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Oncology

PREVENTION OF OXALIPLATIN-INDUCED SENSITIVE NEUROTOXICITY BY CALCIUM/MAGNESIUM INFUSIONS

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ABSTRACT **BACKGROUND:** The use of Calcium (Ca) and Magnesium (Mg) in combination with oxaliplatin-based chemotherapy in metastatic colorectal cancer (MCRC) to reduce neuropathy remains controversial. We evaluate this association regarding the objective response rate (ORR) and the incidence of sensitive neurotoxicity grade 2 and 3 (sNT grade 2-3).
PATIENTS AND METHODS: They were 2 groups: Group A (Ca and Mg with oxaliplatin) and group B (oxaliplatin alone). Chi-square test was used to compare ORR and the incidence of sNT grade 2-3 in the 2 groups.
RESULTS: There were 52 patients in group A and 57 patients in group B. There was no significant difference between the two groups in ORR (46.2% versus 54.4%; p = 0.445); while the incidence of sNT grade 2-3 was lower for the combination (23.1% versus 45.6%; p = 0.016).
CONCLUSION: The use of Ca and Mg with oxaliplatin-based chemotherapy in MCRC is beneficial.

KEYWORDS : Calcium – Magnesium – Oxaliplatin – Sensitive neurotoxicity.

INTRODUCTION:

Oxaliplatin is a major drug in the treatment of colorectal cancer either in the adjuvant or metastatic setting (1-5). Its tolerability profile is generally good, but sensitive neurotoxicity (sNT) is the major problem limiting its use (6-8). Some medical teams have proposed the use of Calcium (Ca) and Magnesium (Mg) to prevent the neurotoxicity of oxaliplatin. However, this association remains controversial. Indeed, some studies have reported a decrease in oxaliplatin efficacy secondary to Ca and Mg addition (9). We evaluate in this study the impact of this addition to oxaliplatin-based chemotherapy in metastatic colorectal cancer (MCRC) regarding the objective response rate (ORR) and the incidence of sNT grade 2-3.

PATIENTS AND METHODS:

This is a retrospective study of 109 patients treated by XELOX (capecitabine plus oxaliplatin) for MCRC between January 2007 and December 2014 in the Military Hospital Mohammed V of Rabat. They were divided into 2 groups: Group A (1g each of Ca gluconate and Mg sulfate IV over 30 minutes before and after oxaliplatin infusion) and group B (oxaliplatin alone).

SPSS 21.0 version was used for all statistical analysis. The Pearson's Chi-square test was used to evaluate the difference between the two groups in ORR and sNT grade 2-3. A p value < 0.05 was considered to be statistically significant.

RESULTS:

- **Patients' characteristics:**

One hundred and nine patients were included in this study. Patient's characteristics are described in table 1.

Table 1: Patients' characteristics

	Group A	Group B
Age	52.3 (28-74)	50.6 (27-77)
Sex:		
• Male	24 (46.1%)	30 (52.6)
• Female	28 (53.9%)	27 (47.4%)
Tumor site:		
• Colon	31 (59.6%)	37 (64.9%)
• Rectum	21 (40.4%)	20 (35.1%)
Sites of metastasis:		
• Liver	35 (67.3%)	36 (63.2%)
• Peritoneum	22 (42.3%)	20 (35.1%)
• Lung	15 (28.8%)	18 (31.6%)
• Other	14 (26.9%)	17 (29.8%)
Cumulative dose of oxaliplatin (mg/m^2)	850 (390-1300)	690 (390-1040)
Patients receiving bevacizumab	48 (92.3%)	54 (94.7)

- **Response to treatment:**

There were 24 (46.2%) patients with ORR in the group A versus 31 (54.4%) patients in group B. Statistically, there was no significant difference in ORR between the two groups (p=0.445). More details on tumor responses are presented in Table 2.

Table 2: Tumor response

	Group A	Group B
Complete Response (CR)	2 (3.8%)	4 (7%)
	p = 0.681	
Partial Response (PR)	22 (42.4%)	27 (47.4%)
	p = 0.700	
Objective Response Rate (ORR)	24 (46.2%)	31 (54.4%)
	p = 0.445	
Stabilization Disease (SD)	13 (25%)	11 (19.3%)
	p = 0.497	
Progression Disease (PD)	15 (28.8%)	15 (26.3%)
	p = 0.832	

- **Neurosensory toxicity:**

There were less significant sNT grade 2-3 in patients receiving Ca and Mg (23.1% in group A versus 45.6% in group B; p=0.016). The detailed results are presented in Table 3.

Table 3: Oxaliplatin related sNT

	Group A	Group B
NP grade 2	10 (19.2%)	21 (36.8%)
	p = 0.056	
NP grade 3	2 (3.8%)	5 (8.8%)
	p = 0.441	

NP grade 2-3	12 (23.1%)	26 (45.6%)
	p = 0.016	

DISCUSSION:

The advent of oxaliplatin in the MCRC treatment was a major therapeutic advance. Indeed, its use in combination with 5-fluoro-uracil (FOLFOX) or capecitabine (XELOX) significantly improves survival in either first or second line treatment (4, 5, 10, 11).

Although its overall safety profile is good, its neurotoxicity is a frequent dose-limiting toxicity. Indeed, sNT occurs in approximately 40 to 60% of patients treated with oxaliplatin for MCRC either by FOLFOX or XELOX (12, 13). To prevent this side effect, some medical teams have proposed the use of Ca and Mg in association with oxaliplatin.

Gamelin et al. have published in 2004 a retrospective study of 161 patients treated with oxaliplatin-based chemotherapy for MCRC; 96 had received Ca and Mg while the others had not. The ORR was similar in the two groups with a significant reduction of neurotoxicity in patients receiving Ca/Mg (14).

Some case reports have suggested a beneficial effect of orally Ca and Mg in the prevention of peripheral neuropathy. However, there are no studies including a wide number of patients available in the literature (15).

The CONCEPT trial (Combined Oxaliplatin Neuropathy Prevention Trial) is the main study that has shown interest at the issues of oxaliplatin neurotoxicity (16). The study was aborted in June 2007 due to a very reduced response rate in patients receiving infusions of Ca/Mg versus those who did not (17.3% versus 32.9%).

A phase III study presented at the American Society of Clinical Oncology in 2009, compared among 104 patients treated with FOLFOX for a colon cancer in an adjuvant setting the effect of Ca/Mg addition regarding neurotoxicity (18). This study shows that Ca/Mg significantly reduces chronic neurotoxicity, but there was no impact on the acute neurotoxicity.

In 2013, a meta-analysis of 4 prospective and 3 retrospective clinical trials involving 1170 patients with colorectal cancer treated by Oxaliplatin-based chemotherapy (802 received Ca/Mg and 368 did not) has demonstrated that Ca/Mg infusions decrease significantly the incidence of Oxaliplatin-induced neurotoxicity (19).

Recently, a Phase III trial enrolled 353 patients with colon cancer undergoing adjuvant chemotherapy with FOLFOX. They were randomly assigned to intravenous Ca/Mg before and after Oxaliplatin, Ca/Mg before and placebo after, or placebo before and after. There were no statistically significant neuropathy between the three arms. The conclusion of this study is that using Ca/Mg does not protect against Oxaliplatin-induced acute neurotoxicity (20).

Our findings support the use of Ca and Mg in combination with Oxaliplatin in MCRC. Indeed, this association, while remaining efficient (ORR: 46.2% in group A versus 54.4% in group B; p=0.445) reduces significantly the rate of sNT grade 2-3 (23.1% in group A versus 45.6% in group B; p=0.016).

However, due to the controversial findings about the use of Ca/Mg (14-20), more prospective studies are needed to evaluate the impact of Ca/Mg association to Oxaliplatin-based chemotherapy in terms of ORR and sNT to clarify the question concerning the treatment efficacy and toxicity.

CONCLUSION:

Oxaliplatin-based chemotherapy is a standard treatment of MCRC. Although its efficacy, its neurotoxicity is a frequent dose-limiting toxicity. We demonstrate in our study that the use of Ca and Mg in association with Oxaliplatin reduces sNT while keeping treatment efficacy. However more prospective studies are needed to confirm these data.

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Ethical statement and Consent:
This study was approved by the ethics committee of the military hospital of Rabat.

All patients gave their informed consent prior to their inclusion in the study.

REFERENCES:

1- Thierry A, Corrado B, Matilde N, et al. Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. J Clin Oncol 2009; 27:3109-16.
2- Kuebler JP, Wieand S, O'Connell MJ, et al. Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07. J Clin Oncol 2007; 25:2198-2204.
3- Howard SH, Lowell LH, Ramesh KR, et al. Safety and Efficacy of Oxaliplatin and Fluoropyrimidine Regimens with or without Bevacizumab As First-Line Treatment of Metastatic Colorectal Cancer: Results of the TREE Study. J Clin Oncol 2008; 26:3523-29.
4- Saltz LB, Carke S, Diaz-Rubio E, et al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. J Clin Oncol 2008; 26:2013-19.
5- Seymour MT, Mughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomized controlled trial. Lancet 2007; 370:143-52.
6- Wolf SL. New data question treatment for oxaliplatin neurotoxicity. Clin J Oncol Nurs 2008; 12(1):14.
7- Adelsberger H, Quasthoff S, Grosskreutz J, et al. The chemotherapeutic oxaliplatin alters voltage-gated Na+ channel kinetics on rat sensory neurons. Euro J Pharmacol 2000; 406:25-32.
8- Amstrong CM, Cota G. Calcium block of Na+ channels and its effect on closing Rate. Proc Natl Acad Sci USA 1999; 96:4154-57.
9- Kurniali PC, Luo LG, Weitberg AB. Role of calcium/magnesium infusion in oxaliplatin-based chemotherapy for colorectal cancer patients. Oncology 2010; 24:289-92.
10- Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III non-inferiority study. Annals of Oncology 2008; 19:1720-26.
11- Scheithauer W, Kornek GV, Schuell B, et al. Second-line treatment with oxaliplatin + ralitrexed in patients with advanced colorectal cancer failing fluoropyrimidine/ leucovorin-based chemotherapy. Annals of Oncology 2001; 12:709-14.
12- Cassidy J, Clarke S, Diaz ER, et al. Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First Line Therapy for Colorectal Cancer. J Clin Oncol 2008; 26:2006-12.
13- Diaz ER, Tabernero J, Gomez AE, et al. Phase III Study of Capecitabine Plus Oxaliplatin Compared With Continuous-Infusion Fluorouracil Plus Oxaliplatin As First-Line Therapy in Metastatic Colorectal Cancer: Final Report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 2007; 25:4224-30.
14- Gamelin L, Boisdron MC, Delva R, et al. 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. Clinical Cancer Research 2004; 10:4055-61.
15- Saif MW et al. Oral calcium ameliorating oxaliplatin-induced peripheral Neuropathy. J Appl Res 2004; 4:576-82.
16- Grothey A, Hart LL, Rowland KM, et al. Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): Final results of the phase III CONcePT trial. J Clin Oncol 2008; 26 (15S):4010.
17- Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer- a GERCOR study. J Clin Oncol 2006; 24:394-400.
18- Grothey A, Nikcevich DA, Sloan JA, et al. Evaluation of the effect of intravenous calcium and magnesium (CaMg) On chronic and acute neurotoxicity associated with oxaliplatin: Results from a placebo-controlled phase III trial. J Clin Oncol 2009; 27 (15S):4025.
19- Wen F, Zhou Y, Wang W, et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis. Annals of Oncology 2013; 24:171-78.
20- Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/alliance). J Clin Oncol 2014; 32:997-1005.