

Epidermal growth factor receptor inhibitor–induced hypomagnesemia: a survey of practice patterns among Canadian gastrointestinal medical oncologists

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ABSTRACT

Background The optimal management of hypomagnesemia (hMg) induced by epidermal growth factor receptor inhibitors (EGFRIs) for advanced colorectal cancer is unclear. We surveyed gastrointestinal medical oncologists in Canada to determine practice patterns for the management of EGFRi-induced hMg.

Methods Based on distribution lists from the Eastern Canadian Colorectal Cancer Consensus Conference and the Western Canadian Gastrointestinal Cancer Consensus Conference, medical oncologists were invited to participate in an online questionnaire between November 2013 and February 2014.

Results From the 104 eligible physicians, 40 responses were obtained (38.5%). Panitumumab was more commonly prescribed than cetuximab by 70% of respondents, with 25% prescribing cetuximab and panitumumab equally. Most respondents obtain a serum magnesium level before initiating a patient on an EGFRi (92.5%) and before every treatment (90%). Most use a reactive strategy for magnesium supplementation (90%) and, when using supplementation, favour intravenous (iv) alone (40%) or iv and oral (45%) dosing. Magnesium sulfate was used for iv replacement, and the most common oral strategies were magnesium oxide (36.4%) and magnesium rougier (18.2%). Under the reactive strategy, intervention occurred at hMg grade 1 (70.3%) or grade 2 (27%). Of the survey respondents, 45% felt that 1–5 of their patients have ever developed symptoms attributable to hMg, and 35% have had to interrupt EGFRi therapy because of this toxicity, most commonly at grade 3 (30%) or grade 4 (45%) hMg. The most important question about EGFRi-induced hMg was its relevance to clinical outcomes (45%) and its symptoms (37.5%).

Conclusions In Canada, various strategies are used in the management of EGFRi-induced hMg, including prophylactic and reactive approaches that incorporate iv, oral, or a combination of iv and oral supplementation. Clinicians are concerned about the effect of hMg on clinical outcomes and about the symptoms that patients experience as a result of this toxicity.

Key Words Epidermal growth factor receptor inhibitors, hypomagnesemia, management, surveys

Curr Oncol. 2019 April;26(2):e162-e166

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INTRODUCTION

Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) have been evaluated in clinical trials for advanced colorectal cancer and, as monotherapy and in combination with chemotherapy, have been associated with significant improvements in progression-free survival and

overall survival^{1–5}. Two EGFR inhibitors (EGFRIs), cetuximab and panitumumab, are Health Canada–approved for use in advanced colorectal cancer. Common side effects of those drugs include acneiform rash, hypersensitivity reactions, diarrhea, and hypomagnesemia (hMg). Although hMg was not initially recognized as a side effect of EGFRIs, more recent studies have defined its incidence and severity⁶.

Magnesium is the second most common intracellular cation (after potassium) in humans and is located mainly intracellularly in bone, muscle, and soft tissue⁷. It is a cofactor in many enzymatic reactions including ATP generation, which is important for glucose metabolism; synthesis of fat, proteins, and nucleic acids; muscle contraction and relaxation; and normal neurologic function⁸. Most ingested magnesium is eliminated in the feces; the remainder (approximately 30%) is filtered by the kidney, with the largest proportion being reabsorbed and stored in bone, muscle, and soft tissue⁷. Notably, to maintain magnesium homeostasis, renal excretion and intestinal absorption of magnesium vary depending on plasma level⁷. Recognized symptoms of hMg include tetany, weakness (including respiratory muscles), mental status changes, and cardiac arrhythmias⁹.

Mechanistically, Groenestege *et al.*¹⁰ elucidated the cause of EGFRI-induced hMg. In a genetic analysis of two sisters with isolated recessive renal hMg, mutations in the *EGF* gene were discovered. Through EGF, EGF stimulates a magnesium channel called TRPM6 (the transient receptor potential cation channel, subfamily, member 6) which is located in the distal convoluted tubule. In the tubule, EGFRI cause decreased stimulation of the TRPM6 magnesium channel, the result being magnesium wasting in the urine in the setting of low serum magnesium levels. The TRPM6 channels are also present in the gut and are thought to be involved in active magnesium transport, and EGFRI might therefore inhibit magnesium absorption in the gut as well¹¹.

Clinically, hMg attributable to monoclonal antibodies against EGFR is well described. Tejpar *et al.*¹² studied serum magnesium in patients ($n = 98$) receiving EGFRI in phase I–III clinical trials and found that 97% experienced decreased levels over time. More recently, the ASPCC trial showed that the rate of grade 3 or 4 hMg was higher with the use of panitumumab than of cetuximab (7% and 3% respectively)¹³. In addition, all-grade hMg also appeared to be more frequent with panitumumab than with cetuximab (27% vs. 17.7%).

Currently, the optimal form of magnesium replacement and the level at which to intervene remain uncertain. Published guidelines are opinion-based because no prospective studies have adequately evaluated those questions^{9,14,15}. As a result, we surveyed gastrointestinal medical oncologists in Canada to determine practice patterns for the management of EGFRI-induced hMg.

METHODS

Questionnaire

A questionnaire was developed to assess the mechanistic understanding of hMg, practices for monitoring magnesium levels, methods of magnesium replacement, observed adverse events of hMg, and the perceived clinical importance of hMg on the part of medical oncologists (Table 1). The questionnaire was created using SurveyMonkey (<http://www.surveymonkey.com>).

After Research Ethics Board approval was obtained, the questionnaire was disseminated online by e-mail to medical oncologists nationwide using distribution lists

from the Eastern Canadian Colorectal Cancer Consensus Conference and the Western Canadian Gastrointestinal Cancer Consensus Conference. Redeemable Starbucks coupons were given as incentive to participate. Data were collected from November 2013 to February 2014.

Analysis

Data were analyzed in a descriptive fashion. The proportion of respondents choosing each answer was calculated.

RESULTS

Participants

From 104 eligible participants identified, 40 responses obtained (38.5%). Of those respondents, 70% indicated that they prescribed panitumumab more commonly than cetuximab for advanced colorectal cancer, with 25% prescribing cetuximab and panitumumab equally, and only 5% favouring cetuximab. In the past year, 35% indicated that they had treated 1–5 patients with EGFRI; 37.5%, 6–10 patients; 25%, 11–20 patients; and 2.5%, more than 20 patients.

Mechanistic Understanding

Most respondents (70%) indicated that the mechanism of toxicity was inhibition of a magnesium channel in the kidney alone. Only 25% recognized that inhibition occurs at both the kidney and the intestine.

Monitoring

Almost all respondents (92.5%) indicated that they routinely obtain a baseline serum magnesium level before initiation of an EGFRI and before every EGFRI treatment (90%). Only 1 respondent (2.5%) reported routinely obtaining an electrocardiogram to assess the baseline QTc interval before initiating EGFRI therapy.

Management of hMg

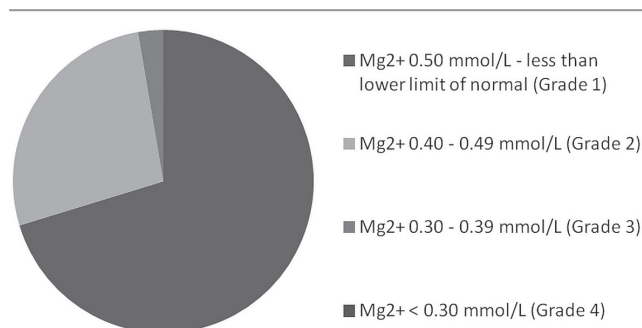
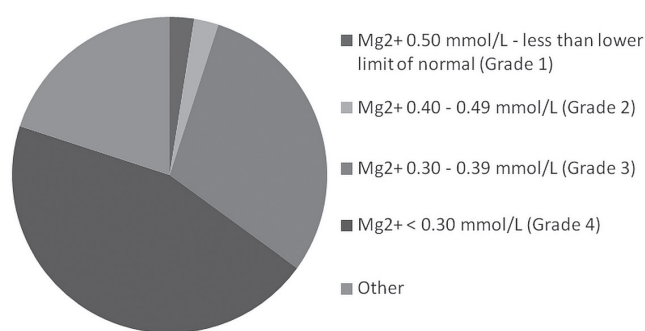
Most respondents indicated using a reactive strategy for magnesium supplementation (90%). Of those using such a strategy, 40% said that they supplemented with an intravenous (iv) replacement alone; 10%, with an oral replacement alone; and 45%, with a combination of iv and oral replacement. The remaining 5% said that they did not supplement at all. Magnesium sulfate was always used in iv replacement. The most common oral replacement strategies were magnesium oxide (36.4%) and magnesium rougier (18.2%). When using a reactive strategy, clinicians most commonly intervened (Figure 1) when hMg reached grade 1 (70.3%) or grade 2 (27%).

Some respondents (15%) indicated use of a prophylactic replacement strategy. Of those respondents, 45% used iv replacement only, 45% used iv and oral replacement, and 10% used oral replacement only (Figure 2).

Of our survey respondents, 35% indicated having interrupted therapy in response to hMg. Of those who chose to interrupt therapy, the decision to interrupt was usually at grade 3 (30%) or grade 4 (45%) hMg (Figure 2). On a 1–5 Likert scale¹⁶ measuring satisfaction with their magnesium supplementation strategy, respondents scored an average of 3.18.

TABLE 1 Questions included in the online survey

1.	Which of the two agents (panitumumab and cetuximab) have you most commonly prescribed in the treatment of advanced colorectal cancer?
2.	Approximately how many patients have you treated with either epidermal growth factor (EGFR) inhibitor in the past year?
3.	What is your understanding of the mechanism of EGFR inhibitor-mediated hypomagnesemia?
4.	Do you routinely obtain a baseline serum magnesium level prior to initiating therapy?
5.	How frequently do you check serum magnesium levels during therapy?
6.	What is your general approach to managing serum magnesium levels during therapy?
7.	If you replace reactively, what form of magnesium do you use?
8.	If you answered intravenous, oral, or both in question 7, please specify formulations and doses.
9.	If a reactive strategy is used, at what level of hypomagnesemia do you initiate replacement?
10.	If you supplement prophylactically, what form of magnesium do you use?
11.	If you answered intravenous, oral, or both in question 10, please specify formulations and doses.
12.	Do you routinely obtain an electrocardiogram for the purpose of measuring a baseline QTc interval prior to initiating therapy?
13.	Have any of your patients treated with an EGFR inhibitor experienced a serious arrhythmia in the setting of hypomagnesemia?
14.	In your patients who have been treated with EGFR inhibitors, how many do you feel have developed symptoms due to hypomagnesemia?
15.	Have you ever had to interrupt EGFR inhibitor therapy because of hypomagnesemia?
16.	At what level of hypomagnesemia do you interrupt EGFR inhibitor therapy?
17.	Based on your observations, are you concerned about a possible association of EGFR inhibitor-induced hypomagnesemia and outcomes (that is, better or worse survival)?
18.	At present, how satisfied are you with your current magnesium supplementation strategy?
19.	In your opinion, what is the most important question regarding EGFR inhibitor-induced hypomagnesemia that should be considered?
20.	Do you think a Canadian consensus guideline for the management of EGFR inhibitor-induced hypomagnesemia would be useful?

**FIGURE 1** Level of hypomagnesemia at which replacement was initiated in patients undergoing treatment with epidermal growth factor inhibitors (EGFRIs).**FIGURE 2** Level of hypomagnesemia at which therapy with epidermal growth factor inhibitors (EGFRIs) was interrupted.

Adverse Events

No respondents reported the development of a serious arrhythmia because of hMg induced by an EGFRi. Of the survey respondents, 45% reported that they recalled 1–5 patients who had developed symptoms attributable to hMg, and 35% had had to interrupt EGFRi therapy as a result of symptoms.

Importance in Clinical Practice

Of the survey respondents, 90% were not concerned about a possible association of EGFRi-induced hMg and treatment outcomes (positive or negative). The respondents felt that the most important questions to be addressed about EGFRi-induced hMg (Figure 3) were relevance to clinical outcomes (45%) and symptom profile (37.5%). Respondents were highly interested (90%) in a Canadian consensus guideline addressing this issue.

DISCUSSION

Currently, no guidelines addressing the management of hMg in patients taking EGFRis have been developed. We therefore conducted a survey to determine how, clinically, medical oncologists handle hMg in the context of EGFRi treatment.

Current common practice is to obtain baseline serum magnesium before initiating treatment with an EGFRi and before each cycle of treatment. Our survey demonstrates that the current approach to managing hMg is generally reactive, with most physicians opting to use the iv or a combination of the iv and the oral route for administration. Furthermore, treatment regimens are most commonly

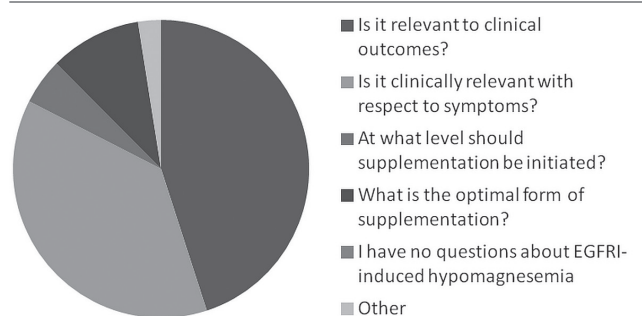


FIGURE 3 Opinions of medical oncologists about the most important question to consider with respect to hypomagnesemia induced by epidermal growth factor inhibitors (EGFRIs).

interrupted for symptomatic cases of hMg, which tend to be more prevalent at higher grades of hMg.

Given the various physiologic roles of magnesium in the body and the potential consequences arising from its depletion, detecting and rectifying discrepancies is important. However, many questions remain. Firstly, the optimal method of measuring serum magnesium is still a matter of debate. Currently, most oncologists use serum magnesium before initiation of an EGFRI and before every EGFRI treatment to infer the total body level; however, those two measures do not necessarily correlate. In fact, only 1% of total body magnesium is found in extracellular fluid and only 0.3% is found in serum. Despite being a poor predictor of total body magnesium, serum magnesium remains the most practical and inexpensive means of assessing acute changes⁷.

The use of iv magnesium to restore physiologic levels also has issues. Administering magnesium in this manner results in an abrupt, yet transient, increase in plasma concentration. However, uptake of magnesium at the cellular level is slow, and sustained correction is therefore needed for adequate repletion. Theoretically, proper iv repletion would take days (4–5 g over 12–24 hours), which is not feasible in an outpatient setting. Furthermore, in the presence of a sudden increase in serum magnesium, a calcium sensing receptor at the loop of Henle partially inhibits resorption, which could further hinder restoration. Also, repeatedly obtaining peripheral access can be impractical, and in some cases, a central venous line might be required, which is not without risk^{17,18}. High-dose oral supplementation might overcome many of those challenges. In states of low intraluminal magnesium, intestinal absorption is predominantly active and therefore a saturable process. Active transport of magnesium in the gut is thought to be mediated in part by the TRPM6 channel, although the mechanistic details are unclear¹¹. The use of EGFRI leads to less stimulation of that channel. In states of high intraluminal magnesium, passive transport is predominant. That method of absorption would be logical to optimize in the context of EGFRI use, given that the TRPM6 channel is less available. Using high-dose oral supplementation might therefore be a more effective and practical way of providing a sustained increase in available magnesium on an outpatient basis. However, it should be noted that oral magnesium supplementation is known to

cause diarrhea^{19,20}. Interestingly, our study showed that iv magnesium repletion is used by most medical oncologists either with or without oral supplementation.

The type of supplement used is another variable that should be optimized. A study looking at 16 healthy volunteers found that absorption of magnesium oxide is lower (4%) relative to other compounds, including magnesium chloride, magnesium L-lactate, and magnesium aspartate²¹. Another study in 46 healthy volunteers also showed that magnesium oxide is suboptimally absorbed, and that magnesium citrate provides the highest plasma levels both acutely and at 60 days after administration²². Despite the heterogeneity of magnesium absorption studies, a review by Rylander²³ concluded, based on current evidence, that magnesium citrate is the most appropriate formulation for supplementation and other therapeutic purposes. In the present study, 100% of the respondents who specified the form of iv supplementation they used, said that they used magnesium sulfate. Of the respondents who specified the form of oral supplementation they used, 7 (50%) used magnesium oxide, 5 (36%) used magnesium glucoheptonate, 1 (7%) used magnesium sulfate, and 1 used magnesium gluconate (7%).

Aside from the method of repletion, another point of contention is determining whether hMg is symptomatic and warrants treatment in cancer patients. Magnesium deficiency produces symptoms that can overlap with the symptoms caused by advancing cancer and chemotherapy. In fact, symptoms of hMg have not been prospectively documented using validated questionnaires. However, severe magnesium deficiency (grade 3 or 4) in patients with cancer has been associated with general symptoms including fatigue, cramping, and somnolence¹². Alteration in mentation and tachycardia have also been reported^{3,12}. Because of the inability to attribute a cause to certain symptoms, the point at which hMg should be treated (if at all) is unclear. Although no deaths attributable to hMg have been reported in patients with cancer treated with EGFRI, cases of EGFRI dose reduction and treatment discontinuation have been documented²⁴. A recent systematic review showed that there are currently no high-quality studies of hMg treatment in the context of EGFRI use¹⁵. Recently, our group completed a feasibility study assessing an integrated consent model to compare oral supplementation using magnesium oxide with supplementation using magnesium citrate in patients with hMg from EGFRI and platin agents (NCT02690012 at <http://ClinicalTrials.gov/>).

Another factor that remains unclear is the effect of hMg in the context of carcinogenesis. In healthy cells, magnesium deficiency induces growth arrest by altering the expression of cell-cycle regulatory proteins, DNA duplication, and mitosis²⁵. Generally, magnesium levels correlate with the growth rate of cells. However, cancer cells are able to grow independently, and their growth rate does not correlate with the magnesium concentration *in vitro*²⁶. Interestingly, a magnesium-deficient diet in mice resulted in decreased growth of the primary tumour, but increased metastatic potential²⁷. An antitumour effect of hMg in humans remains to be elucidated, and we have no conclusive evidence that carcinogenesis is affected.

The present study is limited by its sample size and moderately low response rate of 38.5%. It is possible that

individual institutions might have blocked e-mail messages arriving from SurveyMonkey, and therefore some individuals might not have received the survey. Respondents were not asked to undertake a formal chart review, and thus the estimations provided are subject to recall bias. The sample population might also not be completely representative of all prescribers of EGFRI, given that the e-mail addresses came from individuals who were on conference e-mail lists.

CONCLUSIONS

Hypomagnesemia is a common side effect of treatment with EGFRI. However, evidence about the consequences of this toxicity and its symptom profile is conflicting. Further, no evidence-based guidelines have currently been developed for the management of hMg in the context of cancer treatments using EGFRI. In the present study, we have summarized the treatment practices of Canadian medical oncologists, but have also highlighted the need for more research to clearly delineate the clinical repercussions of hMg, and how and when intervention should be initiated.

ACKNOWLEDGMENTS

This research was funded by an unrestricted grant from Amgen.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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