

Review

Efficacy of Magnesium Supplementation in Cancer Patients Developing Hypomagnesemia Due to Anti-EGFR Antibody: A Systematic Review

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Abstract. *Background/Aim:* Hypomagnesemia is a common side effect of anti-epidermal growth factor receptor (EGFR) antibodies, which may lead to arrhythmia. However, there are no evidence-based guidelines for magnesium (Mg) supplementation in the management of hypomagnesemia in patients with anti-EGFR antibodies. Therefore, we performed a systematic review to address clinical questions regarding these cancer patients. *Materials and Methods:* Three electronic databases were searched for articles published until June 18, 2021. The main outcomes used were “anti-EGFR antibody” and “hypomagnesemia”. *Results:* After screening 78 references in PubMed, Cochrane Library, and ICHUSHI-web databases, three studies were included in the review. One study revealed the effectiveness of Mg supplementation in the management of hypomagnesemia in patients receiving cetuximab. However, no studies have investigated whether

correcting hypomagnesemia can lead to the suppression of arrhythmias as a clinical outcome. *Conclusion:* Weak evidence suggests that Mg supplementation, as a preventive measure when developing hypomagnesemia following the initiation of anti-EGFR antibody therapy, may prevent the worsening of hypomagnesemia, and subsequently prevent associated arrhythmia occurrence.

Recently, the effectiveness of monoclonal antibodies that specifically target the epidermal growth factor receptor (EGFR) has been reported in patients with cancer, as evidenced by several clinical trials. The anti-EGFR antibodies cetuximab and panitumumab, which are often used either alone or in combination with chemotherapy, have significantly improved clinical outcomes in RAS wild-type colorectal cancer (CRC), head and neck cancer, and squamous cell lung carcinoma (1-5). Among the several types of adverse events (AE) and side effects (SE), hypomagnesemia is a frequently observed SE with a relatively high prevalence of approximately 40%, which may cause tetany, weakness (including in respiratory muscles), alterations in mentation, and cardiac arrhythmias (6-10). However, to date, there is no established guideline for Mg supplementation in the management of hypomagnesemia caused by anti-EGFR antibodies.

Hence, this study aimed to systematically review Mg supplementation as a preventive measure against hypomagnesemia induced by anti-EGFR antibody treatment in patients with cancer as a clinical practice guideline for the management of kidney injury and other types of severe adverse effects during anticancer drug therapy (11, 12).

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Key Words: Cancer, anti-EGFR antibody, hypomagnesemia, review.

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Table I. Search strategy.

Study	Database and Topic
	1. PubMed (MEDLINE)
#1	"Mg Deficiency/chemically induced "(mh) OR hypomagnesemia* (tiab)
#2	"Antibodies, Monoclonal, Humanized"(mh) OR "ErbB Receptors/antagonists and inhibitors"(mh)
#3	epidermal growth factor receptor inhibitor*(tiab) OR EGFR inhibitor*(tiab) anti-EGFR*(tiab) OR cetuximab*(tiab) OR panitumumab*(tiab)
#4	#2 or #3
#5	"Mg"(mh) OR Mg*(tiab)
#6	#1 and #4 and #5
	2. Cochrane Library (The Cochrane Controlled Trials Register)
#1	(mh "Mg Deficiency"/CI)
#2	hypomagnesemia*: ti, ab, kw
#3	#1 or #2
#4	(mh "Antibodies, Monoclonal, Humanized") OR (mh "ErbB Receptors"/AI)
#5	((("epidermal growth factor receptor" OR EGFR) NEAR/2 inhibitor*) OR "anti EGFR" OR cetuximab* OR panitumumab*): ti, ab, kw
#6	#4 or #5
#7	(mh "Mg") OR Mg*: ti, ab, kw
#8	#3 and #6 and #7
#9	#3 and #6 and #7 in Trials
#10	Pubmed: an
#11	#9 not #10
	3. Ichushi-web (Japan medical abstracts society)
#1	Antibodies, Monoclonal, Humanized /TH
#2	("ErbB Receptors"/TH) and (SH=Antisubstance-inhibitor)
#3	EGFR inhibition/AL or EGFR antibody/AL or anti-EGFR/AL or Cetuximab/AL or Panitumumab/AL
#4	#1 or #2 or #3
#5	Hypomagnesemia/TH or Hypomagnesemia/AL
#6	(Mg /AL and (administration/AL or replenishment/AL or Replacement/AL)) or (Mg/TH or "Mg sulfate"/TH)
#7	#4 and #5 and #6

Materials and Methods

Search strategy. We first launched a committee for “A clinical practice guideline for the management of kidney injury during anticancer drug therapy” under the directions of the Japanese Society of Nephrology (JSN), Japan Society of Clinical Oncology (JSCO), Japanese Society of Medical Oncology (JSMO), and The Japanese Society of Nephrology and Pharmacotherapy (JSNP). The committee outlined the initial project scope, key principles, relevant patients/populations, intervention, comparison, and outcome (PICO) framework. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to combine the results of the systematic review with expert opinions to address the following clinical question: Is additional Mg supplementation recommended if a patient receiving anti-EGFR antibody develops hypomagnesemia? The committee with an expert librarian (T.S. mentioned in the acknowledgments) conducted a systematic literature search up to June 18, 2021, using PubMed (MEDLINE), Cochrane Library, and ICHUSI-Web databases by means of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The following search keywords were considered: “hypomagnesemia”, “epidermal growth factor receptor inhibitor”, and “magnesium”. Table I lists the search syntaxes.

Inclusion and exclusion criteria. The criteria for literature inclusion were as follows: participants who were adults over 18 years old, cancer patients eligible for treatment, which includes anti-EGFR antibody drugs, and patients without kidney dysfunction that needed special consideration. The analysis included only studies written in English or Japanese. The main outcomes of the present study were the rate of treatment continuation, cardiac events, electrocardiographic abnormalities, and hypomagnesemia.

Study selection. The process of determining eligibility for the selected articles involved two phases. During the initial phase of study selection, we assessed the eligibility of the studies by reviewing their titles and abstracts. During the second phase, we acquired and examined the full texts of all papers based on our inclusion and exclusion criteria. This systematic review comprised (P) participants receiving anti-EGFR antibody, which were categorized as follows: (I) intervention: supplementation of Mg for hypomagnesemia; (C) comparison: Mg supplementation unless symptoms or events occurred, regardless of serum Mg levels; and (O) outcomes: continuation of anti-EGFR antibody without interruption.

For the initial screening, two different reviewers (T.K. and T.F.) evaluated all titles and abstracts, and for the subsequent screening, they assessed the full texts, in accordance with the guidelines from the Minds Handbook for Clinical Practice Guideline Development 2020

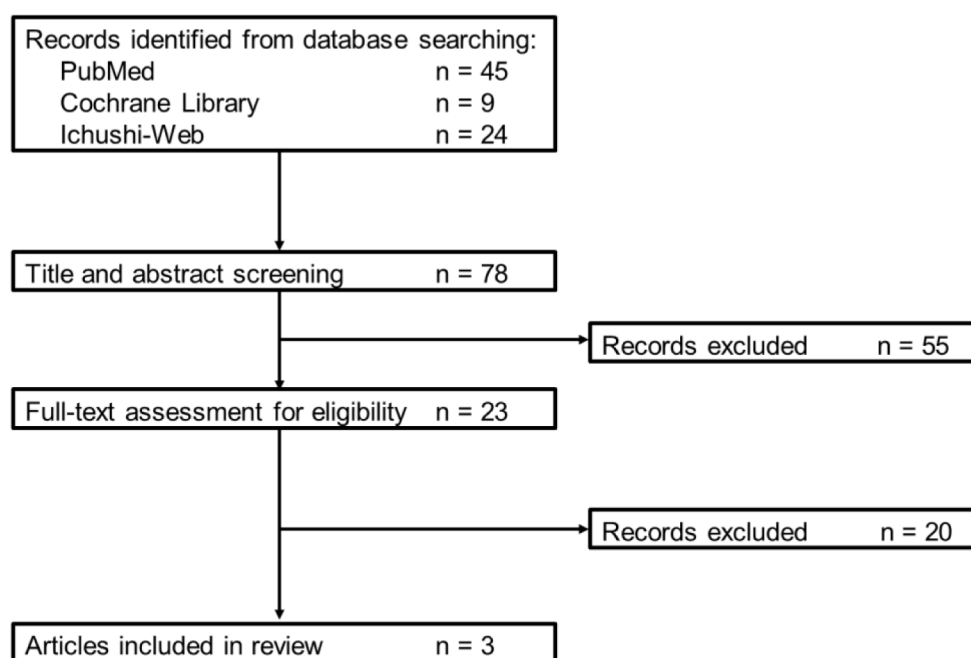


Figure 1. Diagram of study selection, systematic review, and meta-analysis according to Minds guideline handbook 2020 (13).

ver. 3.0 (13). Ethical approval was deemed unnecessary as this study did not involve confidential personal data or patient intervention.

Risk of bias assessment. Two reviewers assessed the risk of bias for each included study using the Minds Handbook for Clinical Practice Guideline Development. Studies were graded as having a “low risk”, “high risk”, or “moderate risk” of bias across the following seven specified domains: randomization, concealment, blinding (performance bias), blinding (detection bias), incomplete outcome data, selective outcome report, and other biases. For analyses involving five or more studies, if the primary outcome exhibited low or moderate heterogeneity, funnel plots were created to investigate potential biases such as publication, selection, or reporting biases.

Rating the quality of evidence. Two reviewers independently rated the quality of the evidence according to the GRADE approach (14). We used the Cochrane risk of bias tool to assess bias risk (15). The two reviewers assessed the individual studies extracted and generated an “evaluation sheet” for each critical and important outcome. This evaluation considered the study design limitations, integrated bias risk, contributing factors, relevance to the PICO, and the number of patients or risk events. Using the evaluation sheets for all outcomes, the reviewers then compiled the “Body of Evidence” for the clinical question. This assessment factored in study design limitations, bias risk, inconsistency, relevance, precision, and other considerations, following the grading methods proposed by the Minds Tokyo GRADE center, categorized as A (strong), B (moderate), C (weak), and D (very weak). The reviewers compiled a qualitative systematic review and condensed the systematic review reports for presentation to the clinical guideline committee. A recommendation was made in consideration of the balance of the relative benefits and harms of anti-angiogenic agents,

the quality of the evidence, and patient preferences using the GRADE approach. The guideline committee voted on the recommendations and their strengths related to this clinical question. Consent was secured from 75% of the participants. If 75% agreement was not obtained in the first vote, voting members engaged in further discussion before conducting a revote. A written explanation was provided for the developed recommendation, elucidating the decision made by the guideline member overseeing this clinical question.

Conflicts of interest and selection of systematic review members. No specific industry, including the systematic review committee, participated in this consensus meeting. Members of the systematic review committee were invited to join the chair and Clinical Practice Guidelines Development Committee.

Results

Study characteristics. Of the 78 references that were extracted from the PubMed (n=45), ICHUSHI (n=24), and Central (n=9) databases in the first screening, 55 were removed based on the titles and abstracts. We analyzed 23 references (all records from PubMed) that were identified for potential inclusion and full-text reviews, and three studies were included in the qualitative analysis (Figure 1). Two studies were excluded for the following reasons: a review paper (n=1) (10) and inaccurate timing of Mg supplementation as determined by the attending physician (n=1) (16). Another eligible study was identified as a qualitative study (17). Cardiac events and electrocardiographic abnormalities were

Table II. Grading of Recommendations Assessment, Development, and Evaluation table summarizing the quality of the evidence for each outcome.

Outcomes	Continue treatment	Grade 3 or grade 4 hypomagnesemia
No. of studies	1	1
Study design	Case series	Case series
Risk of bias	Very serious	Very serious
Inconsistency	Serious	Serious
Imprecision	Serious	Serious
Indirectness	Very serious	Not serious
Others	Not serious	Not serious
Rate of outcome (%)	100	0
Quality of evidence ^a	D	D
Significance of outcome ^b	7	5

^aA, strong; B, moderate; C, low; D, very low. ^bSignificance of outcome was determined by guideline committee when setting up PICO by a 1-10 point evaluation (10: most important).

not considered in this study. Therefore, we analyzed the remaining two outcomes: the rate of treatment continuation and hypomagnesemia. The quality of evidence for each outcome is presented in Table II.

Preventing persistent hypomagnesemia. Demizu *et al.* performed a prospective interventional trial that initiated oral Mg oxide treatment at the beginning of cetuximab treatment, according to an in-hospital manual (17). Additionally, in patients who experience hypomagnesemia and reach grade 1 severity (< LLN-1.2 mg/dl; < LLN-0.5 mmol/l) according to Common Terminology Criteria for Adverse Events (CTCAE), they suggest starting intravenous (IV) infusion of Mg sulfate promptly. Only four out of five patients developed grade 1 hypomagnesemia, whereas hypomagnesemia occurred in nine of ten patients after cetuximab treatment before the implementation of the in-hospital manual, suggesting that preventing Mg supplementation might contribute to better management of hypomagnesemia in patients receiving cetuximab treatment.

Preventing the incidence of cardiac events and electrocardiogram abnormality. No studies have investigated whether supplementation for hypomagnesemia can lead to the suppression of arrhythmias as a clinical outcome. Further research is necessary to establish the potential causal links or benefits.

Discussion

Magnesium plays a crucial role in numerous vital physiological processes, acting as an essential cofactor in many enzymatic reactions in all tissue types including the skeletal muscle, heart, blood vessels, and brain. It is crucial to ensure proper supplementation for patients experiencing severe hypomagnesemia during treatment to prevent life-

threatening complications, such as ventricular arrhythmias, which could lead to sudden death. Anti-EGFR antibodies, including cetuximab and panitumumab, are monoclonal antibodies designed to target EGFR and are established treatments for unresectable advanced or recurrent CRC, head and neck cancers, and lung cancers (18-20). These antibodies are commonly administered either as monotherapy or in combination with chemotherapies, such as irinotecan, FOLFOX, or FOLFIRI (21, 22). However, a notable SE associated with anti-EGFR treatment is hypomagnesemia, which is thought to be linked to the inhibition of Mg reabsorption through the suppression of the transient receptor potential melastatin-6 in the distal renal tubules (7, 23), which serves as an ion channel facilitating the transport of Mg into cells and plays a role in Mg reabsorption.

Although Mg supplementation is generally initiated when the patient's serum Mg concentration drops to 1 mg/dl, the optimal approach for preventing hypomagnesemia during anti-EGFR treatment remains unclear. Therefore, in this systematic review, we aimed to determine whether Mg supplementation in cancer patients improves hypomagnesemia during treatment, which may lead to arrhythmia.

We found an interventional study that initiated intravenous Mg infusion for the development of grade 1 hypomagnesemia, potentially aiding in the prevention of the exacerbation of hypomagnesemia (17). However, there have been no reports regarding the continuation of anti-EGFR treatments following the onset of hypomagnesemia, including any interruptions or delays in treatment. Furthermore, no studies have examined whether correcting hypomagnesemia can suppress the development of arrhythmias as a clinical outcome. Taken together, no clear SEs from Mg supplementation have been reported, and the lack of large-scale studies necessitates the accumulation of further cases to identify arrhythmias that can be avoided by intervention.

Study limitations. First, there were no randomized studies included in this review, and further prospective investigations are required to validate the efficacy of Mg supplementation in preventing critical SEs. Second, we did not assess the serum calcium levels, which could pose a limitation because the coexistence of hypomagnesemia and hypocalcemia is a recognized risk factor for severe hypomagnesemia in cancer chemotherapy and pharmacology.

Conclusion

Weak evidence suggests that Mg supplementation during the development of hypomagnesemia after starting anti-EGFR antibody therapy may prevent the worsening of hypomagnesemia. After the initiation of EGFR inhibitors, hypomagnesemia should be monitored appropriately, and proper Mg supplementation should be considered to enable continuation of treatment.

Conflicts of Interest

The Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

TK systematically reviewed related literature and drafted the manuscript. SK, TK, YF, and YY systematically reviewed related literature. YA participated in the entire coordinating of this systematic review. All Authors approved the final version of the manuscript for submission and agreed to be accountable for the contents.

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