Original Study

Management of Epidermal Growth Factor Receptor Inhibitor-Induced Hypomagnesemia: A Systematic Review

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Abstract

Hypomagnesemia is a common side effect of treatment with epidermal growth factor receptor inhibitor. Guidelines recommend intravenous magnesium replacement to treat this toxicity; however, our systematic review has found little evidence to support this approach. Prospective studies are needed to define the best strategy to manage epidermal growth factor receptor inhibitor-induced hypomagnesemia.

Background: Despite occurring in 30% of patients, there are no evidence-based guidelines on the management of epidermal growth factor receptor inhibitor (EGFRI)-induced hypomagnesemia. Based on expert opinion, severe hypomagnesemia should be treated by intravenous magnesium replacement. A systematic review of published data of intervention on EGFRI-induced hypomagnesemia was performed. **Methods:** Articles from 1960 to March 2015 were identified from Medline, Embase, Cochrane Central Register of Controlled Trials, and PubMed using a peer-reviewed systematic search strategy. Eligible studies included randomized controlled trials or observational studies that evaluated management of hypomagnesemia in adult patients treated with EGFRIs. Risk factors for severe hypomagnesemia were also assessed. The quality of included studies was rated using Jadad scores. **Results:** A total of 1327 references were identified, and 6 studies, involving 486 patients, met inclusion criteria for analysis. There were no randomized controlled trials, and all included studies were of poor quality. From the studies included in this review, severity of EGFRI-induced hypomagnesemia was associated with length of EGFRI treatment, concomitant platinum chemotherapy, increasing age, and baseline magnesium concentration. In most patients with grade 3 or 4 hypomagnesemia, high-dose intravenous magnesium replacement did not achieve sustainable magnesium repletion beyond 72 hours. Oral magnesium supplementation was not effective or tolerable. Severe hypomagnesemia has been associated with tachycardia and mental alteration. After discontinuation of EGFRI therapy, hypomagnesemia generally resolves within weeks to months. **Conclusions:** There is an absence of high-quality evidence for the management of EGFRI-induced hypomagnesemia. As hypomagnesemia is often refractory to frequent intravenous or oral replacement, there is a need for prospective trials of new interventions for this common toxicity.

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Introduction

Epidermal growth factor receptor (EGFR) overexpression has been identified in many common tumor sites such as colorectal, lung, pancreas, and head and neck.[1] Inactivation of the EGFR pathway is now part of the standard of care for a variety of malignancies and can involve 2 mechanisms of action. Monoclonal antibodies (mAbs) such as cetuximab and panitumumab bind to the extracellular domain of EGFR to interrupt the downstream signaling cascade, which leads to tumor apoptosis and stimulated immunologic response.[2] Oral tyrosine kinase inhibitors such as erlotinib and gefitinib inactivate the intracellular domain of EGFR.[1]

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EGFR inhibitor (EGFRI)-induced hypomagnesemia was first reported in 2005,[3] and the mechanism has been linked to insufficient TRMP6 channel activation caused by EGFR signaling inhibition.[4-6] Up to 97% of patients experience reductions in serum magnesium levels during therapy with EGFR-targeting antibodies.[7] Relative risk of developing grade 3 or 4 hypomagnesemia from cetuximab is 3.9%-27%[7-10] and 5.4% with panitumumab.[11]

Magnesium is essential for many critical physiologic functions involving the skeletal muscle, heart, blood vessels, and brain. Adequate replacement is important for patients who develop severe hypomagnesemia during treatment, as hypomagnesemia can lead to treatment deviations, or rarely, life-threatening complications such as ventricular arrhythmias that may lead to sudden death.[12-15] The optimal management of hypomagnesemia induced by EGFR-targeting antibodies is not well studied. Therapeutic options for magnesium repletion may include oral or intravenous supplementation, or a combination of the above. Aggressive intravenous magnesium replacement may pose a significant inconvenience for patients, as magnesium infusions require hours to administer. In some cases, repeated attempts for peripheral access can be poorly tolerated or impractical, and central venous access may be required for frequent infusions.[2,3] Oral magnesium supplementation is easier to administer, but its poor absorption from the gastrointestinal tract and associated diarrhea limit its use.[16]

To date, no evidence-based guidelines exist, and a systematic evaluation of the management of EGFRI-induced hypomagnesemia is lacking. Furthermore, the efficacy of oral compared with intravenous replacement is unclear. We hypothesized that there are few robust studies available to guide clinical decision-making; therefore, we undertook a systematic review of the current literature evaluating interventions on hypomagnesemia induced by EGFR inhibition. We also sought to evaluate potentially actionable risk factors for hypomagnesemia.

Methods

Articles from 1960 to March 2015 were identified from Medline, Embase, Cochrane Central Register of Controlled Trials, and PubMed using a peer-reviewed systematic search strategy (see Supplemental Table 1 in the online version). Conference abstracts and posters from the American Association of Cancer Research, the European Society for Medical Oncology, and the American Society for Clinical Oncology going back to 2009 were searched in Embase. Results were limited by English language.

A broad screening strategy was used to identify all relevant studies appropriate for full-text article review. To ensure the identification of all potential relevant articles, including any citations that might have been indexed inappropriately, we screened all articles involving systemic therapy and hypomagnesemia after consultation with a medical librarian (A.S.). Given the known association of platinum chemotherapy with hypomagnesemia, studies involving platinum chemotherapy were also screened. Inclusion criteria were randomized control trials (RCTs) or observational studies published as original studies that evaluated management of hypomagnesemia in adult patients treated with EGFRIs. No restrictions were given for disease site, disease status, prior/concurrent systemic chemotherapy, concomitant malabsorption disorders, or other therapies that may potentiate hypomagnesemia, including proton pump inhibitors and loop diuretics. Review articles, letters, case reports, conference abstracts not published as full articles, animal, and in vitro studies were excluded.

One reviewer (D.J.) screened all titles and abstracts. Another reviewer (M.V.) screened abstracts 1-450 while a third reviewer (K.D.) screened abstracts 451-916. Disagreements for inclusion of abstracts for full-text review were resolved by consensus of the 3 reviewers. The full text of these articles were retrieved and evaluated for inclusion by 3 reviewers (D.J., M.V., and K.D.). The reference lists from the articles selected for full-text review were reviewed and screened according to the same criteria.

Articles retained after full-text review were analyzed, and the following data were obtained: name of first author, year of publication, study design, country of origin, sample size, tumor sites included, EGFRI agent and duration, incidence of hypomagnesemia, intervention, and efficacy.

Quality assessment using the Jadad scores for included studies is summarized in Table 1. As previously described, studies are scored from 0 to 5 according to the presence of 3 key methodological features of randomization, blinding, and accountability of all patients to assess methodological quality.[21]

Results

Identification of Included Studies

A total of 1327 references were retrieved, of which 916 were screened (Figure 1). Two reviewers (D.J. and M.V.) initially disagreed on 3 abstracts screened for full-text review, while 2 (D.J. and K.D.) were in full agreement. Fifty-nine studies reported hypomagnesemia induced by EGFRIs and underwent full-text review. Ultimately, 6 were retained for this review involving EGFRI therapy, including a total of 486 patients with mostly advanced colorectal cancer (CRC) (n = 426) and squamous cell carcinoma of the head and neck (HNSCC; n = 46). There were 2 prospective studies, 4 retrospective studies, and no RCTs. There was complete agreement among the 3 reviewers regarding the final articles included for analysis. The main characteristics of included studies are illustrated in Table 1. Of 486 patients, 289 were treated with cetuximab and 197 with panitumumab. Cetuximab was used to treat both CRC and HNSCC, whereas patients received panitumumab only for CRC.

Incidence of Hypomagnesemia

Hypomagnesemia was characterized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 and 3.0 published by NCI. Definitions of grades of hypomagnesemia were consistent, except 1 study used a modified CTCAE version 3.0 criteria with a slightly different cutoff for grade 1 hypomagnesemia.[19] Out of 486 patients, hypomagnesemia occurred in 216 patients; in 35 patients, it was severe (grade 3 or 4). The incidence of hypomagnesemia in studies evaluating cetuximab is 35.4%-100%, which was severe in 1.7%-27.1% of patients. The overall incidence of hypomagnesemia secondary to panitumumab is 28.9%-85.7%.

Risk Factors for Hypomagnesemia

Treatment duration of EGFRI varied between 2 weeks and 1 year. The grade of hypomagnesemia was strongly associated with