a]
	24 patients	25 patients	
Oxaplatin dose reduction			0.19[a]
Needed	1(4%)	5(20%)	
Not needed	23(96%)	20(80%)	
Daily activity			0.005 [a]
Interference	3(12.5%)	13(52%)	
Not	21(87.5%)	12(48%)	
Severe Leucopenia	2(8%)	4(16%)	0.66 [a]

[a] Comparisons performed using Fisher Exact test

Fig. 1 Effect of ALA on the incidence of Oxaliplatin induced neurotoxicity after 2 cycles of chemotherapy

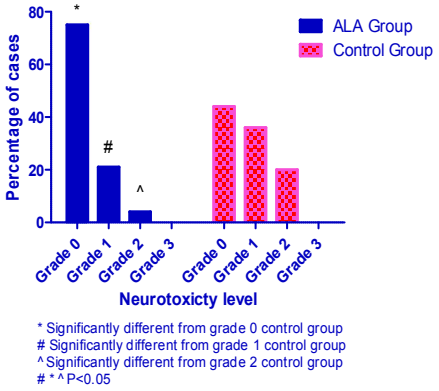


Fig. 2 Effect of ALA on the incidence of Oxaliplatin induced neurotoxicity after 4 cycles of chemotherapy

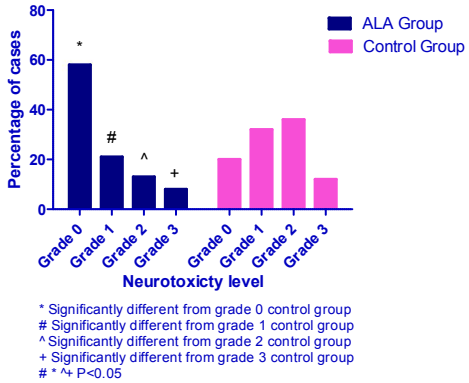
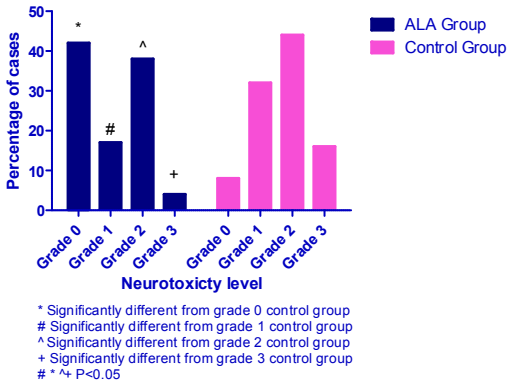


Fig. 3 Effect of ALA on the incidence of Oxaliplatin induced neurotoxicity after 6 cycles of chemotherapy



The mechanism of platinum drug neurotoxicity may involve drug accumulation within the peripheral nervous system, especially in the dorsal root ganglia [30]. The use of glutathione can prevent the initial accumulation of platinum adducts in the dorsal root ganglia and thereby reduce neurotoxicity [31]. One possible mechanism underlying oxaliplatin- induced neuropathy is that an oxaliplatin metabolite, such as oxalate, may alter the properties of voltage-gated sodium channels or slow down the clearance of platinum compounds from the peripheral nervous system [32, 33]. Therefore, using calcium and magnesium infusions to chelate oxalate may reduce the incidence and intensity of oxaliplatin- induced neuropathies [34].

Several neuromodulatory agents such as glutamate [22], calcium magnesium infusions [34], antiepileptic drugs like carbamazepine and gabapentin [7], amifostine [35], and glutathione [31] have demonstrated some activity in the prophylaxis and treatment of oxaliplatin-induced acute neurotoxicity. However, randomized trials demonstrating a prophylactic or therapeutic effect of these agents on oxaliplatin's cumulative neurotoxicity are still lacking.

In the current study, supplementation with ALA significantly reduced the incidence and severity of peripheral neurotoxicity as well as the need for dose reduction of oxaliplatin in these patients (Tables 3 and 5). These properties may increase the therapeutic index of oxaliplatin. The potential role of A LA as a neuroprotectant may be better understood in the context of the current hypothesis explaining chemotherapy-induced neuropathy.

Oxidative Stress plays an important role in the pathological mechanism of oxaliplatin-induced neurotoxicity [36]. The use of antioxidant may share in reduction of this toxicity.ALA is used in the treatment of peripheral neuropathy such as diabetic peripheral neuropathy in preclinical animal models, owing to its superior neuroprotective effects and function of nerve repair [20, 23]. To our knowledge, the clinical use of ALA in the prevention of oxaliplatin-induced neurotoxicity has not yet been investigated. ALA is a powerful antioxidant and several studies have demonstrated an improvement in

neuropathic symptoms and deficits among diabetics.[20] Results of a meta analysis[37] provided evidence that treatment with ALA 600 mg/day over 5 weeks is safe and significantly improves both neuropathic symptomatology and neuropathic deficits to a clinically meaningful degree in patients with symptomatic polyneuritis.

The usefulness of nerve conduction studies in objectively assessing peripheral neuropathy remains controversial. Despite, sensory nerve conduction may be affected significantly after oxaliplatin-based treatment, the severity of clinical sensory neuropathy does not always correlate with findings of nerve conduction studies. For example, it has been reported that the symptoms of oxaliplatin-induced neuropathy could be remarkably reduced after discontinuation of oxaliplatin treatment; however, abnormalities of sensory nerve conduction were shown to be remained [38]. In a study conducted by Cascinu*et al.* [31], sensory nerve conduction was significantly affected by oxaliplatin only in patients receiving placebo, but not in those receiving glutathione, which was consistent with our clinical findings.

In addition to reducing the incidence and severity of peripheral neuropathy, ALA supplements may also improve ADL (consistent mainly with fine motor coordination) for cancer patients receiving oxaliplatin. We noticed that 12.5% (n 3) of patients who received ALA supplementation, compared with 52% (n 13) of those who did not (p = 0 .02), had Interference with activities of daily living (ADL). Because of peripheral neuropathy measurement is not always reproducible, and the level of symptoms or signs on physical examination is not always predictive of ADL disability, performance of ADL is considered a very important indicator of outcome in patients receiving neurotoxic chemotherapeutic agents. In comparison with other neuroprotective agents, the cost of using oral ALA supplements as a neuroprotective strategy is affordable, with an additional advantage of suppression of colorectal tumor cell growth through blockade of NF-κB signaling.[39]

In summary, our data suggest that oral ALA has a potential neuroprotective effect in patients treated with oxaliplatin , and may therefore improve the therapeutic index. Larger placebo-controlled, randomized studies are needed to confirm the application of ALA as a protective agent against oxaliplatin-induced neurotoxicity.

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