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Calcium and Magnesium Prophylaxis for Oxaliplatin-Related Neurotoxicity: Is It a Trade-off Between Drug Efficacy and Toxicity?

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ABSTRACT

Oxaliplatin-based chemotherapy regimens are the current standard treatment in the management of colorectal cancer. Neurotoxicity is the major cause of treatment delay, dose reduction, and cessation of oxaliplatin. Evidence regarding the role of calcium and magnesium prophylaxis to prevent oxaliplatin-related neurotoxicity is conflicting and further randomized data are needed to answer this question accurately. The purpose of this paper is to provide a critical overview of various studies that have been conducted so far to evaluate the preventative role of calcium and magnesium prophylaxis against oxaliplatin-related neurotoxicity. ***The Oncologist*** 2011;16:1780–1783

INTRODUCTION

Oxaliplatin-based chemotherapy regimens are the current standard treatment for both adjuvant and metastatic colorectal cancer (mCRC), with response rates of up to 53% [1–3]. Besides myelosuppression, neurotoxicity is the major cause of treatment delay, dose reduction, and cessation of oxaliplatin. The neurotoxic effects are almost always sensory and can manifest either as acute neuropathy or chronic cumulative neuropathy. The acute form is transient in nature and develops either during or just after the oxaliplatin infusion and seldom lasts >7 days. It is usually triggered by cold and can manifest as tingling, paresthesia, jaw spasms, limb stiffness, and muscle cramps. The incidence of acute neuropathy secondary to oxaliplatin ranges from 80%–98% [4]. The chronic sensory neuropathy is more disabling and commonly manifests as numbness or tingling of the hands and feet [1, 3]. This form of neuropathy develops in about 10%–20% of patients after a cumulative oxaliplatin dose of 750–850 mg/m^2.

The chronic form of oxaliplatin-related neurotoxicity is generally thought to be reversible. Results from trials regarding the reversibility of oxaliplatin-induced neurotoxicity, however, have been inconsistent with data regarding the long-term neurotoxicity related to oxaliplatin. In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study [3], up to 40% of patients continued to experience at least grade 1 sensory neuropathy 12 months after completion of treatment, with 1.1% and 0.5% experiencing grade 3 sensory neuropathy at 12 and 18 months after completion of chemotherapy, respectively. Land et al. [5] reported the results of a phase III study (NSABP C-07) in 2007 comparing the efficacy and neurotoxicity of adjuvant bolus fluorouracil and leucovorin (FULV) with FULV/oxaliplatin (FLOX) combination in stage II or III colon cancer. Mean patient reported neurotoxicity was higher in the oxaliplatin arm throughout the 18 months of study ($p <$ .0001). Observer-reported neurotoxicity was 68% in the FLOX group compared to 8% in the FULV group at their first on-treatment assessment. Time to resolution of sensory symptoms was significantly longer and persisted beyond 2 years in about 10% of patients in the oxaliplatin group. A greater number of patients in the FLOX group (70%) had unresolved neurotoxicity compared to the FULV group (36%) ($p <$ .0001).

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Pietrangeli et al. [6] used neurophysiological examinations to compare the neurotoxicity of two different cumulative doses of oxaliplatin (862 and 1,033.5 mg/m^2) and showed both an acute, transient neuropathy and a cumulative dose-related sensory neuropathy in nearly all the patients. Sixteen percent of patients continued to experience symptoms secondary to neurotoxicity after 5 years of follow-up, indicating persistence of this type of neuropathy. Park et al. [7] specifically investigated the long-term neurological sequelae related to oxaliplatin using subjective and objective assessments of neurotoxicity up to a median follow up of 25 months. They found that 79.2% patients had residual symptoms at 25 months post treatment with oxaliplatin. The results of these studies show long-term persistence of neuropathic symptoms secondary to oxaliplatin in contrast to the general perception of reversibility.

The exact mechanism of oxaliplatin-related neuropathy is unknown. It is speculated that the acute form is directly or indirectly related to the chelation of calcium by oxalate (a metabolite of oxaliplatin) leading to neuronal hyperexcitability as a result of inability to disinhibit calcium-dependent sodium (Na+) channels [8, 9]. Oxaliplatin has also been shown to modulate voltage gated Na+ channels in the axons by slowing Na+ channel inactivation kinetics [10–12]. The chronic cumulative sensory neuropathy secondary to oxaliplatin is thought to be due to dorsal root ganglion damage and neuronal cell death as Na+ channels are expressed on dorsal root ganglion neuronal cells [13, 14].

The proposed pathogenesis of oxaliplatin-induced neurotoxicity led to the hypothesis that calcium (Ca) and magnesium (Mg) infusions can be used as chelators of oxalate to inhibit its action on the Na+ channels and thus provide protection against the neurotoxic effects of oxaliplatin. Various studies have investigated the use of calcium and magnesium infusions (Ca/Mg) using 1 g of Ca and 1 g of Mg given over 15–30 minutes immediately prior to and immediately after oxaliplatin infusion, adding up to 1 hour to the standard oxaliplatin infusion time.

The initial study in this field was a nonrandomized, retrospective analysis of 161 patients with advanced CRC who were treated with three different oxaliplatin-based regimens published by Gamelin et al. [15]. A total of 96 patients received 1 g of calcium gluconate and 1 g of magnesium sulfate before and after oxaliplatin while the remaining 65 patients served as the control group. The median administered cumulative oxaliplatin dose was 910 mg/m^2 in the Ca/Mg prophylaxis group but was only 650 mg/m^2 in the control group. In the Ca/Mg prophylaxis group, only 4% stopped chemotherapy as a result of neurotoxicity compared with 31% in the control group ($p <$ .001). Grade 3 neurotoxicity was also less frequently observed in the Ca/Mg group (8% versus 20%, $p = .003$). The tumor response rate (RR) was similar in both groups. The weaknesses of this study are that it was retrospective, non-randomized, and unblinded. Therefore the results may be explained by differences between the two groups other than the use of Ca/Mg prophylaxis, and there may have been bias in the reporting and assessment of neuropathic symptoms and signs.

Knijn et al. [16] retrospectively assessed the effect of Ca/Mg infusions on the incidence of neurotoxicity and on clinical outcome in mCRC patients treated in the phase III CAIRO2 (Capecitabine, oxaliplatin, and bevacizumab with or without cetuximab) study. The incidence of grade 1–4 neurotoxicity in the Ca/Mg+ group and the Ca/Mg$^-$ group was 85% and 92%, respectively ($p = .02$). The incidence of greater than grade 2 neurotoxicity was 40% and 45%, respectively ($p = .22$). There was no significant difference between the two groups in terms of RR, progression-free survival (PFS), or overall survival (OS). The major limitations of this study were that neurotoxicity was only assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale and that the administration of oxaliplatin was limited to a maximum of 6 cycles rather than the standard 12 cycles used in adjuvant setting.

Ca/Mg prophylaxis has also been tested prospectively. The Combined Oxaliplatin Neuropathy Prevention Trial (CONcePT) study for first-line therapy of mCRC was designed in a 2×2 fashion to evaluate potential reduction in cumulative neurotoxicity associated with oxaliplatin through intermittent administration of oxaliplatin and the use of Ca/Mg prophylaxis. This trial was prematurely terminated in 2007 as the independent data monitoring committee (IDMC) found that the Ca/Mg infusion reduced the efficacy of the chemotherapy regimen with a 17.3% RR to treatment in the arms receiving Ca/Mg prophylaxis as compared with 32.9% in those not receiving Ca and Mg. Hochster et al. [17] subsequently undertook a central, blinded radiology review of scans in 140 randomized patients enrolled in the CONcePT trial in early 2008, which showed the findings of the IDMC to be incorrect. The review found that the RR favored patients treated with Ca/Mg although the difference was not statistically significant ($p = .70$). There was a significant 50% reduction in severe neuropathy between the Ca/Mg and the placebo group.

The preliminary results of the French NEUROXA (Neurotoxicity of oxaliplatin) study [18] were released in response to the IDMC report of the CONcePT trial. This study included 144 patients who were randomly assigned, in a double-blinded fashion, to receive Ca/Mg or placebo. Early, still-blinded analysis revealed significantly lower frequency and grade of oxaliplatin-related neurotoxicity in one arm (5% versus 24% grade 3 neurotoxicity according to NCI CTCAE; $p < .001$). There was no difference in objective RR (50% versus 53%, $p = .45$), PFS ($p = .79$), and OS ($p = .45$). However, these results are still blinded and this study included patients in both the palliative and adjuvant settings. One of the major issues with this study is that neuropathy was assessed only through the NCI CTCAE scale and neither an oxaliplatin-specific scale nor patient reported outcomes were included.

Grothey et al. [19] recently published the results of the North Central Cancer Treatment Group (NCCTG) N04C7 double-blind, placebo-controlled trial in the adjuvant setting of colon cancer. The study was closed prematurely with only 104 of the planned 300 patients enrolled due to the initial results from the CONcePT trial. This study showed Ca/Mg prophylaxis decreased the incidence of chronic cumulative ≥grade 2 sensory neuropathy, irrespective of whether it was measured

by NCI CTCAE ($p = .038$) or by the oxaliplatin-specific scale ($p = .018$). However, Ca/Mg prophylaxis did not result in decrease in the incidence of acute cold-induced neurotoxicity. This result is unexpected given the rationale of the acute chelation of Ca/Mg by oxalate on which this study was based, as well as the findings of other studies. One criticism of this study was that patients with a number of comorbidities such as diabetes mellitus and vitamin B12 deficiency were not excluded from the study. The authors' response was that various comorbidities including diabetes mellitus were not thought to be relevant in a pooled analysis of several trials by Ramanathan et al. [20], who examined whether the presence of diabetes mellitus influences the incidence, severity, and course of oxaliplatin-related neurotoxicity in patients with mCRC. Other weaknesses of the study were the lack of standardized timing and objective assessment of sensory neuropathy.

Chay et al. [21] analyzed the preventative role of Ca/Mg infusion against oxaliplatin-related neurotoxicity using formal nerve conduction studies for assessment of neuropathy along with NCI CTCAE criteria and oxaliplatin-specific scales. This study was terminated early due to the results from CONcePT trial, and the sample size was small ($n = 27$). There was a trend toward reduced subjective acute sensory neuropathy with Ca/Mg infusion, which was not significant. Interestingly, Ca/Mg failed to reduce the rate of cumulative sensory neuropathy and instead increased the rate of abnormal nerve conduction studies, suggesting a significant difference in perceived sensory and objective neuropathy. Ishibashi et al. [22] also did not report any significant difference in the incidence of neurotoxicity between the Ca/Mg and the placebo group.

There are significant discrepancies in the findings of both retrospective and prospective studies in this area. Knijn et al. [16] found reductions in acute but not chronic neurotoxicty, whereas Grothey et al. [19] reported improvement in chronic but not acute neurotoxicity. The analysis by Gamelin et al. [15] demonstrated reduction in acute neurotoxicity and reduction in the severity of chronic type. Lack of objective, standardized measurement of neurotoxicity is a significant contributory factor. The two major retrospective analyses (Gamelin et al. and Knijn et al.) used the NCI CTCAE criteria for measuring neurotoxicity whereas the prospective studies have utilized various other tools as well, including patient questionnaires (Grothey et al.), oxaliplatin-specific scale (Grothey et al.), Debiopharm neurotoxicity scale (Ishibashi et al.), and nerve conduction studies (Chay et al.). Patient questionnaires assess the impact of neuropathy on the individual, as does physician enquiry; however, these measures may not necessarily accurately reflect the degree of functional and structural nerve damage. Therefore, results may differ depending on which measures are utilized.

Furthermore, there is a lack of standardization in timing of assessment of neurotoxicity and inadequate assessment of long-term neurotoxicity related to oxaliplatin between studies investigating Ca/Mg prophylaxis. Also, because of the initial concerns raised by the IDMC examining the CONCePT trial, many of the major trials were terminated early and are thus underpowered. The NCCTG has initiated another prospective randomized, double-blinded trial aimed at addressing these issues.

In conclusion, oxaliplatin-related neuropathy impacts on patients' quality of life and in some cases compromises patients' treatment as a result of dose reduction, delay, or cessation of oxaliplatin. Current evidence indicates that Ca/Mg infusions are safe to administer and do not reduce the efficacy of oxaliplatin-based chemotherapy. Although there are several studies that show the infusions may reduce the rates of oxaliplatin-related neuropathy, there are significant weaknesses in the research reported thus far. Further randomized data are needed to accurately determine the efficacy of Ca/Mg prophylaxis on both acute and chronic oxaliplatin-related neurotoxicity. Should these data prove Ca/Mg prophylaxis to be effective, pharmaco-economic analysis will be required to determine the additional cost to cancer services of the infusion in terms of nursing staff and chemotherapy unit chair time, prior to the acceptance of Ca/Mg prophylaxis into routine clinical practice.

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See the accompanying commentary on pages 1667–1668 of this issue.