Role of Pregabaline in prevention of Oxaliplatine neuropathy.

Emad Sadaka[1] and Alaa Maria[2]

Clinical Oncology Department, Faculty of Medicine, Tanta University, Gharbia, Egypt.
[1]emad_sadaka@hotmail.com [2]alaamaria1@hotmail.com

Abstract: Background: Neuropathy occurs in most of patients receiving oxaliplatine. Many neuromedulatory drugs were tested in prevention and treatment of oxaliplatine induced neuropathy. The aim of this pilot study is to evaluate the role of pregabalin "PGB" (an antiepileptic drug approved as a treatment for neuropathy) in prevention of oxaliplatine induced acute neuropathy. **Methods:** Forty-seven patients with resected stage III and high risk stage II colon cancer were treated with FOLFOX4 protocol in 2 groups, the PGB group (23 patients) and the control group (24 patients) throughout the period From Jan. 2010 to Dec. 2011 at Clinical Oncology Department, Tanta University Hospital. **Results:** The PGB group showed lower incidence of all neurological grade of toxicity. After 2 cycle, Grade 1-2 toxicity presented in 21.7% and 45.8% for the PGB group and control group respectively (p=0.08). No patient showed grades 3-4 neurological toxicity in both groups. After 4 cycles, PGB group showed a significantly lower incidence of neurological toxicity, Grades 1-2 neurological toxicity presented in 34.8% vs. 62.5% for the control group and grade 3-4 in 4.3% vs. 16.7% respectively (p=0.02). After 6 cycles, PGB group maintained a significantly lower incidence of neurological toxicity (p=0.04). The need for oxaliplatine dose reduction was insignificantly lower in the PGB group 4.3% vs. 14.7% in the control group (p=0.2). Interference of daily activity was significantly lower in the PGB group than the control group (13% vs. 41.7% respectively; p=0.03). Patient in the PGB group showed a comparable DFS rate at 2 year with the control group (74.8% vs. 69.3% respectively, p=0.39). **Conclusion:** Pregabalin significantly reduced the oxaliplatine induced neuropathy without compromising survival.

[Emad Sadaka and Alaa Maria. **Role of Pregabaline in prevention of Oxaliplatine neuropathy**. *J Am Sci* 2013;9(3):198-202]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 26

Keywords: Oxaliplatine, Neuropathy, Pregabalin**.**

1. Introduction

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. Estimated new cases from colon cancer in the United States are 103,170 in the year 2012. [(1)]

Oxaliplatine is a platinum derivative with activity against advanced colorectal cancer. The updated results of the MOSAIC trial compared the benefit of adding oxaliplatine to 5-FU/Leucovorin (LV) (FOLFOX-4) as adjuvant treatment compared with 5-FU/LV alone. The 3-year disease free survival (DFS) rate with FOLFOX-4 was 78.2% vs. 72.9% for 5-FU/LV alone (p=0.002). At 5 years, overall survival rate remained superior with FOLFOX-4 (73.3% vs. 67.4%; p=0.03). [(2)]

In the MOSAIC study, the main side effect of FOLFOX-4 was the anticipated sensory neuropathy. The overall incidence of grade 3 neurotoxicity was 12.4%. However, the neurotoxicity proved reversible in the vast majority of patients so that at 12 and 18 months after discontinuation of therapy only 1.1% and 0.5% of patients, respectively, had residual grade 3 neurotoxicity.[(3)]

The acute, transient neurotoxicity observed with oxaliplatine occurs in nearly all patients. This toxicity is rapid in onset, occurring during or within hours of infusion. The symptoms are peculiar in that they are often induced or aggravated by exposure to cold. There may be manifestations of distal sensory and motor toxicity. The sensory component consists of paresthesias and/or dysesthesias in the distal extremities and/or the perioral region. [(4, 5)]

Symptoms generally persist between cycles and increase in intensity with cumulative dose. The symptoms may be severe enough to limit patients from performing their activities of daily living. Importantly, these symptoms are consistently reversible with the majority of patients recovering from grade 3 neurotoxicity to grade 1 or less within 6–12 months of therapy discontinuation. [(6)]

Several neuromodulatory agents such as calcium and magnesium infusion[(7)], carbamazine[(8)], amifostine[(9)], gabapentin[(10)], glutathione[(11)] and glutamine[(12)] have demonstrated some activity in prophylaxis and treatment of oxaliplatin induced acute neurotoxicity.

Pregabalin (PGB) is an antiepileptic drug used for neuropathic pain. It was approved in the European Union in 2004 as adjunctive therapy of partial seizures in adults, pain from diabetic neuropathy and post-herpetic neuralgia. Pregabalin is well absorbed (> 90%) and its absorption is dose independent. [(13)]

Isufi *et al.* [13] & Saif *et al.*[14] assessed the efficacy of pregabalin in the treatment of oxaliplatine-induced neurotoxicity. Among a total of 23 patients, the majority of patients with neuropathy improved by 1 to 2 grades. They conclude that pregabalin significantly reduced the severity of oxaliplatine-induced sensory neuropathy.

On the basis of these considerations, a pilot study is conducted in patients with colon cancer to assess the efficacy of pregabalin in preventing oxaliplatine induced neuropathy.

2. Material and Methods

This study conducted at Clinical Oncology department, Tanta University Hospital, from Jan. 2010 to Dec. 2011. Forty-seven patients with adenocarcinoma of the colon were included.

Patients eligible for adjuvant chemotherapy with FOLFOX 4 protocol include resected stage III and high risk stage II, age range up to 65 years old, no evidence of metastatic spread, an Eastern Cooperative Oncology Group (ECOG) performance status score 0-1, adequate blood counts with TLC of 3,000/uL or more, HB 10 gm/dL or more and platelet count 100,000/uL or more, adequate liver and renal functions (serum total bilirubin less than 1.5 mg/dl and creatinine less than 1.5 mg/dl) were included. No neuromodulator drug other than PGB is allowed.

Patients with previous history of neuropathy or having risk factors for development of peripheral neuropathy such as diabetes mellitus, central nervous system disease were excluded.

All patients were treated with 6 cycles of FOLFOX-4 protocol in 2 groups, first group received pregabalin (n=23; pregabalin group) and the second group did not receive pregabalin (n=24; control group). Pregabalin was giving orally in a dose of 75 mg twice daily starting on the day before oxaliplatine infusion and continued for one week from the oxaliplatine infusion day.

Neurological examination was done for all patient to assess the grade of neurotoxicity at a baseline and after 2, 4 and 6 cycles of chemotherapy according to the national Cancer Institute Common Toxicity Criteria (NCI-CTC).[15] Interference with activities of daily living (ADL) such as bathing, personal hygiene, self feeding, dressing, and getting around inside the home were recorded. The oxaliplatine dose was reduced to 75 mg/m^2 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 neuropathies or persistent functional impairment, oxaliplatine was omitted from the regimen.

Ethical committee approval & Statistical Analysis

The study was approved by the Research Ethics Committee, Quality Assurance Unit, Faculty of Medicine, Tanta University and a signed consent form was obtained from each patient.

Neuropathy, ADL & non neurological toxicity in both treatment groups were analyzed using the Chi-square test. The DFS curve of both groups was plotted using the Kaplan-Meier method and the statistical difference was compared using the log-rank test. Analyses were performed using the Statistical Package for the Social Science (SPSS, Chicago, IL USA, V-12) software package. A p-value <0.05 was considered statistically significant.

3. Results

Forty-seven patients enrolled in this study were divided into 2 groups, the PGB group (23 patients) and the control group (24 patients). The distribution of patients characteristics between the 2 groups was showed in Table (1) and they were balanced with no differences between the treated groups as regard the age, gender, performance status, pathological grade, serum CEA level, tumor size (T) and nodal status (N).

Table (2) shows the incidence of neurological toxicity in both groups. The PGB group showed lower incidence of all neurological grade of toxicity. After 2 cycle, Grade 1-2 toxicity presented in 5/23 patients (21.7%) and 11/24 (45.8%) for the PGB group and control group respectively. The difference was not significant (p=0.08) in spite of the apparent lower toxicity for the PGB group. No patient showed grade 3-4 neurological toxicity in both groups. After 4 cycles, PGB group showed a significantly lower incidence of neurological toxicity, Grade 1-2 neurological toxicity presented in 34.8% vs. 62.5% for the control group and grade 3-4 in 4.3% vs. 16.7% respectively (p=0.02). After 6 cycles, PGB group maintained a significantly lower incidence of neurological toxicity, Grade 1-2 neurological toxicity presented in 47.8% vs. 62.5% for the control group and grade 3-4 in 8.7% vs. 25% respectively (p=0.04).

The impact of PGB supplementation on oxaliplatine dose reduction, daily activity, survival and non neurological toxicity was recorded in Table (3). The need for oxaliplatine dose reduction was insignificantly lower in the PGB group 4.3% vs. 14.7% in the control group (p=0.2). Interference of daily activity was significantly lower in the PGB group than the control group (13% vs. 41.7% respectively; p=0.03). There was no significant difference, as regard the non-neurological toxicity, between the 2 groups. Patient in the PGB group showed a comparable DFS rate at 2 year with the control group (74.8% vs. 69.3% respectively; p=0.39), Fig (1).

4. Discussion

Oxaliplatine plays a key role in the treatment of colorectal cancer. The dose-limiting side effect of this platinum analogue is neurotoxicity. In up to 15% of patients, the dose-limiting toxicity is a transient, acute, and predominantly peripheral neuropathy. The importance of the drug makes early discontinuation or dose reduction due to neurotoxicity is undesirable. Significant efforts have been undertaken in an attempt to prevent and/or circumvent the development of neurotoxicity. [12, 16]

In current study, 23 colon cancer patients treated with FOLFOX-4 and received pregabaline (PGB group) showed a significant lower incidence of grade 3-4 neurological toxicity than the control group after 4 cycles (p=0.02) and after 6 cycles (p=0.04).

Saif *et al.* [14] evaluated the role of PGB in reduction of oxaliplatine-induced neuropathy. Patients with gastrointestinal cancers were treated with PGB upon development of oxaliplatine-induced neuropathy more than grade 2 (NCI-CTC 3.0). Neuropathy improved from G3 to G2 in 13% of patients and from G3 to G1 in 9%. Six (26%) patients remained stable at G2 and no pts remained at G3. Pregabalin significantly reduces the severity of oxaliplatine-induced neuropathy.

The ability of performing the activity of daily living (ADL) is considered a very important indicator of outcome in patients receiving neurotoxic chemotherapeutic agents.[12] In this study, interference with ADL was significantly lower in patients received PGB than the control group (13% vs 41.7%; p=0.03).

Oxaliplatine dose reduction was lower in the pregabalin group than in the control group (4.3% vs. 16.7%, p=0.3). The DFS rate at 2 years were comparable in the PGB group 74.8% vs. 69.3% in the control group (p= 0.39).

Wang *et al.* [12] performed a study on 86 patients with metastatic colorectal cancer (MCRC). Patients were randomized to receive glutamine or do not receive (control group). A significantly lower incidence of grade 3–4 neuropathy was noted in the glutamine group after four cycles (4.8% vs. 18.2%) and six cycles (11.9% vs. 31.8%). By adding glutamine, interference with ADL was lower (16.7% vs. 40.9%), and need for oxaliplatine dose reduction was lower (7.1% vs. 27.3%). There were no significant differences in response to chemotherapy between-group (52.4% vs. 47.8%) or grade 3–4 non-neurological toxicities (26.2% vs. 22.8%). They concluded that oral glutamine significantly reduces the incidence and severity of peripheral neuropathy of MCRC patients receiving oxaliplatine without affecting response to chemotherapy and survival.

Table (1): Patients Characteristics

	PGB group	Control group	Total
	23 patients (49%)	24 patients (51%)	47 patients (100%)
Age~			
≥55	12 (52%)	12 (50%)	24 (51%)
<55	11 (48%)	12 (50%)	23 (49%)
Gender			
M	17 (73.9%)	17 (70.8%)	34 (72.3%)
F	6 (26.1%)	7 (29.2%)	13 (27.7%)
PS			
0	15 (65.2%)	17 (70.8%)	32 (68%)
1	8 (34.8%)	7 (29.2%)	15 (32%)
Grade			
1-2	14 (60.9%)	13 (54.2%)	27 (57.4%)
Poor	9 (39.1%)	11 (45.8%)	20 (42.6%)
CEA			
Normal	8 (34.8%)	8 (33.3%)	16 (34%)
High	15 (65.2%)	16 (66.7%)	31 (66%)
T			
2	6 (26.1%)	5 (20.8%)	11 (23.4%)
3	17 (73.9%)	19 (79.2%)	36 (76.6%)
N			
0	9 (39%)	10 (41.7%)	19 (40.4%)
1	11 (48%)	11 (45.8%)	22 (46.8%)
2	3 (13%)	3 (12.5%)	6 (12.8%)

~Median=55 years (range 41-71)
PGB, Pregabaline; PS, Performance status; CEA, Carcinoembryonic antigen; T, Tumor size; N, Nodal status

Table (2): Incidence of Oxaliplatin induced neurotoxicity

	PGB 23 patients	Control 24 patients	*p*
After 2 cycles			0.08
Grade 0	18 (78.3%)	13 (54.2%)	
Grade 1-2	5 (21.7%)	11 (45.8%)	
Grade 3-4	0 (0%)	0 (0%)	
After 4 cycles			0.02
Grade 0	14 (60.9%)	5 (20.8%)	
Grade 1-2	8 (34.8%)	15 (62.5%)	
Grade 3-4	1 (4.3%)	4 (16.7%)	
After 6 cycles			0.04
Grade 0	10 (43.5%)	3 (12.5%)	
Grade 1-2	11 (47.8%)	15 (62.5%)	
Grade 3-4	2 (8.7%)	6 (25%)	

Table (3): Impact of oral pregabalin supplementation

	PGB group 23 patients	Control 24 patients	*p*
Oxaliplatin dose reduction			0.2
Needed	1 (4.3%)	4 (14.7%)	
not needed	22 (95.7%)	20 (83.3%)	
Daily activity			0.03
Interference	3 (13%)	10 (41.7%)	
Not	20 (87%)	14 (58.3%)	
DFS at 2 years	74.8%	69.3%	0.39
Grade 3-4 non neurological toxicity			0.67
Leucopenia	2 (8.7%)	3 (12.5%)	

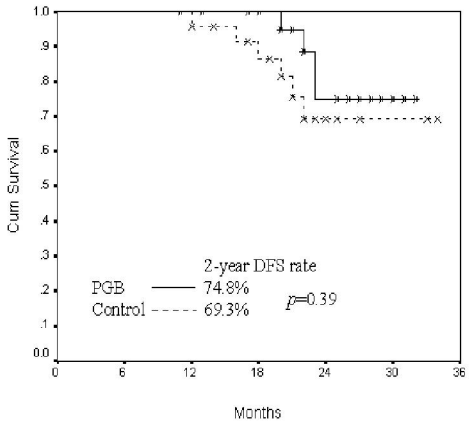

Fig (1): 2-year DFS rate for pregabalin group vs. the control group

Many neuromodulatory drugs were used to prevent and treat oxaliplatine induced neuropathy. Among 102 patients, Ca/Mg decreased the incidence of chronic, cumulative, grade 2 or greater sensory neurotoxicity, as measured by NCI-CTC (p=0.038). In addition, No effect on acute, cold-induced sensory neurotoxicity was found. No substantial differences in adverse effects were noted between Ca/Mg and placebo. This study supports IV Ca/Mg as an effective neuroprotectant against oxaliplatine-induced cumulative sensory neurotoxicity in adjuvant colon cancer.[7]

Arena *et al.* [9] investigated the effects of amifostine, a cytoprotective agent, on the prevention of peripheral neuropathy (PN) in patients receiving FOLFOX for the treatment of advanced CRC. They concluded that patients with advanced CRC who received amifostine with FOLFOX chemotherapy had a decreased incidence and severity of PN compared with patients who did not receive amifostine. Similar results were reported by Rudolph *et al.* [17] where patients received amifostine at a dose of 910 mg/m^2 as a 10-minute intravenous infusion just prior to chemotherapy had significantly reduced incidence of PN (p=0.048).

Mariani *et al.* [18] treated 15 CRC patients with oxaliplatine based regimen with mean cumulative dose 255 mg/m^2 (range, 85-1190 mg/m^2). Patients received gabapentin at the dose of 100 mg twice a day immediately after the onset of neuropathic symptoms. The dosage was increased by an additional 100 mg per day if symptoms continued for 3 days. Symptoms disappeared in all patients treated and recurred in 2 patients who discontinued their gabapentin treatment.

Mitchell *et al.* [10] assessed the impact of gabapentin on oxaliplatine neurotoxicity. Patients with previously untreated MCRC were recruited sequentially to 2 cohorts: the second included the addition of gabapentin. The median relative dose intensity of oxaliplatine and requirement for dose reductions or delays because of neurotoxicity were similar in the 2 cohorts. There was no grade 4 neurotoxicity. Whereas grade 3 neurotoxicity was observed in 10% of patients treated with gabapentin versus 21% of patients treated with mFOLFOX alone, there was no statistically significant difference in the severity of neurotoxicity between the 2 cohorts (p=0.89) or the time to recover from grade 2/3 neurotoxicity (p=0.97).

Carbamazepine is an anticonvulsant drugs which used as a protective agent against oxaliplatine-induced neurotoxicity. In a non-randomized pilot study, 40 pretreated patients suffering from advanced CRC received oxaliplatine based regimen with median cumulative dose 722 mg/m^2. Ten patients received carbamazepine 200-600 mg orally continuously until the end of chemotherapy. Grade 2-4 neuropathy did not occur in any patient. In contrast, this toxicity was observed in 30% of the control group (n = 30) who had received an even lower cumulative dose of oxaliplatine (510 mg/m^2).[8]

Agafitei *et al.*[19] evaluated the effect of celecoxib on neurotoxicity in patients with MCRC. Celecoxib 200 mg bid was added to the regimen consisting of continuous infusion 5-FU 200 mg/m^2/d for 10 weeks with a 2-week break and oxaliplatin 130 mg/m^2 every 3 weeks (CIFOX). Among 263 patients, 73 patients received celecoxib and 179 did not. None of the 73 patients who received celecoxib experienced any grade 3 or 4 neurotoxicity, compared with 10 of the 179 patients who did not receive celecoxib (0% vs 6%; p=0.024).

These data suggest that pregabalin significantly reduced the oxaliplatine induced neuropathy without compromising survival in colon cancer patients treated with adjuvant oxaliplatine. Larger randomized studies are needed to confirm the role of pregabalin as a protective agent against oxaliplatine-induced neuropathy.

5. Abbreviations

FU, flurouracil; LV, leucovorin; DFS, disease free survival; PGB, pregabalin; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TLC, total leucocytes count; HB, hemoglobin; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; ADL, activity of daily living; CEA, carcinoembryonic antigen. PN, peripheral neuropathy; CRC, colorectal cancer; MCRC, metastatic colorectal cancer.

6. Competing interest

The authors declare that they have no competing interests.

7. Corresponding author
Alaa Mohamed Maria
Clinical Oncology Department, Faculty of Medicine, Tanta University, Al Gaish St., Tanta 11312, Gharbia, Egypt.
alaamaria1@hotmail.com

8. References

1) America Cancer Society.: Cancer facts and figures 2012. Atlanta, Ja: American Cancer Society, 2012. available on line. last assesst January 5, 2012.
2) De Gramont A., Boni C., Navarro M., *et al.* (2007): Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with median follow up of six years. Proc Am Soc Clin Oncol, 25:165s.
3) Andre T., Boni C., Mounedji-Boudiaf L., *et al.* (2004): Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med, 350: 2343–51.
4) Grolleau F., Gamelin L., Boisdron-Celle M., *et al.* (2001): A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. J Neurophysiol, 85: 2293–2297.
5) Wilson R., Lehky T., Thomas RR., *et al.* (2002): Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol, 20: 1767–1774.
6) Grothey A., Deschler B., Kroening H., *et al.* (2002): Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol, 21: 129a.
7) Gamelin L., Boisdron-Celle M., Delva R., *et al.* (2004): Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res, 10: 4055-4061.
8) Eckel F., Schmelz R., Adelsberger H., *et al.* (2002): Prevention of oxaliplatin-induced neuropathy by carbamazepine. A pilot study. Dtsch Med Wochenschr, 127(3): 78-82.
9) Arena F., Kurzyna-Solinas A., Stark RF., *et al.* (2007): Amifostine pretreatment for patients with advanced colorectal cancer receiving FOLFOX chemotherapy. J Clin Oncol, 25 (18S): 19663.
10) Mitchell PL., Goldstein D., Michael M., *et al.* (2006): Addition of Gabapentin to a modified FOLFOX regimen does not reduce Oxaliplatin-induced neurotoxicity. Journal of Clinical Colorectal Cancer, 6 (2); 146-51.
11) Lecomte T., Landi B., Beaune P., *et al.* (2006): Glutathione *S*-Transferase P1 Polymorphism ($Ile^{105}Val$) predicts cumulative neuropathy in patients receiving Oxaliplatin-based chemotherapy. Clin Cancer Res, 12; 3050.
12) Wang WS., Lin JK., Lin TC., *et al.* (2007): Oral Glutamine is effective for preventing Oxaliplatin-induced neuropathy in colorectal cancer patients. The Oncologist, 12: 1372-3.
13) Isufi I., James E., Keley K., *et al.* (2009): Pregabalin (PGB) in treatment of oxaliplatin-induced neuropathy. J Clin Oncol, 27 (suppl; abstr e15045).
14) Saif MW., Syrigos K., Kaley K. *et al.* (2010): Role of Pregabalin in Treatment of Oxaliplatin-induced Sensory Neuropathy. Anticancer Research, 30 (7): 2927-33.
15) Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. http://ctep.cancer.gov, Publish Date: August 9, 2006.
16) Lersch C., Schmelz R., Eckel F., *et al.* (2002): Prevention of Oxaliplatin-Induced Peripheral Sensory Neuropathy by Carbamazepine in Patients with Advanced Colorectal Cancer. Clinical Colorectal Cancer, 2(1): 54-8.
17) Rudolph S., Fahlke J., Kuhn R., *et al.* (2001): Randomised trial with or without amifostine to reduce neurotoxic side effects under chemotherapy with oxaliplatin (L-OHP), FA/5-FU. Proc Am Soc Clin Oncol, 20: 302b.
18) Mariani G., Garrone O., Granetto C., *et al.* (2000): Oxaliplatine induced neuropathy: could gabapentin be the answer? Proc Am Soc Clin Oncol, 19: 609a.
19) Agafitei RD., Schneider S., Iqbal S., *et al.* (2004): Effect of celecoxib on neurotoxicity in patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin (CIFOX). J Clin Oncol, 22 (14): Suppl. 3600

1/20/2013