

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

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ABSTRACT

Purpose: Oxaliplatin is active in colorectal cancer. Sensory neurotoxicity is its dose-limiting toxicity. It may come from an effect on neuronal voltage-gated Na channels, via the liberation of its metabolite, oxalate. We decided to use Ca and Mg as oxalate chelators.

Experimental Design: A retrospective cohort of 161 patients treated with oxaliplatin + 5-fluorouracil and leucovorin for advanced colorectal cancer, with three regimens of oxaliplatin (85 mg/m²/2w, 100/2w, 130/3w) was identified. Ninety-six patients received infusions of Ca gluconate and Mg sulfate (1 g) before and after oxaliplatin (Ca/Mg group) and 65 did not.

Results: Only 4% of patients withdrew for neurotoxicity in the Ca/Mg group versus 31% in the control group ($P = 0.000003$). The tumor response rate was similar in both groups. The percentage of patients with grade 3 distal paresthesia was lower in Ca/Mg group (7 versus 26%, $P = 0.001$). Acute symptoms such as distal and lingual paresthesia were much less frequent and severe ($P = 10^{-7}$), and pseudolaryngospasm was never reported in Ca/Mg group. At the end of the treatment, 20% of patients in Ca/Mg group had neuropathy versus 45% ($P = 0.003$). Patients with grade 2 and 3 at the end of the treatment in the 85 mg/m² oxali-

platin group recovered significantly more rapidly from neuropathy than patients without Ca/Mg.

Conclusions: Ca/Mg infusions seem to reduce incidence and intensity of acute oxaliplatin-induced symptoms and might delay cumulative neuropathy, especially in 85 mg/m² oxaliplatin dosage.

INTRODUCTION

Oxaliplatin combined with 5-fluorouracil (5FU) is now considered a standard treatment for metastatic colorectal cancer (1, 2) and is also under evaluation in the adjuvant setting (3). Its overall safety profile is good, but neurotoxicity is a frequent dose-limiting toxicity. The peculiar acute neurotoxicity of oxaliplatin (including cold-related dysesthesia and sometimes accompanied by muscle contractions), which may occur shortly after drug administration, differs greatly from cisplatin neurotoxicity and is not explained by morphological damage of the nerve (3, 4). These clinical manifestations of this acute neurotoxicity resemble those described in patients with congenital myotonia or tetany (5). Therefore, we hypothesized that oxaliplatin had a unique direct effect on nerve excitability. We suspected that oxalate, one of the oxaliplatin metabolites, responsible for acute neurotoxic effects of ethylene glycol poisoning (6) and known chelator of both Ca and Mg, might be involved in this acute neurotoxic effect via Ca and/or Mg chelation. We tested the effectiveness of both Ca and Mg infusions in several oxaliplatin-treated patients who developed the manifestations of acute neurotoxicity (including those with pseudolaryngospasm). The immediate and important improvement in both the pseudolaryngospasm and other acute neurotoxicities we observed prompted us to extend that approach to their preventive treatment, and we began to administer Ca and Mg before and just after oxaliplatin infusion to prevent the acute neurological manifestations that can occur during or within the hours following oxaliplatin administration.

We recently demonstrated in *in vitro* models that the acute (and possibly chronic) neurotoxicity associated with oxaliplatin may be either directly or indirectly linked (via the chelation of calcium by oxalate) to an effect on neuronal voltage-gated sodium (Na⁺) channels (7, 8).

Therefore, since 1996, when oxaliplatin was made widely available for patients with advanced colorectal cancer, we empirically started treating patients receiving oxaliplatin for advanced colorectal cancer with Ca and Mg infusions. After several years of empirical use, the very encouraging results, described by the nurses, the patients, and the treating physicians of our department prompted us to review these data and conduct a retrospective analysis of our patients' experiences after approval by our institutional Review Board to perform that study.

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Table 1 Chemotherapy regimens

Regimen	FOLFOX4	FOLFOX6	FUFOX
	OXA ^a 85	OXA 100	OXA 130
Oxa	85 mg/m ² /2 weeks 2-h infusion	100 mg/m ² /2 weeks 2-h infusion	130 mg/m ² /3 weeks 2-h infusion
5FU	Bolus 400 mg/m ² d1&d2 infusional 600 mg/m ² 22-h d1&d2	Bolus 400 mg/m ² d1 infusional 2400–3000 mg/m ² 46 h	1800 mg/m ² /week (8-h infusion)
LV	400 mg/m ² d1&d2	400 mg/m ² d1	200 g/m ² /week, bolus

^a Oxa, oxaliplatin; 5FU, 5-fluorouracil; LV, leucovorin; d1, day 1; d2, day 2.

PATIENTS AND METHODS

Patients and Treatments. Patients received second line therapy with oxaliplatin + high-dose 5FU continuous infusion and leucovorin (LV) for advanced colorectal cancer on the development of progression on 5FU/LV (Mayo Clinic regimen) in the years 1996–2000. All of the files presented here were identified from our database of patients undergoing a systematic pharmacokinetic study of 5FU at the initiation of treatment (9). The doses of 5FU were optimized in each patient according to pharmacological findings and thus permitted to dramatically reduce 5FU-induced toxic effects and limit the interference with our study about oxaliplatin toxic side effects.

Oxaliplatin was given in a 2-h infusion, routinely preceded by 3 mg of granisetron and 20 mg of dexamethasone, and followed by 30 mg of metoclopramide and 48 mg of methylprednisolone for 3 days. Three different regimens were used (Table 1), according to the evolution of the standard practice in Centre Paul Papin between 1996 and 2000.

The files from 161 patients, representing 1134 delivered cycles of chemotherapy, were reviewed and analyzed. Ninety-six of the 161 patients received infusions of Ca/Mg (the Ca/Mg group) as prevention of their symptoms and 65 patients did not.

The treatment consisted of Ca gluconate and Mg sulfate, 1 g each, delivered i.v. over 15 min just before the oxaliplatin infusion and repeated at the same dose after the completion of the oxaliplatin infusion (7, 9). Ca gluconate and Mg sulfate were given in the same bag. Ca/Mg infusions were not administered to patients with known hypercalcemia or already treated with thiazidic diuretics or digitalic.

Of the 66 patients who did not receive Ca/Mg infusion (the control group) in that time period, 42 were treated in the first years of practice when Ca/Mg was not yet used in our institution, and 23 were enrolled in clinical trials that did not allow any concomitant treatments.

Efficacy and Toxicity Assessment. In this case series, according to the standard practice of our institution, tumor response was evaluated after 3 months of treatment, correspond-

ing to four or six cycles of treatment. Response to treatment was classified according to WHO criteria. Confirmation of response at least 1 month after first evaluation was not done outside of clinical studies. Treatment with oxaliplatin/5FU/LV was continued to a total of at least 6 months, except for progressive disease or toxicity. Toxicity was evaluated repetitively, every week in FUFox regimen, because 5FU was administered weekly in daily hospitalization, or every 2 weeks in FOLFOX 4 and FOLFOX 6 regimens, and graded in the patients' files according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 1 scale. In addition, a specific neurotoxicity scale (10, 11) was used for oxaliplatin-related neurotoxicity (Table 2).

The Doses of 5FU and Oxaliplatin Were Adjusted According to Standard Practice for Toxicity. In the event of grade 2 neurotoxicity (specific scale), the oxaliplatin dose remained unchanged, and the following cycle was delayed until resolution. In case of recurrence of toxicity, the dose was reduced by 20%. In case of grade 3 toxicity, treatment was interrupted until resolution of the symptoms and then restarted with a 20% decrease of the dose. In case of other NCI-CTC grade 2 toxicities, the oxaliplatin dose remained unchanged, but the cycle was delayed until resolution. In case of recurrence, the dose was reduced by 20%. In case of any grade 3 toxicity, treatment was interrupted until resolution and then restarted with a 20% dose decrease. Treatment was permanently stopped in case of any grade 4 toxicity.

In the review of the data, we captured from the files the main specific neurotoxicity symptoms such as distal, oral and perioral paresthesias, cold induced or not, pharyngolaryngeal dysesthesia and pseudolaryngospasm, trismus, cramps and pain in the limbs, abdominal pain, acute diarrhea, and asthenia. Pharyngolaryngeal dysesthesia were defined as cold-related dysesthesia occurring during swallowing, whereas pseudolaryngospasm was defined as acute noncold-related feeling of difficulty in breathing, frequently occurring during oxaliplatin infusion. Cumulative doses of oxaliplatin, as well as dose intensities,

Table 2 Neurotoxicity scales

Scale	National Cancer Institute	Oxaliplatin
	Neurosensory	Specific Scale
Grade 1	Mild paresthesia, loss of deep tendon reflexes	Paresthesia, dysesthesia of short duration
Grade 2	Moderate paresthesia, mild or moderate objective sensory loss	Paresthesia, dysesthesia persisting between cycles
Grade 3	Paresthesia interfering with function, severe objective sensory loss	Paresthesia, dysesthesia causing functional impairment

Table 3 Patient characteristics

	Ca/Mg infusions	No Ca/Mg	Total
No. of patients	96	65	161
Age (mean \pm SE)	62 \pm 11	61 \pm 13	61.5 \pm 10.3
Male/female (%)	60/40	60/40	60/40
Performance status 0-1/2-3 (%)	91/9	92/8	91/9
Primary tumor site: colon/rectum/both (%)	63/33/4	65/31/5	64/32/4
FOLFOX4-OXA 85, <i>n</i> (%)	29 (30)	13 (21)	42 (26)
FOLFOX6-OXA 100, <i>n</i> (%)	25 (26)	9 (14)	34 (21)
FUFOX-OXA 130, <i>n</i> (%)	42 (44)	43 (45)	85 (53)

duration of treatment, number, and reason for drop outs, were collected and analyzed. We evaluated treatment efficacy after 3 months of treatment, but data were collected only in the 130 mg/m² group to have two sufficient and homogeneous populations in term of number of patients.

Statistical Analysis. Descriptive statistics were performed to compare the two groups of patients in terms of baseline characteristics, cumulative doses, dose intensity, response to chemotherapy, dropouts, toxicity (all grades and grades 3), and incidence of specific neurotoxicity symptoms. Percentages were compared, and the differences were statistically evaluated using the χ^2 test. According to the number of patients in each group, Yates modification could be applied.

For the comparison of distribution of samples we used, the χ^2 test of independence of two distributions (all calculated effectives were >5). The methods used to analyze the cumulative toxicity was Kaplan-Meier and log-rank testing.

RESULTS

Patient Characteristics. Patient characteristics are displayed in Table 3.

A total of 42 patients (29 Ca/Mg, 13 no Ca/Mg) received FOLFOX 4, 34 patients (25 Ca/Mg, 9 no Ca/Mg) FOLFOX 6, and 85 patients (42 Ca/Mg and 43 no Ca/Mg) FUFOX. None of the patients had previously received oxaliplatin or other platinum agents.

The Ca/Mg group and the group without Ca/Mg were comparable for age, gender, performance status, primary tumor site, and previous chemotherapy.

Effect of Ca/Mg on the Efficacy of Oxaliplatin-Based Chemotherapy. Table 4 summarizes the details of oxaliplatin/5FU/LV chemotherapy modalities in the two groups of patients. Significantly fewer patients stopped treatment for toxicity (any type) in the Ca/Mg group compared with the group without Ca/Mg: 33 *versus* 51% ($P < 0.02$). The difference was also significant in the subgroup oxaliplatin 130 mg/m². Mean cumulative oxaliplatin doses were slightly higher in the Ca/Mg group compared with the group without oxaliplatin, but the difference was not significant. Likewise, treatment duration was not significantly longer in the Ca/Mg group. The relative dose intensity was similarly good in both groups.

We evaluated treatment efficacy after 3 months of treatment. Data were collected only in the 130 mg/m² group to have two homogeneous populations in term of number of patients. The response rate (best response) was 45% in the group with Ca/Mg compared with 35%, percentage of stable disease was 34 *versus* 46% and progressive disease was 21 *versus* 18%.

Effect of Ca/Mg on Oxaliplatin Toxicity. No Ca/Mg-induced toxicity has been reported in the 96 patients having received this treatment. The main effects of Ca/Mg infusions on oxaliplatin neurotoxicity are summarized in Table 5. Acute neurotoxic symptoms were less frequent and less severe in the Ca/Mg group.

Distal and lingual paresthesia, cold induced or not, trismus, cramps and pains in the limbs, and diarrhea were significantly less frequently reported; pharyngolaryngeal dysesthesia were

Table 4 Effect of Ca/Mg on the efficacy of oxa chemotherapy (oxa/5FU/LV)^a

	FOLFOX4		FOLFOX6		FUFOX		Total		
	OXA 85		OXA 100		OXA 130		Ca/Mg	No Ca/Mg	
	Ca/Mg	No Ca/Mg	Ca/Mg	No Ca/Mg	Ca/Mg	No Ca/Mg			
Patients	29	13	25	9	42	43	96	65	
Mean total OXA doses mg \pm SD (Range)	705 \pm 314 255-1360	659 \pm 245 245-950	907 \pm 392 200-1800	746 \pm 266 520-1200	801 \pm 530 390-3490	668 \pm 406 130-2500			
	$(P = 0.61)$		$(P = 0.31)$		$(P = 0.15)$				
No. of cycles									
Mean \pm SD (Range)	8 \pm 3.5 (3-16)	7.5 \pm 3.6 (3-12)	9.5 \pm 3.9 (4-18)	8.1 \pm 2.6 (6-12)	6.4 \pm 4.9 (3-33)	5.2 \pm 3.2 (1-20)	NA	NA	
	$(P = 0.9)$								
Patients (%) on study after									
3 cycles	100	100	100	100	100	83	NA	NA	
6 cycles	76	69	96	100	62	44			
9 cycles	38	38.5	48	44	21	12			
12 cycles	34.5	23	36	11	5	2			
OXA relative dose intensity	0.93	0.92	0.94	0.90	0.95	0.93	NA	NA	
Dropouts—any toxicity %	25	31	52	55	26	56	33	51	
	$P = 0.2$		$P = 0.8$		$P = 0.002$		$P = 0.02$		

^a Oxa, oxaliplatin; 5FU, 5-fluorouracil; LV, leucovorin; NA, not applicable.

Table 5 Effect of Ca/Mg on oxaliplatin toxicity^a

	OXA 85		OXA 100		OXA 130		Total	
	Ca/Mg	No Ca/Mg	Ca/Mg	No Ca/Mg	Ca/Mg	No Ca/Mg	Ca/Mg	No Ca/Mg
No. of patients	28	13	25	9	42	43	96	65
No. of cycles	(155)	(62)	(150)	(44)	(218)	(177)	(523)	(283)
Cycles 1-6: percentage of cycles with \geq grade 2 symptoms								
Distal paresthesia	6	38	4	40	8	68 ($P:10^{-7}$)	6	51 ($P = 10^{-8}$)
Lingual paresthesia	0	28	1	28	3	47 ($P:10^{-4}$)	2	35 ($P = 10^{-7}$)
PLD ^b	0	9	0	0	0	15	0	9 ($P = 10^{-8}$)
Trismus	0	4	0	0	0	18	0.6	9 ($P = 10^{-7}$)
Limbs contractions	0	4	0	4	2	15	0.8	9 ($P = 10^{-7}$)
Limbs pain	0	0	0	0	1	4	0.4	2.5
Diarrhea	9	26	3	30	13	28 ($P:0.6$)	10	27 ($P = 0.006$)
Asthenia	9	9	6	44	21	48 ($P:10^{-2}$)	13	41 ($P = 10^{-4}$)
Distal paresthesia, grade 3	0	7	0	6	1	13	0.4	11 ($P = 10^{-8}$)
Pseudolaryngospasm, grade 3 (%)	0	0	0	0	0	3	0	2 ($P = 10^{-4}$)
Percentage of patients who experienced at least 1 grade 3 paresthesia	7	15	4	22	9.5	30 ($P:0.5$)	7	26 ($P = 0.001$)
Percentage of weight loss at 3 months								
Stable	90	77	100	89	88	72	92	75
<5%	3	8	0	0	9.5	12	5	9
<10%	3	15	0	0	2	12	2	11
<20%	3	0	0	11	0	5	1	5
Stable versus <5% versus \geq 5% $P = 0.001$								
Dropouts (%) for neurotoxicity any grade	0	15	4	33	7	35 ($P:0.003$)	4	31 ($P = 0.000003$)
Dropouts (%) due to grade 3 chronic neurotoxicity	0	8	0	11	0	14 ($P:0.02$)	0	12 ($P = 0.0016$)
Chronic neuropathy at the end of treatment (%)								
Grade 0	79	46	64	33	60	36	65	37
Grade 1	18	15	8	34	12	17	13	18
Grade 2	3	15	16	11	16	31	12	25
Grade 3	0	23	12	22	12	17	8	20 ($P = 0.003$)

^a In parentheses, the significance of the difference between the two groups, with and without Ca/Mg.

^b PLD, pharyngolaryngeal disesthesia.

never reported in the Ca/Mg group versus 9% in the no Ca/Mg group ($P = 10^{-8}$). The percentage of patients presenting a grade 3 NCI-CTC scale or specific neurotoxicity scale at any time on oxaliplatin treatment was significantly lower in the Ca/Mg group than in the control group (7–26%; $P = 0.001$).

Only 4% of patients withdrew for neurotoxicity in the Ca/Mg group versus 31% in the control group ($P = 0.000003$). The difference was also highly significant in the oxaliplatin 130 mg/m² subgroup ($P = 0.003$).

We compared the severity of chronic neurotoxicity at the end of treatment in patients who had received at least three treatment cycles in the two groups of patients. Neurotoxicity at the end of treatment was less frequent and less severe in the treated group, compared with the control group ($P = 0.003$; Table 5). Furthermore, when patients experienced neuropathy at the end of treatment, the reversibility appeared to be more important and more rapid in the Ca/Mg group, as shown on Fig. 1, especially for 85 mg/m² oxaliplatin dosage.

We investigated two other markers of tolerance of treatment: fatigue and weight loss (Table 5). Patients with Ca/Mg had significantly less intense and prolonged asthenia ($P = 10^{-4}$), and most of them kept unchanged their weight after 3 months of treatment compared with no Ca/Mg group ($P = 0.01$).

Fig. 2 summarizes the effect of Ca/Mg infusions on the severity of sensory neuropathy rated according to NCI-CTC and

the specific neurotoxicity scale in the whole population (161 patients). We reviewed neurotoxicity grading at two different cumulative oxaliplatin doses (Fig. 2A; ~400 mg/m²), corresponding to three cycles of 130 mg/m², four cycles of 100 mg/m², five cycles of 85 mg/m² regimens; and (Fig. 2B; ~500 mg/m²), corresponding to four cycles of 130 mg/m², five cycles of 100 mg/m², and six cycles of 85 mg/m². Patients receiving Ca/Mg infusions had significantly less frequent and less severe neurotoxic effects because 95% of them had grade 0 or grade 1 neurotoxicity. The χ^2 test of independence of the two distributions, with and without Ca/Mg, showed that they were highly independent.

Men and women had about the same incidence of oxaliplatin-induced neurotoxicity, but women seemed to have more severe neuropathy: in the group without Ca Mg, 7% had grade 3 (NCI-CTC) neuropathy at cycle 1 and 45% at cycle 3 compared with 0 and 18% of men. We found no difference according to age of patients.

DISCUSSION

The main aim of this retrospective study of our population of 161 colorectal patients receiving oxaliplatin/5FU/LV was to assess the efficacy of Ca/Mg infusions in preventing acute and possibly chronic oxaliplatin-induced neurotoxicity.

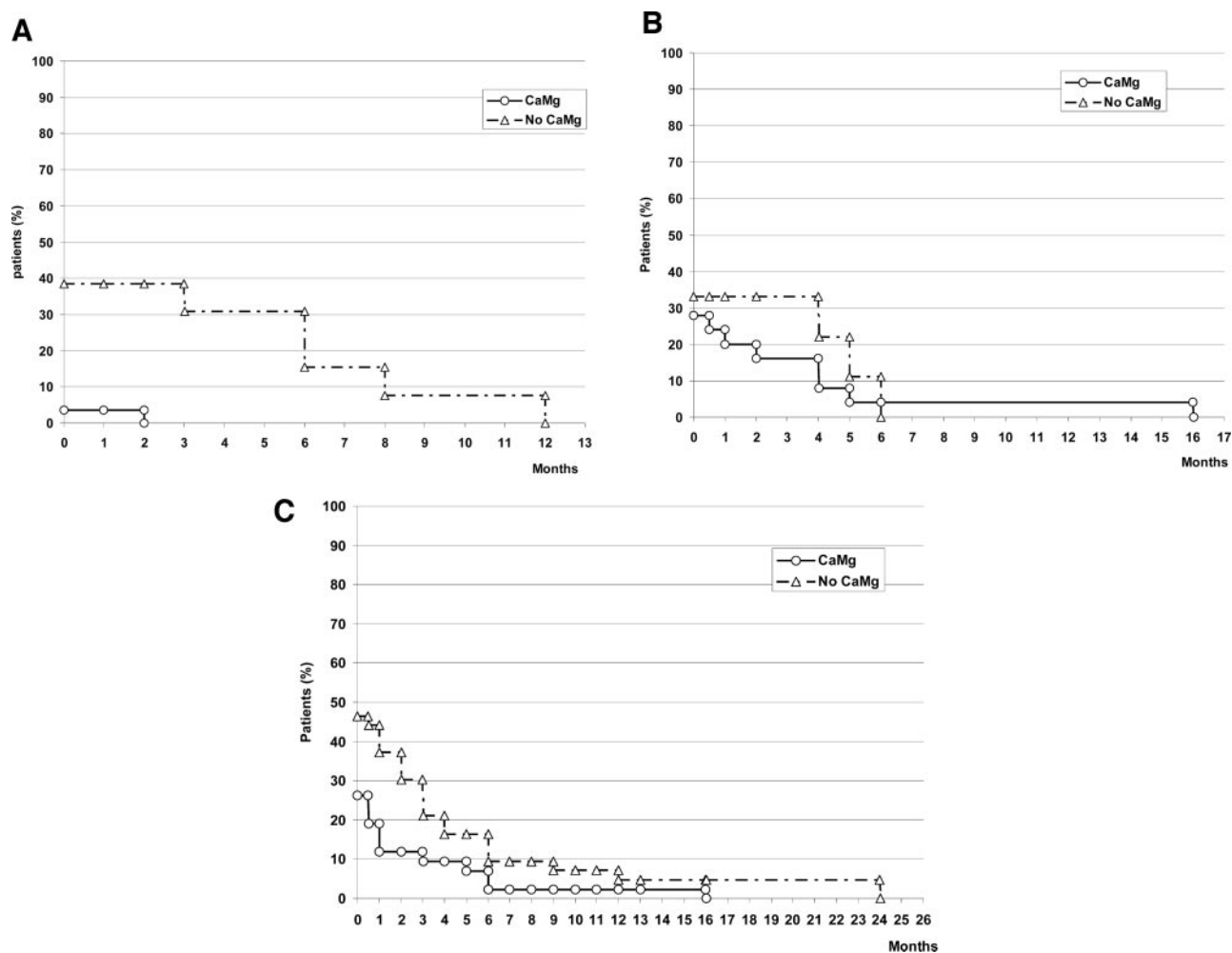


Fig. 1 Duration of grade ≥ 2 neuropathy in the two groups of patients and in the three subgroups: A, 85 mg/m²; B, 100 mg/m²; C, 130 mg/m².

Because this study is retrospective, not randomized and not blind, therefore, patients of the control group may differ from patients in the Ca/Mg group because they were either treated early after the commercial availability of oxaliplatin or were included in randomized clinical trials excluding the use of concomitant experimental treatments. Furthermore, the patients and the medical and nursing staff may have been biased in their reporting or assessment of signs and symptoms due to a placebo effect.

Despite these limitations, patients receiving Ca/Mg and controls were comparable for most baseline characteristics and support the hypothesis that sodium channel disturbances related to intracellular Ca/Mg pool may be responsible for the acute neuropathy.

The comparison of the two groups of patients showed that only 4% of patients withdrew for neurotoxicity in the Ca/Mg group *versus* 31% in the control group ($P = 0.000003$). However, it should be noted that in FOLFOX4 and FOLFOX6 groups, more patients were given calcium magnesium infusion, making the results more open to bias and placebo effect. Drop-outs for grade 3 neurotoxicity are probably less influenced by placebo effect. The difference in dropping out because of grade

3 neurotoxicity is less important but remains significant ($P = 0.0016$). The difference in term of mean cumulative doses and duration of treatment did not reach significance threshold.

Ca/Mg infusions did not decrease treatment efficacy. In the group oxaliplatin (130 mg/m²), the response rate was 45% in the group with Ca/Mg compared with 35%, percentage of stable disease was 34 *versus* 46%, and progressive disease was 21 *versus* 18%. This was not the main purpose of this posthoc study, and consequently, we cannot draw any firm conclusions. However, efficacy appeared to be at least as good in the group of patients with Ca/Mg infusions, compared with the group without Ca/Mg. The response rate was high in this series: a confirmatory computed tomography scan was not systematically performed to confirm the response. Also, bolus standard 5FU/LV regimen was used in first line treatment of these patients, whereas in the second line, oxaliplatin was combined with infusional 5FU.

The fact that neurotoxicity requires treatment discontinuation in a much smaller percentage of patients may allow more patients to benefit from oxaliplatin containing treatment until disease progression.

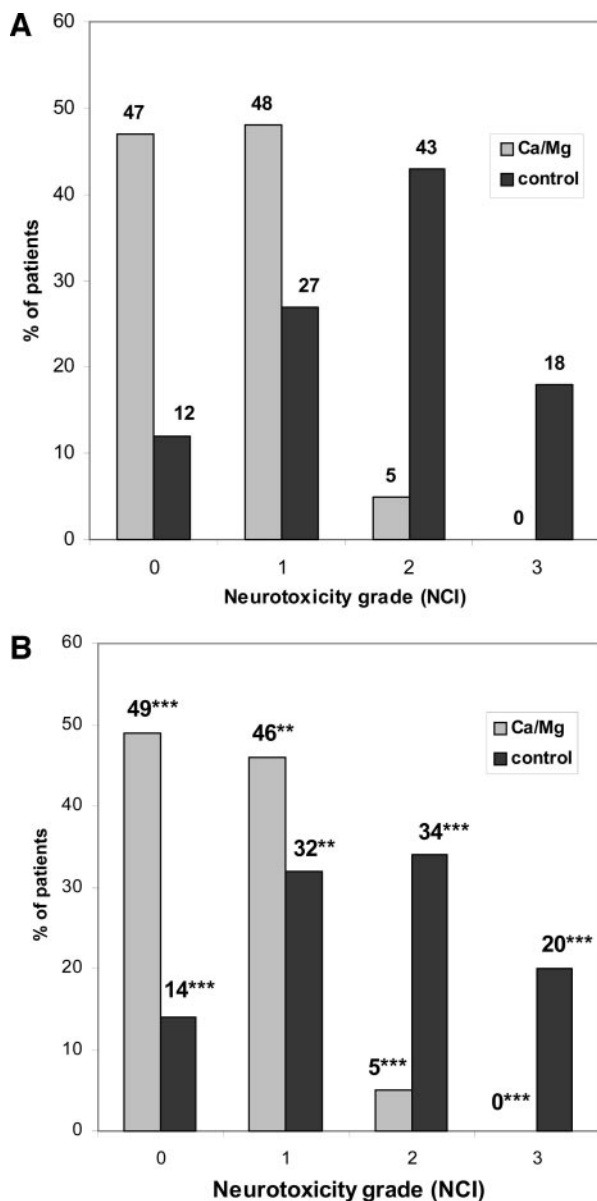


Fig. 2 Ca/Mg effect on percentage of patients with neuropathy (National Cancer Institute), according to equivalent cumulative oxaliplatin doses (161 patients): A, ~390–425 mg, corresponding to three cycles of 130 mg/m², four cycles of 100 mg/m², five cycles of 85 mg/m² regimens; and B, ~500–520 mg/m², corresponding to four cycles of 130 mg/m², five cycles of 100 mg/m², and six cycles of 85 mg/m² (χ^2 test of distributions was highly significant \ll 0.001).

Acute neuromuscular manifestations, especially distal and lingual paresthesia, cold induced or not, were very rare in the Ca/Mg group compared with the other one in the whole population of patients and in every oxaliplatin dosage subgroup. The difference is highly significant ($P = 10^{-8}$ and 10^{-7} , respectively). The frequency of grade 3 neurotoxic effects, severely interfering with patients' comfort and autonomy, was deeply reduced. We can say that Ca/Mg infusions had a deep impact on patients' quality of life. On the same way, other acute toxic effects such as trismus, phar-

ngolaryngeal dysesthesia, and cramps and pains in the legs were significantly less frequent. Pseudolaryngospasm, a very bothersome toxicity, never occurred when patients were receiving Ca and Mg, which is really helping the management of oxaliplatin infusions in the day hospital. It is noteworthy that we found less frequent and less severe diarrheas in the Ca/Mg group, even if oxaliplatin was combined with 5FU. Ca/Mg infusions had a positive effect on acute, severe, and short-lasting diarrhea, occurring during the few hours immediately after the oxaliplatin infusion or even during infusion. Thus, oxaliplatin-induced could be caused by an increased excitability of parasympathetic nerves, probably mediated by oxaliplatin effect on voltage-gated Na channels. This finding is of importance because oxaliplatin combined with bolus or short-term 5-FU regimens may be associated with a higher incidence of diarrhea.

We found also a positive effect on asthenia and body weight. Patients with Ca/Mg experienced less severe and prolonged asthenia and more frequently kept their weight unchanged than in the control group, probably because of improved neurological status.

We also investigated the effects of Ca/Mg on cumulative neurotoxicity because it can alter patients' quality of life, and little is known about its relationship with acute neurosensory symptoms: do they share a common mechanism or do they represent two distinct types of toxicity?

Incidence of cumulative grade 3 neuropathy has been previously evaluated as 18% in 85 mg/m² weekly oxaliplatin schedule in MOSAIC adjuvant trial (3). This frequency was probably underestimated, efficacy being the main objective and neurotoxicity not being closely followed up.

In our series, patients with Ca/Mg appeared to have significantly less frequent and severe chronic grade 3 toxicity than controls ($P = 0.003$; Table 5). At the end of treatment with oxaliplatin, 65% of patients in the Ca/Mg group and 37% in the control group had no neuropathy. Ca/Mg infusions were more efficient in 85 mg/m² schedule (0 versus 23% grade 3 neurotoxicity) than in 100 and 130 mg/m² dosages, suggesting a dose effect of Ca/Mg necessary to chelate oxalate. Moreover, when patients in the Ca/Mg group had grade 3 toxicity, it seemed to be more rapidly reversible upon oxaliplatin withdrawal than in control patients, especially with 85 mg/m² oxaliplatin, where the difference was significant (Fig. 1).

According to these results, the two types of neurotoxicity (acute and cumulative) may indeed be linked. However, neurotoxic effects do not fully disappear with the use of Ca/Mg infusions, especially in the subpopulation treated with oxaliplatin at the highest dose of 130 mg/m². Possibly, dosage and administration schedule could be optimized, and patients might optimally benefit from more intensive or oral prolonged preventive treatment.

We and others (8, 11, 12) observed in preclinical investigations in different models that oxaliplatin appeared to act on Na channels. We additionally demonstrated that oxaliplatin acted via oxalate selectively on a subpopulation of Ca-dependent Na channels (8).⁵ Repeated administration of oxali-

⁵ Presented at 92nd Annual Meeting of the American Association for Cancer Research, March 24–28, 2001, New Orleans, LA, 2001 (abstract 5020).

platin could hinder processes such as neurotransmitter release, growth cone elongation, and gene expression and then selectively damage this population of Na channels and induce a persistent neuropathy (13, 14).

Finally, in our experience, Ca and Mg infusions are well tolerated and not toxic. Our approach compares favorably with other alternatives such as carbamazepine, glutathione, α lipoic acid, or amifostine (15–19), which can generate toxic side effects, can interfere with oxaliplatin efficacy, or whose results are not confirmed.

A prospective, multicenter, double-blind, randomized, placebo-controlled study on 160 patients is currently underway to confirm the efficacy of Ca and Mg infusions in the prevention of acute and chronic oxaliplatin-related neurological symptoms. In conclusion, our data suggest that Ca/Mg infusions reduce the incidence and intensity of acute oxaliplatin-induced neurosensory and neuromuscular and visceral symptoms and might decrease or delay the incidence of cumulative sensory neuropathy, allowing for higher oxaliplatin doses and longer treatment duration.

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