

# Calcium and Magnesium Use for Oxaliplatin-Induced Neuropathy: A Case Study to Assess How Quickly Evidence Translates Into Practice

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## Abstract

Substantial research efforts have focused on methods of treating and preventing oxaliplatin-associated neuropathy, the dose-limiting toxicity associated with this drug. Administration of intravenous calcium and magnesium (CaMg) before and after oxaliplatin has been the most studied approach to preventing oxaliplatin-induced neuropathy. Although early reports demonstrated potential benefit, subsequent larger trials failed to confirm the efficacy of CaMg in preventing this adverse effect. This article explores how accumulating evidence for and against the use of CaMg for preventing oxaliplatin-induced neuropathy has impacted clinical practice. (*J Natl Compr Canc Netw* 2015;13:1097–1101)

Oxaliplatin-induced peripheral neuropathy is a common toxicity that may last for years, which has resulted in extensive interest in identifying interventions to prevent its occurrence. Administration of intravenous doses of calcium and magnesium (CaMg), before and after oxaliplatin, has been the most studied approach to preventing oxaliplatin-induced neuropathy. This approach was based on a hypothesis that the sensory neurotoxicity of oxaliplatin was, at least partly, related to chelation of intracellular Ca ions caused by the oxalate ring structure interfering with Ca-gated nerve ion channels.<sup>1</sup>

Over the years, results of several retrospective and prospective clinical studies of CaMg as a neuroprotectant

for oxaliplatin-induced neurotoxicity have been presented and published, with contradictory conclusions. A key influential study by Gamelin et al<sup>2,3</sup> reported the results of a retrospective review of patients receiving oxaliplatin therapy along with intravenous CaMg, with a comparison of these results to a historical control group who did not receive CaMg.<sup>2,3</sup> Oxaliplatin was discontinued because of neurotoxicity in 31% of patients who had not received CaMg historically, but in only 4% of patients who had received intravenous CaMg ( $P=.000003$ ). Both acute and chronic oxaliplatin-induced neurotoxicity seemed to be less frequent with CaMg, and there was no evidence of a reduced antineoplastic efficacy from FOLFOX in the group who received CaMg.<sup>2</sup>

These findings prompted many oncologists to start administering intravenous CaMg to patients receiving oxaliplatin in routine clinical practice. Additionally, prospective randomized controlled trials were developed to further investigate this promising therapy. One of these trials, the Combined Oxaliplatin Neurotoxicity Prevention Trial (CONcePT), enrolled patients with metastatic colorectal cancer. In 2007, a Letter to the Editor in the *Journal of Clinical Oncology* (JCO) reported that a data monitoring committee had identified a lower disease response rate in patients receiving CaMg, leading to the closure of the trial.<sup>4</sup> This publication doused enthusiasm for this treatment and led to the closure of at least 3 other randomized placebo-controlled trials that had been ongoing across the world, including an adjuvant therapy trial (N04C7) that had accrued approximately 100 patients.

However, a subsequent review of the data monitoring committee report showed that it was aberrant, and a subsequent Letter to the Editor in JCO illustrated that

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no true decrease in response rates had occurred in the patients randomized to CaMg.<sup>5</sup>

Although the CONcePT study results, presented at the 2008 ASCO Annual Meeting, could not demonstrate benefit for CaMg over placebo,<sup>6</sup> results from the prematurely closed N04C7, a phase III, placebo-controlled study of intravenous CaMg for the prevention of oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer, did support that CaMg protected against oxaliplatin-induced sensory neurotoxicity.<sup>7</sup> Further analysis of the N04C7 data showed that, although CaMg decreased cumulative sensory neurotoxicity in the first 3 months of therapy, it did not affect oxaliplatin-induced acute neuropathy; this information was presented at the 2009 ASCO Annual Meeting.<sup>8</sup> The peer-reviewed publication of the N04C7 data in *JCO* in 2011 provided more enthusiasm for using CaMg with oxaliplatin.<sup>9</sup> Understanding that the results of the previous trial were compromised by its premature closure and suboptimal sample size, a subsequent larger placebo-controlled clinical trial was initiated by the N04C7 investigators.<sup>10</sup>

This larger, randomized, placebo-controlled phase III trial, N08CB, which was presented at the May 2013 ASCO Annual Meeting<sup>10</sup> and published online in *JCO* in December 2013,<sup>11</sup> demonstrated convincingly negative results, with no suggestion that CaMg infusions substantially improved either chronic or acute oxaliplatin-induced neuropathy. These negative data supported the results of 3 additional smaller randomized trials, none of which demonstrated any value for intravenous CaMg for the prevention of oxaliplatin-induced neuropathy.<sup>12-14</sup>

The goal of this current study was to assess the extent to which the use of CaMg use with oxaliplatin changed clinical practice in response to the presentation and publication of contradictory results over time.

## Materials and Methods

The effect of changing evidence on practice changes was assessed using 2 separate approaches. This assessment included using detailed clinical data to look at the effect at a single center and then using national claims data to assess the changes in patterns of care on a larger scale. This allowed us to assess both a center-level and a national-level effect of this changing evidence and to assess whether the results from these 2 approaches were concordant or discordant.

## Data Sources

Mayo Clinic medical record and billing data provided information on the use of CaMg among patients treated with oxaliplatin at the Mayo Clinic in Rochester, Minnesota, a large integrated, multispecialty group practice. All patients receiving oxaliplatin from January 1, 2003, to June 30, 2014, were identified, and the proportion who also received intravenous CaMg, on the same day as oxaliplatin, was calculated over time. Patients who did not provide consent for the use of their medical records were excluded from the analysis, in accordance with Minnesota state law. Of the 9523 Mayo Clinic patients, 9142 (96%) gave research authorization, whereas 381 (4%) did not. The Institutional Review Board of Mayo Clinic approved the study.

In addition, a national retrospective analysis of the use of CaMg among patients being treated with oxaliplatin was performed using administrative claims data from Optum Labs Data Warehouse (OLDW), which includes privately insured and elderly patients enrolled in Medicare Advantage in the United States.<sup>15</sup> The OLDW has data on approximately 100 million enrollees from geographically diverse regions across the United States, with the greatest representation from the South and Midwest. The plan provides fully insured coverage for inpatient, outpatient, and pharmacy services ([https://www.optum.com/content/dam/optum/resources/product-Sheets/5302\\_Data\\_Assets\\_Chart\\_Sheet\\_ISPOR.pdf](https://www.optum.com/content/dam/optum/resources/product-Sheets/5302_Data_Assets_Chart_Sheet_ISPOR.pdf)). Medical claims include International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes; ICD-9 procedure codes; Current Procedural Terminology, Version 4 (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. Study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and, because this study involved analysis of preexisting, deidentified data, it was exempt from Institutional Review Board approval.

## Population

Using the HCPCS, we identified all patients who had received oxaliplatin (HCPCS code J9263) from January 1, 2003, through June 30, 2014. The use of CaMg on days of oxaliplatin therapy was determined by evaluating HCPCS codes on claims

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(Mg HCPCS code J3475; Ca HCPCS codes J0641, J0640, J0610). Our main outcome of interest was the proportion of CaMg on same-day oxaliplatin therapy.

### Control Group

To ensure that the observed variability in rates of CaMg use was not an artifact of the datasets, data from 2 other clinical situations were obtained, based on drug-specific billing codes, and analyzed. First, we identified the concurrent use of Mg in patients receiving cisplatin (HCPCS codes J9060, J9062) and, second, we identified the concurrent use of Mg in patients receiving cetuximab (HCPCS code J9055). We assessed trends in the use of CaMg with oxaliplatin over the same period using the OLDW data.

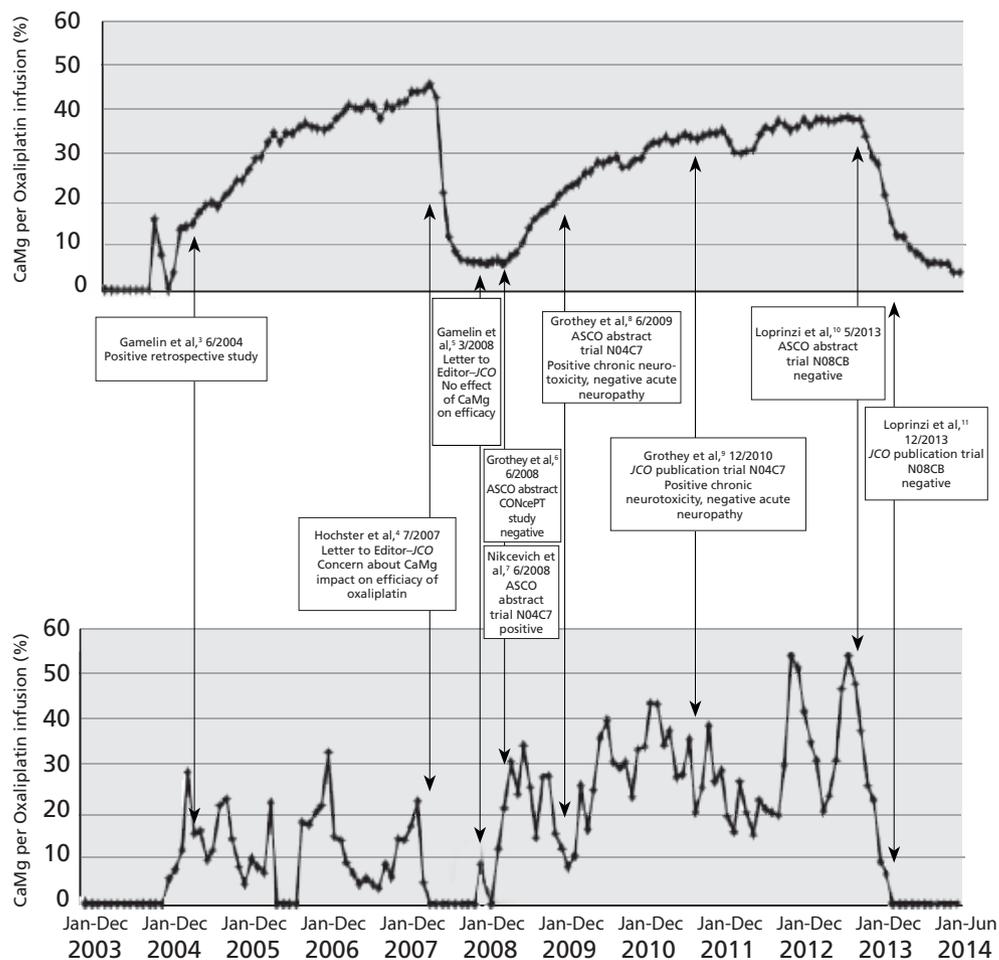
## Results

### Mayo Clinic Data

From January 1, 2003, to June 30, 2014, a total of 9142 oxaliplatin infusions were given to 1457 unique patients. Among the patients receiving the 9142 oxaliplatin infusions, 1771 also had same-day CaMg infusions. The use of CaMg varied over time, which temporally appeared to be responsive to the positive and negative trial results illustrated in Figure 1.

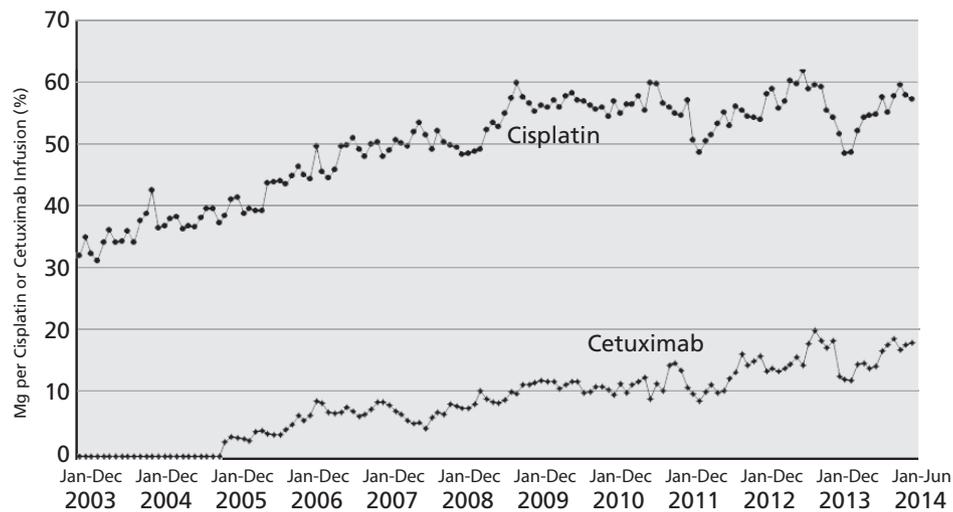
### Optum Labs Data

To better understand whether the changes in practice observed at Mayo Clinic occurred broadly, we explored the national rates of CaMg use in OLDW. From January 1, 2003, to June 30, 2014, 306,937 oxaliplatin infusions were given to 41,165 unique patients. Figure 1 illustrates the frequency of CaMg use with concurrent oxaliplatin over time. Monthly



**Figure 1** Use of calcium and magnesium (CaMg) over time, including Optum data (top) and Mayo data (bottom), depicted with reference to the discussed publications/presentations. Online publication dates are used when available.

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**Figure 2** Concurrent use of magnesium in patients receiving cisplatin versus cetuximab.

administration rates fluctuated greatly over the decade of interest, ranging from 0% to 44%, with rates increasing gradually to 44% between 2004 and 2007, after the positive ASCO presentation by Gamelin et al<sup>2</sup> and the subsequent publication.<sup>3</sup> A substantial decrease then occurred after the Letter to the Editor in *JCO* that proposed a risk of reduced efficacy of oxaliplatin with CaMg, published online in July 2007.<sup>4</sup> The use of CaMg then again appeared to increase after a subsequent Letter to the Editor reported that there was no impact on oxaliplatin efficacy,<sup>5</sup> and 2 abstracts presented at ASCO Annual Meetings reported benefit.<sup>7,8</sup> Most recently, rates dramatically decreased around the time when the negative study results were presented at the 2013 ASCO Annual Meeting.<sup>10</sup>

### Control Group Sample Data

Figure 2 illustrates the concurrent use of Mg in patients receiving cisplatin and, also, the use of Mg in patients receiving cetuximab. The former shows a mild increase in use over time, whereas the latter shows a steady continuous increase in the same-day Mg infusions given with cetuximab. Neither group showed peaks or valleys similar to those seen in CaMg use with oxaliplatin.

### Discussion

These data reveal the rapid adoption of evolving evidence over the past decade regarding the use of intravenous CaMg to prevent oxaliplatin-associated neuropathy. Although the relevant scientific evi-

dence, until recently, was based on small, sometimes retrospective, studies, clinicians clearly changed practice quickly in response to the presentations at the ASCO and publications (including Letters to the Editor) in *JCO*.<sup>2-9</sup> This occurred both in a single clinical practice and more broadly across the United States.

In some cases, early adopters of a new treatment are congratulated for their wise foresight because they save lives and/or improve the quality of life for many patients even before final data are reported. For example, clinicians who started offering trastuzumab to women with early-stage breast cancer based on early, less-than-definitive, data were later applauded for this prescient decision.<sup>2-9</sup> Additionally, physicians who opted to continue bevacizumab after colon cancer disease progression based on preliminary evidence<sup>16</sup> were subsequently proven to have made a wise choice.<sup>17</sup>

In other cases, early adopters of a new treatment may cause net harm. For example, high-dose chemotherapy with stem cell transplant rescue for breast cancer appeared to be promising initially, and was offered to many patients nationally before randomized clinical trials failed to reveal any significant benefit for this approach.<sup>18</sup> Many patients experienced substantial toxicity (including treatment-related mortality) from these transplants,<sup>18</sup> which were performed without definitive proof of efficacy.

In the case of intravenous CaMg, no apparent harm came to the patients. However, there were costs

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to patients and oncology practices. Although CaMg is a relatively inexpensive intervention, it did result in about an hour of extra time in the chemotherapy unit for patients, not to mention an increased financial cost, with nursing administration and pharmacy expenses. It was reassuring to note the rapid cessation of CaMg therapy after the final definitive data became available.

A limitation to the approach used in this study is that it was retrospective in nature, as opposed to being prospectively obtained.

Rapid changes in practice based on preliminary data may be more common when the data pertain to the prevention of a major clinical problem for which few treatments are available. A large unmet need (such as for ways to protect patients against oxaliplatin-related neurotoxicity) may be associated with more speedy practice changes than might be associated with a less-substantial clinical problem.

With regard to the comparison of Mg infusion rates with cisplatin versus cetuximab (illustrated in Figure 2), the slow 26.3% increase of Mg infusions with cisplatin represents a gradual change over time. The more marked increase in Mg use with cetuximab likely occurred in response to reports of hypomagnesemia with cetuximab. In 2005, a case series was published describing 154 patients with colorectal cancer treated with cetuximab. Thirty-four patients (22%) had at least one low serum Mg measurement during cetuximab treatment, with 6 patients having grade 3 (<0.9 mg/dL) and 2 having grade 4 (<0.7 mg/dL) hypomagnesemia.<sup>19</sup> Based on this series, the recommendation was made to check Mg levels in symptomatic patients (eg, fatigue or hypocalcemia) receiving cetuximab. Since that publication, other studies have affirmed the relationship between cetuximab treatment and hypomagnesemia.<sup>20,21</sup>

## Conclusions

This study demonstrates the quick penetration and dissemination of pertinent medical information, which is further facilitated by the easy access to information in the Internet age. In addition, the CaMg story highlights the need to conduct well-designed, adequately powered trials to validate initial findings, even if they have already been widely embraced in clinical practice. Increased funding for such trials seems warranted.

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