EXPERT OPINION

Risk of anti-EGFR monoclonal antibody-related hypomagnesemia: systematic review and pooled analysis of randomized studies

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Introduction: The typical class side effect of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (panitumumab and cetuximab) is a cutaneous maculopapular rash, although hypomagnesemia is also described to be a frequent adverse event. The purpose of our meta-analysis is to evaluate the frequency and the relative risk of hypomagnesemia in patients treated with cetuximab or panitumumab in randomized trials.

Area covered: Eligible studies included prospective randomized Phase III controlled trials in which cetuximab or panitumumab were compared with standard anti-neoplastic therapy or best supportive care. Summary incidence rates and relative risks with 95% confidence intervals were calculated.

Expert opinion: The overall incidence of hypomagnesemia was 17% among the patients who received the treatment, whose risk of developing hypomagnesemia turned out to be significantly increased compared with the patients treated with control medication, with an overall relative risk of 5.83 ($p < 0.00001$), where 3.87 refers to cetuximab and 12.55 to panitumumab. The addition of anti-EGFR monoclonal antibodies to standard anticancer therapy showed a significantly increased risk of hypomagnesemia compared with controls. The risk seems to be even higher for panitumumab, probably correlated with the increased risk of other adverse events (e.g., diarrhea and dehydration). Hypomagnesemia does not seem to be linked with any serious complications.

Keywords: cetuximab, colorectal cancer, epidermal growth factor receptor, hypomagnesemia, panitumumab

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1. Introduction

The overexpression of the epidermal growth factor receptor (EGFR) is correlated with poor prognosis in many cases of human cancer. The activation of the EGFR results in a range of various effects, including cell proliferation, differentiation, migration, adhesion and inhibition of apoptosis [1]. It also enhances processes that are crucial to the tumor growth and progression, such as angiogenesis, as well as its invasiveness and metastatic spread [2]. The EGFR is overexpressed by different types of human cancer, while its signaling is upregulated in others due to autocrine stimulation [2,3]. The anticancer agents that affect the EGFR are divided into two main groups: the ones that target the extracellular ligand-binding domain and the ones that block the intracellular tyrosine kinase

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(TK) domain. Cetuximab (C) is a human/mouse chimeric monoclonal antibody (mAb) that binds to the EGFR blocking the EGFR signaling cascade, thus inhibiting the growth of the tumor [4]. Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light-chain constant regions and has an approximate molecular weight of 152 kDa. It has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma (CRC) whose tumors express non-mutated (wild-type) *KRAS*. It also benefits patients with head and neck cancer (in conjunction with radiotherapy or chemotherapy) and improves the progression-free survival in patients affected by lung cancer, when associated with chemotherapy in EGFR-positive disease [5]. Panitumumab (P) is an anti-EGFR mAb which, like C, binds to the EGFR to prevent ligand binding and inhibits the subsequent activation of key downstream signaling molecules involved in tumorigenesis. Unlike C, P is a fully human mAb that does not contain murine portions of the IgG molecule, thus avoiding the formation of human antimouse antibodies, which represent a potential source of immunogenicity [6]. Panitumumab is in particular a recombinant, human IgG2 kappa monoclonal antibody. Panitumumab has an approximate molecular weight of 147 kDa. Panitumumab monotherapy has been approved by the FDA and the EMEA for the treatment of patients with EGFR-expressing mCRC with non-mutated (wild-type) *KRAS* after the failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens. The common toxicities of EGFR-targeting agents differ from those associated with traditional chemotherapy. Given the common pathway through which these agents work, some adverse events are similar. Many patients treated with these agents develop an acne-like rash on the face and the upper part of the body, most likely related to keratinocyte alterations and hair follicle proliferation and maturation [7]. Other adverse events of anti-EGFR agents seem to be class related. Hypomagnesemia in particular, frequently reported in association with C and P, may be related to the blockade of the EGFR in the kidney [8,5,9]. Hypomagnesemia is also a rare event related to nephrotoxicity of some chemotherapeutic drugs such as platinum agents (in particular cisplatin).

This study is a meta-analysis of all eligible randomized controlled trials (RCTs) that compare C or P, added to any standard oncological treatment (chemotherapy and/or best supportive care) with standard treatment alone (chemotherapy and/or best supportive care), with the aim to determine the risk of developing hypomagnesemia as a consequence of these anti-EGFR monoclonal antibody treatments. Selected studies are all those enrolling patients with solid tumors in particular head and neck, lung and colorectal cancers where anti-EGFR drugs have been more implemented.

2. Methods

2.1 Data source

We have searched for quotes taken from PubMed with no date restrictions using the keywords 'cetuximab' and/or 'panitumumab', and 'cancer' or 'carcinoma'. The search was limited to RCTs. In order to find relevant randomized clinical trials, we have also searched for abstracts and virtual meeting presentations among the various conferences held at the American Society of Clinical Oncology (especially if data about hypomagnesemia were not reported in published full papers).

2.2 Study selection

The goal of this study was to determine whether C and P contribute to the development of hypomagnesemia in patients with cancer. We have selected only Phase III RCTs in which patients treated with and without these two monoclonal antibodies had been directly compared. Phase I and Phase II trials were excluded due to their lack of control groups and to limit statistical heterogeneity among studies. In particular, the clinical trials that met the following criteria were included in the meta-analysis: prospective Phase III randomized clinical trials in patients with cancer; random assignment to either C or P treatment or control (placebo or best supportive care) in addition to concurrent chemotherapy, radiotherapy and/or biological agents and available data including event or incidence of hypomagnesemia and sample size for the analysis. The quality was assessed using specific criteria such as an adequate blinding of randomization, the completeness of the follow-up and the objectivity of outcome measurements as previously described [10].

2.3 Clinical end points

We have extracted details about the number of patients, the type of cancer treated, the type of treatment, the results and the follow-up from the included studies [10]. The data regarding the occurrence of hypomagnesemia were obtained from the safety profile of each study. The cases of hypomagnesemia in these studies were assessed and recorded according to the National Cancer Institute's common terminology criteria (CTC) for adverse events (version 2 or 3), which have been widely used in cancer clinical trials [11,12]. The major difference between the two versions is observed in a particular category of hypomagnesemia in version 3, which includes grades 1 – 5. For this study, we have simply divided hypomagnesemia into all grades, and grades 3 and 4 for our analysis. We have calculated the relative risk (RR) and the incidence of hypomagnesemia.

2.4 Statistical analysis

RevMan 5.0.24 (Review Manager (RevMan) (Computer program), version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) has been used for statistical analysis. We have calculated the incidence of any

grade and severe (G3 – G4) hypomagnesemia by using the number of patients with hypomagnesemia in the study group and the total number of the patients treated with C and/or P (events/population), as well as the proportion of patients with hypomagnesemia and the exact 95% CI from each study. In order to calculate the RR, the patients assigned to C and/or P have been compared only with the ones assigned to the control group in the same clinical trial. We have analyzed the treatment–effect (regarding the chemotherapy companion of the antibody) relationship by further dividing the studies into two more groups: the ones that contain platinum-based therapies (known to lower magnesium levels) and the others. We have also performed a pathology-driven analysis (colorectal vs lung cancer vs head and neck cancer). For the meta-analysis, we have used either a fixed effects model (weighted with inverse variance) or a random effects model [13]. For each meta-analysis, Cochran's Q statistic and I^2 statistics were first calculated in order to assess the heterogeneity among the proportions of the included trials. If the p value was less than 0.1, the assumption of homogeneity was deemed invalid, and the random effects model was reported after exploring the causes of heterogeneity [14]. Otherwise, the fixed effects model was reported. A two-tailed p value of less than 0.05 was considered statistically significant.

3. Results

Our search yielded 224 clinical studies relevant to either C or P. After excluding review articles, Phase I studies, single-arm Phase II studies, case reports, meta-analyses and observational studies, we have selected 14 randomized clinical trials that included two Phase II and 12 Phase III studies, for the purpose of our analysis (**Table 1**) [15-28]. We decided, as discussed above, to not include Phase II trials in this analysis, so 12 papers were meta-analyzed and included in final results.

The patients were enrolled according to pre-specified eligibility criteria for each trial. Randomized treatment allocation sequences were generated in all trials. All 12 trials had active controls (chemotherapy or best supportive care) [15-17,19,21-23,25-28] and 1 trial had a chemotherapy + placebo blinded arm [20]. Two trials had a best supportive care alone in control arms compared with C or P monotherapy in study arms [19,23]. Four trials used CTC version 2 and four others used version 3, while it is not specified what version was used in the rest of the trials (two used MedDRA (the Medical Dictionary for Regulatory Activites) terminology [27,28]). The follow-up time was not specified in seven trials. All trials reported an acceptable quality level. In none of the analyzed trials, magnesium supplementation (e.g., for prevention of cisplatin-related hypomagnesemia) is mentioned in treatment description sections.

No publication biases were detected for the primary end point of this study: in this case, Begg's test had a two-tailed p value of 0.70 (based on continuity-corrected normal approximation) and Egger's test had a two-tailed p value of 0.097.

Among all the patients who received C or P during the course of the included 12 trials, 7338 of them had available data for toxicity analyses (3564 of them were treated with either C or P, while the others received standard therapy alone).

The incidence of hypomagnesemia was 17% in the study group (95% CI 0.16 – 0.18) and 3% in the control group (95% CI 0.027 – 0.039) ($p < 0.0001$), which is 13.8% in P arms and 20.9% in C arms (p for difference < 0.0001).

Using a random effects (p for heterogeneity $p < 0.00001$) model, the overall RR resulted to be 5.83 (95% CI 3.69 – 9.2, $p < 0.00001$). The risk ratio was respectively 12.55 (95% CI 8.03 – 19.6, $p < 0.00001$; p for heterogeneity 0.32: fixed effects model) and 3.87 (95% CI 3.14 – 4.79, $p < 0.00001$; p for heterogeneity 0.12: fixed effects model) for P and C arms. We can assume that the apparently increased risk associated with exposure to P may be related to the human (IgG2) structure of the drug (C being a chimeric (IgG1) antibody), and in two P trials, it may be due to the high rate of severe diarrhea. The incidence of severe hypomagnesemia was 3.5 and 0.026% ($p < 0.0001$) in treatment arms as well as in control arms. In C arms, this value was 4.2% and in P arms it was 2.8% (p for difference 0.046). The overall RR of severe hypomagnesemia was 10.51 (95% CI 5.82 – 18.96, $p < 0.00001$; p for heterogeneity 0.85: fixed effects model): 9.81 for C (95% CI 4.64 – 20.74, $p < 0.00001$; p for heterogeneity 0.68: fixed effects model) and 11.68 for P (95% CI 4.46 – 30.57, $p < 0.00001$; p for heterogeneity 0.70: fixed effects model) (**Table 2** and **Figure 1**). Only one trial [26] described a magnesium supplementation in 3% of patients due to grade 3/4 hypomagnesemia.

In order to determine the specific contribution of C and P to the development of hypomagnesemia and exclude the effect of any confounding factors, we have calculated the overall RR of hypomagnesemia from the randomized clinical trials in which a comparison between anti-EGFR antibodies and controls had been made in patients who also received concurrent chemotherapy (as well as in those who received platinum-based chemotherapy and the ones who did not). Since patients with different tumors might also be at different risks of hypomagnesemia, due to the differences in the tumor biology and the associated treatments, we have calculated the RR in patients with gastrointestinal malignancies (vs lung and head and neck).

The RRs (random effects model) of hypomagnesemia in patients treated with concurrent chemotherapy in addition to C or P in both control and study arms was 3.63 for C and 9.82 for P, while the patients treated with and without platinum-based chemotherapy reported a RR of 5.26 and 5.58, respectively. These data could be explained through the protective value of magnesium supplementation against chemotherapy-related hypomagnesemia (in particular caused by cisplatin). It must be noted that it has been possible to choose between carboplatin and cisplatin in one trial and that 60% of the patients were treated with cisplatin in the

Table 1. Characteristics of randomized controlled clinical trials included in the meta-analysis.

Author/ref.	Study drug	Trial phase/n°line/design	Disease/stage	Pts enrolled total/ experimental arm	Median duration of treatment	Hypomagnesemia
Burtness/20	C	III All (30% pretreated) CDDP+C vs CDDP+Pl	Head and neck/IV	123/57	18 weeks	G3 – G4 14 vs 0%
Vermorken/15	C	III First line CDDP or CBDCA+5FU vs CDDP or CBDCA+5FU+C	Head and neck/IV	477/222	15 weeks	G3 – G4 5 vs 1%
Sobrero/16 (EPIC TRIAL)	C	III Second line CPT11 vs CPT11+C	Colorectal Cancer/ IV	1587/648	14 weeks (range 0.7 – 97.9)	All grade 33.8 vs 8.4% G3 – G4 3.3 vs 0.4%
Hecht/25 (PACCE TRIAL)	P	IIIb First line Oxaliplatin or irinotecan based regimen + Bevacizumab vs Oxaliplatin or irinotecan based regimen + Bevacizumab + P	Colorectal cancer/IV	1240/528	35.2 weeks (PFS 8.8 months; treatment until PD)	All grade 28.7 vs 2.7% G3 – G4 4.8 vs 0.19%
Lynch/22 (BMS099 TRIAL)	C	III First line CBDCA+TAX vs CBDCA+TAX+C	Non-small cell lung cancer Stage/IIIB – IV	676/338	12 weeks (range 1 – 125)	G3 – G4 8.8 vs 0.7%
Van Cutsem/26	P	III Pretreated with fluoropyrimidine, oxaliplatin, irinotecan BSC vs BSC+P	Colorectal cancer/IV	463/231	8 weeks (PFS 8 weeks)	All grade 36 vs 1% G3 – G4 3% vs UK
Van Cutsem/23 (CRYSTAL TRIAL)	C	III First line FOLFIRI vs FOLFIRI+C	Colorectal cancer/IV	2020/599	25 weeks (range 12.9 – 40.4)	G3 – G4 1.8 vs 0.2% (magnesium level measured only in 20% of patients)
Adams/21 (COIN TRIAL)	C	III First line FOLFOX/XELOX vs FOLFOX/ XELOX +C	Colorectal cancer/IV	804/268	12 weeks (toxicity available in the first 12 weeks of treatment)	All grade 5.9 vs 2.4% G3 – G4 0 vs 0.1%
Jonker/19	C	III Refractory cancer (after 5FU, oxaliplatin, CPT11 or if controindicate) BSC vs BSC+C	Colorectal cancer/IV	572/285	8.1 weeks	All grade 53.5 vs 15.1% G1 36.7 vs 14.6% G2 10.8 vs 0.5% G3 2.7 vs 0% G4 3.1 vs 0%

5FU: 5 fluorouracil; BSC: Best supportive care; C: Cetuximab; CDDP: Cisplatin; CBDCA: Carboplatin; P: Panitumumab; Pl: Placebo; TAX: Docetaxel or paclitaxelp; UK: Unknown.

Table 1. Characteristics of randomized controlled clinical trials included in the meta-analysis (continued).

Author/ref.	Study drug	Trial phase/n°line/design	Disease/stage	Pts enrolled total/ experimental arm	Median duration of treatment	Hypomagnesemia
Tol/17 (CAIRO 2 TRIAL)	C	III All line Capecitabine + Oxaliplatin + Bevacizumab vs Capecitabine + Oxaliplatin + Bevacizumab +C	Colorectal cancer/IV	400/192		G1 – G2 14 vs 36% G3 – G4 1 vs 2%
Siena/27 (PRIME TRIAL)	P	III First line FOLFOX-4 vs FOLFOX-4 +P	Colorectal cancer/IV	1106/556	38.4 weeks	G3 – G4 6 vs < 1%
Peeters/28	P	III Second line FOLFIRI vs FOLFIRI + P	Colorectal cancer/IV	591/1186	Not reported	G3 – G4 8 vs 1%

5FU: 5 fluorouracil; BSC: Best supportive care; C: Cetuximab; CDDP: Cisplatin; CBDCA: Carboplatin; P: Panitumumab; Pl: Placebo; TAX: Docetaxel or paclitaxelp; UK: Unknown.

mentioned studies (carboplatin is known to cause less severe forms of hypomagnesemia). After having excluded this study, only one was left eligible for the analysis (116 patients treated with cisplatin plus or minus cetuximab (C)), with a significant RR of 17. In this study, no mention is made about i.v. magnesium supplementation in association with cisplatin administration.

Conversely, the incidence of hypomagnesemia in patients affected by colorectal, lung, head and neck cancers was 19.2, 8 and 6.8% respectively in experimental arms. It was not possible to calculate the risk of developing hypomagnesemia under different doses of study drugs (all trials utilized the same approved schedules of C and P).

4. Discussion

Our meta-analysis confirms the causative role of anti-EGFR monoclonal antibodies on hypomagnesemia in most randomized clinical trials. The risk seems to be increased in P trials, although it appears to be independent of concurrent chemotherapy or underlying oncological disease.

This meta-analysis highlights the causative role of C and P in anti-EGFR-related hypomagnesemia with an all-grade incidence of 17% and a RR of 5.83 compared with control arms. The risk appears elevated in all neoplastic diseases where the drugs have been tested in randomized trials (colorectal, lung, head and neck cancers), although it turned out to be significantly lower in head and neck and lung cancer patients compared with colorectal ones. The reasons for this are unknown, but most likely it could be related to simultaneous Mg^{2+} implementation following concomitant cisplatin administration. The apparently increased risk with P (12.55 vs 3.87 with C) could be explained by the higher rate of severe diarrhea (up to 28 and 20% in Hecht and Siena trials with irinotecan-based and oxaliplatin-based P combinations). Thus, preventing diarrhea could be a valid measure for preventing hypomagnesemia. These are only the authors' hypotheses and need to be verified prospectively.

4.1 C- and P- related hypomagnesemia: brief literature overview

The first case of anti-EGFR monoclonal antibody-related hypomagnesemia was observed by Schrag and Fakih [29,30], who reported a rate of 36 and 27% of severe (G3 – G4) hypomagnesemia. The first prospective magnesium concentration measurement study was reported by Tejpar *et al.* [31] in a cohort of 98 patients with colorectal cancer treated with EGFR-targeting antibodies either with or without combined chemotherapy. Ninety-five (97%) patients experienced a decrease in serum magnesium concentrations during EGFR-targeting treatment compared with baseline measurements. Serum magnesium concentrations increased back to normal levels after treatment discontinuation. Serum magnesium concentration slopes and time of development of hypomagnesemia were both inversely correlated to the age of patients and the serum magnesium concentration levels observed at the baseline.

Table 2. Incidence and relative risk of all-grade and severe hypomagnesemia.

Study drug (95% CI)	N° of studies	All-grade hypomagnesemia		Incidence (95% CI), %		RR
		N° events/Total N° patients				
		Anti-EGFR Ab	Control	Anti-EGFR Ab	Control	
Overall	12	616/3564	114/3774	17	3	5.83
Cetuximab	8	364/1739	94/1945	20.9	-	3.87
Panitumumab	4	252/1825	20/1829	13.8	-	12.55
Study drug (95% CI)	**N° of studies**	**High-grade hypomagnesemia**		**Incidence (95% CI), %**		**RR**
		N° events/Total N° patients				
		Anti-EGFR Ab	Control	Anti-EGFR Ab	Control	
Overall	12	126/3564	10/3774	3.5	0.26	10.51
Cetuximab	8	74/1739	6/1945	4.2	-	9.81
Panitumumab	4	52/1825	4/1829	2.8	-	11.68

Incidence and relative risk (RR) of all-grade and high-grade hypomagnesemia with cetuximab and panitumumab among patients with various tumor types in randomized clinical trials.

Ab: Antibody; CI: Confidence interval; EGFR: Epidermal growth factor receptor.

Conversely, both were positively correlated to the total duration of the treatment. On the other hand, the incidence of grade 3/4 hypomagnesemia reported in 114 patients who received C therapy for < 3, 3 – 6 and > 6 months for the treatment of colorectal cancer was 6, 23 and 47% respectively [25]. These data clearly suggest a C-treatment-duration-dependent risk in severe hypomagnesemia.

4.2 Etiopathogenesis of hypomagnesemia

The cases of hypomagnesemia associated with anti-EGFR monoclonal antibodies might be caused by other known risk factors such as the use of chemotherapeutic agents (cisplatin) or intestinal malabsorption; protracted vomiting, diarrhea or intestinal drainage; defective renal tubular magnesium reabsorption or rapid shifts of magnesium from extracellular fluids into cells, bones or third spaces. Various forms of renal injury, including those caused by drugs (such as ethanol, diuretics, pentamidine, foscarnet, cyclosporine, aminoglycosides and amphotericin B), may all be factors leading to magnesium depletion, although in the papers analyzed so far, it was excluded that drugs could play any co-causative role in the process.

Magnesium is the major intracellular divalent cation. Normal concentrations of extracellular magnesium and calcium are crucial to normal neuromuscular activity. Hypomagnesemia may cause generalized alterations in neuromuscular functions including tetany, tremor, seizures, muscle weakness, ataxia, nystagmus, vertigo, apathy, depression, irritability, delirium and psychosis. Patients are usually asymptomatic when their serum magnesium concentration levels are > 0.5 mmol/l (1 meq/l; 1.2 mg/dl; CTCAEv.3 G ≤ 1), although the severity of symptoms may not correlate with serum magnesium levels. Cardiac arrhythmias may occur, including sinus tachycardia, supraventricular tachycardia and ventricular arrhythmias. Electrocardiographic abnormalities may include prolonged PR or QT intervals, T-wave flattening or inversion as well as ST straightening. Sensitivity to digitalis toxicity may be enhanced.

As a consequence of cisplatin (known to be a magnesium-depleting agent) damage, humans develop focal tubular necrosis, predominantly in distal convoluted tubules and collecting ducts [31]. When cisplatin induces renal injury, one of the first consequences is a decrease in the values of serum magnesium, which can occur in the presence of otherwise normal tubular function [32].

The EGFR is mainly expressed in distal and collecting tubules and, to a lesser extent, in proximal tubules, glomerular capillary walls, mesangial and parietal epithelial cells, peritubular capillaries and arterioles [33]. The EGFR is involved in maintaining tubular integrity, and its activation leads to the growth and regeneration of tubular epithelial cells after acute tubular necrosis [34]. It is necessary in distal convoluted tubules in order to prevent renal wasting of Mg^{2+} due to the stimulation of the epithelial Mg^{2+} transient receptor potential cation channel, subfamily M, member 6 (TRPM6) [35].

4.3 Clinical features of hypomagnesemia

Mild, asymptomatic hypomagnesemia can be treated with oral magnesium salts, administration of large doses of which may lead to diarrhea. More severe forms of hypomagnesemia should be treated parenterally. But what is the real clinical meaning of mild and severe hypomagnesemia? There are no studies providing evidence of a linear relationship between the grade of hypomagnesemia and the increasing seriousness of complications. Thus, both known and unknown factors

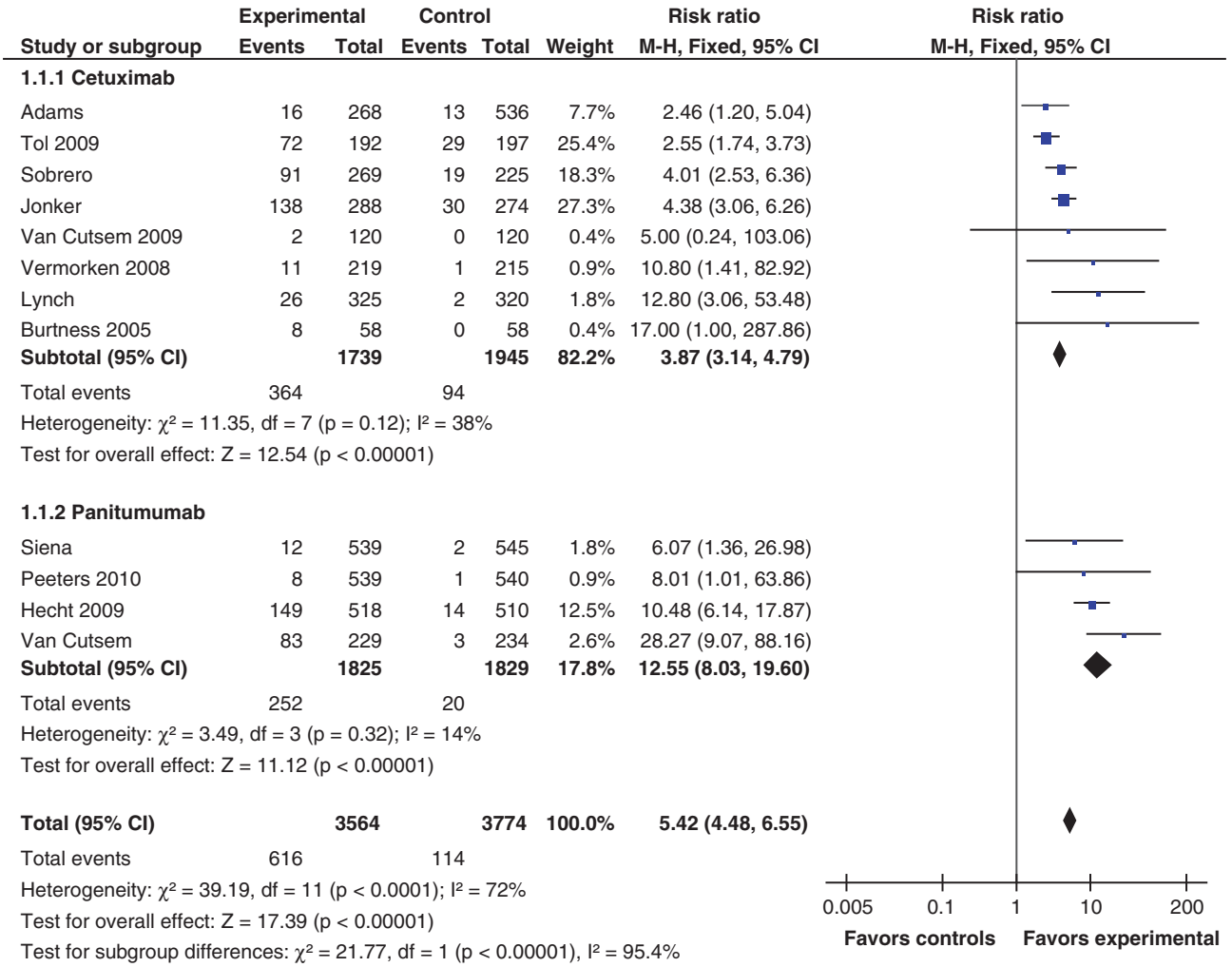

Figure 1. Risk ratio of hypomagnesemia associated with cetuximab and panitumumab.

might make a specific patient more susceptible to serious complications, even at comparatively low grades of hypomagnesemia. Cardiac diseases are well known to increase the risk of cardiac arrhythmias in hypomagnesemic patients and should lead to an increased awareness in hypomagnesemic patients, especially if treated with digoxin or diuretics. However, no studies have been able to objectively determine which level of hypomagnesemia has to be considered the supplementation threshold.

4.4 Prevention of hypomagnesemia

In our meta-analysis, there are no data available from any trials about possible complications related to (severe) hypomagnesemia. As long as the relationship between hypomagnesemia and its possible complications remains poorly elucidated, it seems reasonable to try to prevent hypomagnesemia. According to some studies [36-46] on cisplatin, the best results seem to be achieved by adding magnesium to pre- and post-hydration fluids. Nevertheless, no regimen has proven to be completely protective against hypomagnesemia caused by cisplatin administration.

It is important to recognize age, baseline magnesium concentrations and duration of treatment as risk factors, meaning that certain groups of patients should be screened more frequently and have their magnesium levels repeatedly measured during the treatment, in particular during long-lasting treatments. Comorbidity and polypharmacotherapy have to be considered risk factors for complications caused by hypomagnesemia.

Thus, we have taken into consideration the hypothesis that the risk of developing hypomagnesemia may increase along with the number of cycles. We have calculated the RR of severe hypomagnesemia as a function of duration of treatment (≥ 3 months). The RR was 8.8 for duration ≥ 3 months. The fact that this value is very close to the overall value (8.3) probably means that hypomagnesemia has to be considered

an early event, rather than a cumulative one, and that it normalizes slowly after the end of treatment.

5. Expert opinion

Overall, this meta-analysis says that hypomagnesemia is very often an inconvenience in clinical practice with anti-EGFR monoclonal antibodies. It seems likely to be an early event during the course of treatment. From our point of view, the release of these data leads to three questions. What should the frequency of blood magnesium measurement be? What about any prevention measures? Does hypomagnesemia have a possible role as a predictive biomarker of anti-EGFR drug efficacy or activity?

Due to the frequent C/P schedule of administration (weekly and bi-weekly), it seems reasonable and appropriate to check for hypomagnesemia at least every other cycle during the treatment, in particular for long-term therapy. In particular, the elderly with comorbidities (cardiovascular in particular) and those with multi-drug assumption (polypharmacy) are those at greater risk for complications. However, no serious hypomagnesemia-related adverse events are reported in this meta-analysis. There is also room for prevention in this setting, but appropriate clinical trials are needed. However, calcium–magnesium supplementation for the prevention of oxaliplatin neurotoxicity, for example, could prevent both neurological and metabolic toxicity, in this case hypomagnesemia, particularly when C and P are coupled with platinum-based chemotherapy. When these drugs are prescribed as monotherapy, a judicious addition of i.v. magnesium could be sufficient to prevent complications due to magnesium depletion.

Interestingly, hypotheses regarding the role of magnesium in cancer development and biology might emerge in the near future. It is well known that *in vitro* tumor cells do not need as much extracellular magnesium for their growth as normal cells [47,48]. In comparison with magnesium-sufficient controls, magnesium-deficient mice (xenografted with a variety of solid tumors) showed an approximate reduction of 60% in the growth of primary tumors. The tumors developed in magnesium-deficient mice were significantly less vascularized than those of controls [49]. One hypothesis is that insufficient angiogenesis contributed to the inhibition of primary tumor growth. Indeed, endothelial cells cultured *in vitro* are among the most sensitive to low magnesium availability in terms of impaired proliferation and migration [50], partly because of their reduced sensitivity to angiogenic factors. These data clearly show that magnesium deficiency inhibits primary tumor growth and *in vivo* vascularization; they also support the hypothesis that hypomagnesemia might potentiate the anti-tumor effect exerted by anti-EGFR targeted therapy [51]. The data are complicated by the fact that severe hypomagnesemia was accompanied by a significant leukocytosis [52] in mice models, and these mice developed many more lung metastases than controls [53]. In magnesium-deficient mice, as well as in *in vitro* systems, several proteases promoting tissue remodeling and cell migration were found to be upregulated [51]. On the other hand, the exuberant inflammatory response observed in magnesium-deficient mice could represent an important causative factor for tumor cell extravasation [54,55]. In this context, the low magnesium-induced upregulation of vascular cell adhesion molecule by micro- and macro-vascular endothelial cells [55] may favor the binding of tumor cells in metastatic sites [56]. Whether hypomagnesemic patients treated with C or P would experience the same deleterious effects on tumor growth as in animal models is still unknown. The amount of information derived from preclinical studies reveals a complex scenario in which magnesium depletion could have both anti- and pro-tumoral effects, such as reversible inhibition of tumor growth in its primary site and facilitation of tumor implantation in its metastatic sites.

Recently, in a retrospective cohort of patients treated with C and irinotecan, the predictive role of hypomagnesemia was elucidated [57]. Patients with an early decrease in magnesium levels > 50% compared with the basal level had a higher tumor response rate (55.8 vs 16.7%, $p < 0.0001$), a longer time to progression (6.3 vs 3.6, $p < 0.0001$) and a longer median survival (11.0 vs 8.1, $p = 0.002$). Magnesium circulating level could, therefore, be an easy and inexpensive biomarker to routinely be detected in patients treated with C.

In general, we think it seems reasonable, until proven otherwise, to prevent hypomagnesemia for both clinical and biological reasons.

6. Conclusions

In conclusion, this meta-analysis confirms that the incidence of hypomagnesemia is 0.17 in patients exposed to anti-EGFR monoclonal antibodies C and P and 0.03 in not-exposed patients. This incidence is 0.138 and 0.205 in P and C arms, respectively. Using a random effects model, the overall result was a RR of 5.24. Fortunately, the incidence of severe (G3 – G4) hypomagnesemia was 3.4% (4% in C arms and 2.8% in P arms (p for difference 0.0322)). The overall RR of severe hypomagnesemia was 9.83 (8.92 for C and 11.68 for P). So far, no extracted (published) data have reported any severe complications or cases of death related to magnesium depletion, which could probably be easily prevented with supplementation therapy during cisplatin administration. These results are significant although evident heterogeneity among trials probably related to different timing of magnesium measurements or (unknown) patient-related factors such as comorbidity, side effects of chemotherapy (diarrhea?) or polypharmacy (concomitant magnesium-depleting diuretics?).

It is advisable to continue close monitoring, particularly in patients at highest risk of serious complications (elderly, pretreated and poor performance status patients, carrier of cardiovascular-associated morbidity or magnesium-depleting drug users) and in those who undergo prolonged therapy.

At present, the biological significance of hypomagnesemia is still unknown, and the exact role that magnesium wasting plays on the underlying tumor disease will probably be determined by current studies.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Arteaga CL. The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. J Clin Oncol 2001;19:32s-40s
2. Baselga J. Why the epidermal growth factor receptor? The rationale for cancer therapy. Oncologist 2002;7(Suppl 4):2-8
3. Wells A. Molecules in focus: EGF receptor. Int J Biochem Cell Biol 1999;31:637-43
4. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. J Clin Oncol 2003;21:2787-99
5. Erbitux package insert. March 2006. ImClone Systems Incorporated, New York, NY 10014, USA. and Bristol-Myers Squibb Co; Princeton, NY 08543, USA
6. Cohenuram M, Saif MW. Panitumumab the first fully human monoclonal antibody: from the bench to the clinic. Anticancer Drugs 2007;18:7-15
7. Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? J Clin Oncol 2005;22:5235-41
8. Vectibix (panitumumab) prescribing information. (v3, revOctober 2007) Amgen, Inc.: Thousand Oaks, CA. Available from: http://www.vectibix.com/pdfs/misc/vectibix pi.pdf [Accessed 10 March 2008]
9. Groenestege WM, Thebault S, Van Der Wijst J, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. J Clin Invest 2007;117:2260-7
10. Meade MO, Richardson WS. Selecting and appraising studies for a systematic review. Ann Intern Med 1997;127:531-7
11. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_ 30-992.pdf
12. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88
14. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820-6
15. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116-27
16. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26(14):2311-19
17. Tol J, Koopman M, Rodenburg CJ, et al. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. Ann Oncol 2008;19(4):734-8
18. Butts CA, Bodkin D, Middleman EL, et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin [corrected], with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer. J Clin Oncol 2007;25(36):5777-84; Erratum in: J Clin Oncol 2008;26(19):3295
19. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357(20):2040-8
20. Burtness B, Goldwasser MA, Flood W, et al. Eastern cooperative oncology group. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005;23(34):8646-54; Erratum in: J Clin Oncol 2006;24(4):724
21. Adams RA, Meade AM, Madi A, et al. Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. Br J Cancer 2009;100(2):251-8
22. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010;28(6):911-17
23. Van Cutsem E, Nowacki M, Lang I, et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): the CRYSTAL trial. [abstract 4000]. Program and abstracts of the 43rd American Society of Clinical Oncology Annual Meeting; June 1-5, 2007; Chicago, Illinois
24. Bokemeyer C, Bondarenko I, Makhson A, et al. Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study. [abstract 4035]. Program and abstracts of the 43rd American Society of Clinical Oncology Annual Meeting; June 1-5, 2007; Chicago, Illinois
25. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27(5):672-80
26. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25(13):1658-64
27. Siena S, Cassidy J, Tabernero J, et al. Randomized phase III study of

panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial. [abstract 283]. 2010 Gastrointestinal Cancers Symposium. January 22-24, 2010; Orlando, Florida

28. Peeters M, Price TJ, Hotko YS, et al. Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Patient-reported outcomes (PRO) [abstract 282]. 2010 Gastrointestinal Cancers Symposium. January 22-24, 2010; Orlando, Florida

29. Schrag D, Chung KY, Flombaum C, Saltz L. Cetuximab therapy and symptomatic hypomagnesemia. J Natl Cancer Inst 2005;97:1221-4

30. Fakih MG, Wilding G, Lombardo J. Cetuximab-induced hypomagnesemia in patients with colorectal cancer. Clin Colorectal Cancer 2006;6:152-6

31. Tejpar S, Piessevaux H, Claes K, et al. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncol 2007;8:387-94

•• **The first trial that prospectively measured the magnesium concentration during anti-EGFR antibody therapy in colorectal cancer.**

32. Daugaard G, Strandgaard S, Holstein-Rathlou N-H, et al. The renal handling of sodium and water is not affected by the standard-dose cisplatin treatment for testicular cancer. Scand J Clin Lab Invest 1987;47:455-9

33. Izzedine H, Rixe O, Billemont B, et al. Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. Am J Kidney Dis 2007;50:203-18

34. Nakopoulou L, Stefanaki K, Boletis J, et al. Immunohistochemical study of epidermal growth factor receptor (EGFR) in various types of renal injury. Nephrol Dial Transplant 1994;9:764-9

35. Groenestege WM, Thebault S, Van Der Wijst J, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. J Clin Invest 2007;117:2260-7

36. Hunter RJ, Pace MB, Burns KA, et al. Evaluation of intervention to prevent hypomagnesemia in cervical cancer patients receiving combination cisplatin and radiation treatment. Support Care Cancer 2009;17(9):1195-201

37. Bodnar L, Wcislo G, Gasowska-Bodnar A, et al. Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: a randomised phase II study. Eur J Cancer 2008;44(17):2608-14

38. Saif MW. Management of hypomagnesemia in cancer patients receiving chemotherapy. J Support Oncol 2008;6(5):243-8

39. Hodgkinson E, Neville-Webbe HL, Coleman RE. Magnesium depletion in patients receiving cisplatin-based chemotherapy. Clin Oncol (R Coll Radiol) 2006;18(9):710-18

40. Lofts FJ, Evans TR, Wastnage R, Mansi JL. Magnesium supplements with cisplatin chemotherapy. Eur J Cancer 1996;32A(3):556-7

41. Evans TR, Harper CL, Beveridge IG, et al. A randomised study to determine whether routine intravenous magnesium supplements are necessary in patients receiving cisplatin chemotherapy with continuous infusion 5-fluorouracil. Eur J Cancer 1995;31A(2):174-8

42. Martin M, Diaz-Rubio E, Casado A, et al. Intravenous and oral magnesium supplementations in the prophylaxis of cisplatin-induced hypomagnesemia. Results of a controlled trial. Am J Clin Oncol 1992;15(4):348-51

43. Vokes EE, Mick R, Vogelzang NJ, et al. A randomised study comparing intermittent to continuous administration of magnesium aspartate hydrochloride in cisplatin-induced hypomagnesaemia. Br J Cancer 1990;62(6):1015-17

44. Kibirige MS, Morris-Jones PH, Addison GM. Prevention of cisplatin-induced hypomagnesemia. Pediatr Hematol Oncol 1988;5(1):1-6

45. Willox JC, McAllister EJ, Sangster G, Kaye SB. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. Br J Cancer 1986;54(1):19-23

46. Schilsky RL, Anderson T. Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med 1979;90(6):929-31

47. Sgambato A, Wolf FI, Faraglia B, Cittadini A. Magnesium depletion causes growth inhibition, reduced expression of cyclin D1 and increased expression of p27kip1 in normal but not in transformed mammary epithelial cells. J Cell Physiol 1999;180:245-54

48. Wolf FI, Trapani V. Cell (Patho) physiology of Magnesium. Clin Sci 2008;114:27-35

49. Maier JAM, Nasulewicz-Goldeman A, Simonacci M, et al. Insights into the mechanisms involved in magnesium-dependent inhibition of primary tumor growth. Nutr Cancer 2007;59:192-8

50. Maier JAM, Malpuech-Brugere C, Zimowska W, et al. Low magnesium promotes endothelial dysfunction: implications for atherosclerosis, inflammation and thrombosis. Biochim Biophys Acta 2004;1689:13-24

51. Vincenzi B, Santini D, Galluzzo S, et al. Early magnesium reduction in advanced colorectal cancer patients treated with cetuximab plus irinotecan as predictive factor of efficacy and outcome. Clin Cancer Res 2008;14:4219-24

52. Nasulewicz A, Wietrzyk J, Wolf FI, et al. Magnesium deficiency inhibits primary tumor growth but favors metastasis in mice. Biochim Biophys Acta 2004;1739:26-32

53. Mazur A, Maier JAM, Rock E, et al. Magnesium and the inflammatory response: potential physiopathological implications. Arch Biochem Biophys 2007;458:48-56

54. Kerbel RS. Tumor angiogenesis. N Engl J Med 2008;358:2039-49

55. Bernardini D, Nasulewicz A, Mazur A, Maier JAM. Magnesium and microvascular endothelial cells: a role in inflammation and angiogenesis. Front Biosci 2005;10:1177-82

56. Kobayashi H, Boelte KC, Lin PC. Endothelial cell adhesion molecules and cancer progression. Curr Med Chem 2007;14:377-86

57. Vincenzi B, Galluzzo S, Santini D, et al. Early magnesium modifications as a surrogate marker of efficacy of cetuximab-based anticancer treatment in KRAS wild-type advanced colorectal cancer patients. Ann Oncol 2011;22(5):1141-6

•• **A paper that correlated hypomagnesemia with clinical outcome in colorectal cancer patients.**

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