Clinical relevance and utility of cetuximab-related changes in magnesium and calcium serum levels

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Hypomagnesemia and hypocalcemia are common adverse events during cetuximab treatment. The influence of the chemotherapeutic combination on serum levels is unknown and the predictive value is currently under discussion. This analysis investigated 79 patients who had received cetuximab for at least 6 weeks in the day clinic of the Comprehensive Cancer Center, University of Munich. Calcium and magnesium serum levels were analyzed weekly; tumor response and adverse events were followed. Thirty-eight patients had metastatic colorectal cancer (mCRC) and the predictive value of hypomagnesemia was tested in these patients. During therapy, calcium serum levels decreased to about 97% of the baseline levels and were maintained for the duration of treatment. Magnesium levels showed a significant time-dependent decrease. Serum levels of magnesium were lower when cetuximab was combined with a platinum derivative. After a treatment duration of 12 weeks, magnesium levels decreased to 70% in platinum-treated patients, whereas they decreased to only 90% of baseline in patients who did not receive platinum therapy. In patients treated for mCRC, a decrease of serum magnesium below 95% of the baseline levels 14 days after initiating treatment separated patients significantly in terms of survival times. Magnesium levels decrease in a time-dependent manner during cetuximab therapy. As hypomagnesemia was more prominent in patients receiving platinum agents, magnesium measurements may be advised in these patients. In mCRC patients treated with cetuximab, day-14 magnesium serum levels correlated with treatment efficacy. *Anti-Cancer Drugs* 24:969–974 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Treatment with antibodies directed against the epidermal growth factor receptor (EGFR) has improved antitumor treatment efficacy in several entities. Next to the treatment of mCRC [1–3], the anti-EGFR-antibody cetuximab is approved for the treatment of squamous cell cancer of the head and neck [4], and was also evaluated in other malignancies such as lung cancer and gastric cancer [5,6]. The occurrence of hypomagnesemia as a side effect of cetuximab treatment has been observed within the first trials using cetuximab [7] and appears to be a class effect of anti-EGFR antibodies [8]. The mechanism of hypomagnesemia in anti-EGFR treated patients has been explained by the link between TRMP6 (transient receptor potential member 6) and EGFR signaling. Magnesium is absorbed in the gut and reabsorbed in the ascending loop of Henle by TRMP6 [9], an ion channel. TRMP6 activation is mediated by EGFR signaling [10].

Next to acneiform exanthema [11], hypomagnesemia [12] has also been described as a possible clinical predictor for outcome. However, conflicting data were reported in a recent report, indicating that hypomagnesemia induced by cetuximab monotherapy was associated with inferior survival [13]. Therefore, the predictive value of magnesium and calcium decrease is currently under discussion. The effect of the chemotherapeutic drugs used in combination with cetuximab on the occurrence and frequency of hypomagnesemia has not been elucidated. Furthermore, risk factors defining patients who are more likely to develop hypomagnesemia have not yet been identified.

The present analysis aimed to define the course of magnesium and calcium serum levels during cetuximab exposure and searched for risk factors predicting the development of hypomagnesemia and hypocalcemia. In this context, specific focus was on the effect of different chemotherapy backbones on the development of hypomagnesemia and hypocalcemia.

Patients and methods

Patients receiving cetuximab for cancer treatment in the day clinic of the Comprehensive Cancer Center LMU, Klinikum der Universität, University of Munich, were

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investigated. In this retrospective analysis, patients treated from 2009 to 2011 were included. Cetuximab was administered according to the manufacturer's instructions. After a loading dose of 400 mg/m^2 (120 min intravenously), cetuximab was administered weekly at a dose of 250 mg/m^2 (90–30 min intravenously). Concomitant medication with dimethindene (4 mg intravenously) and dexamethasone (4 mg intravenously) was administered at all treatment cycles. In addition, patients receiving oxaliplatin for colorectal cancer treatment were premedicated with calcium gluconate (1 g intravenously) and magnesium sulfate (1 g intravenously) as prophylaxis for peripheral neuropathy. In evaluable patients, duration of cetuximab exposure of at least 6 weeks was required. To limit the number of parameters included in this analysis and possibly weakening our conclusions, patients treated with panitumumab were excluded from this study.

Clinical parameters

Before each treatment, standard laboratory tests, including serum creatinine, glomerular filtration rate (GFR) calculated using the Cockroft–Gault formula, magnesium, and calcium, were carried out. Toxicity was evaluated by a standardized toxicity form, including acneiform exanthema, skin and nail changes, and diarrhea as cetuximab-specific parameters. Grading was performed according to NCI CTC AE version 3.0 (National Institutes of Health, Bethesda, Maryland, USA). Also, basic patient characteristics (age, sex, tumor type, KRAS mutational status, chemotherapeutic regimen, and treatment line) were determined. Treatment efficacy was defined by best overall response (RECIST 1.0) and survival times (progression-free survival and overall survival). The Ethics Committee of the University of Munich (Grosshadern) approved the study design (#081-13).

Statistical analyses

Logistic regression exploration was carried out for univariate and multivariate analyses to evaluate the influence of baseline characteristics (age, sex, KRAS status, serum creatinine, GFR, tumor type, chemotherapeutic drugs) on changes in the calcium and magnesium serum levels. To define cut-off levels for decrease in magnesium, a receiver-operator characteristics (ROC) curve was constructed and the cut-off was set where the sum of specificity and sensitivity reached its maximum. To calculate differences in response, Fisher's exact test was used. For differences in survival, Kaplan–Meier estimates and log-rank P were calculated. To evaluate the time-dependent manner of magnesium and calcium levels, analysis of variance testing for repeated measurements was carried out.

All statistical tests were two-sided and a P-value of less than 0.05 was considered statistically significant. R (version 2.11.1; R Foundation, Vienna, Austria) and

SPSS PASW 20.0 (SPSS Inc., Chicago, Illinois, USA) software were used for all statistical analyses.

Results

A total of 97 patients received cetuximab during the period from 2009 to 2011. Of these, 79 received cetuximab for a period of at least 6 weeks and therefore were included in this analysis (for baseline characteristics, Table 1a). For each parameter (magnesium and calcium), 1359 serum measurements were available for analysis. The toxicities of interest (hypomagnesemia, hypocalcemia, acneiform exanthema) were as presented in Table 1b and c. In brief, a total of nine patients (11.4%) developed hypomagnesemia reaching NCI CTC grade 3–4 and six patients (7.6%) developed a grade 3–4 hypocalcemia. By plotting the mean magnesium and calcium levels over time in relation to the baseline measurements (Fig. 1), two differences could be observed. Calcium levels decreased nonsignificantly during the first 2 weeks to a level of about 95–97% of baseline and were maintained for the entire duration of treatment. Therefore, calcium levels did not seem to be a valuable parameter to correlate with treatment efficacy. In comparison, magnesium levels decreased significantly (Greenhouse–Geisser $P = 0.03$) in a time-dependent manner without reaching a minimum. Furthermore, a difference could be observed between the magnesium levels in patients treated with any platinum derivative and cetuximab and those who received platinum-free chemotherapy. In patients treated with platinum derivatives, the decrease in magnesium was faster and reached lower levels (about 70% of baseline) than in patients not treated with a platinum derivative, in whom levels reached 85–90% of baseline after a treatment duration of 12 weeks. Using repeated-measures analysis of variance testing, the difference between platinum and nonplatinum patients in terms of the course of magnesium did not differ significantly (Greenhouse–Geisser $P = 0.24$), but showed a trend towards lower levels in platinum-treated patients.

Using Kendall-tau-β rank testing, the occurrence of acneiform exanthema correlated significantly with the decrease of serum magnesium levels (correlation coefficient -0.21; $P = 0.037$).

Univariate and multivariate analyses did not show any association with baseline characteristics and magnesium levels after 2 weeks of treatment (Table 2). With respect to calcium levels, the baseline serum creatinine level was found to be an independent factor for lower calcium levels in univariate [odds ratio (OR) = 0.61; $P = 0.03$] and multivariate (OR = 0.37; $P = 0.006$) analyses (Table 3).

For the subgroup of patients with mCRC, representing the largest subgroup in our analysis, logistic regression analysis indicated that lower magnesium levels at day 14

Table 1 Baseline characteristics and toxicities of interest for cetuximab

	mCRC (n=38)	SCCHN (n=27)	Other[a] (n=14)	Total (n=79)
		n (%)		
(a) Baseline characteristics				
Age (years) (range)	63.3 (35.3–84.2)	62.4 (46.4–86.2)	68.7 (27.9–84.0)	62.2 (27.9–86.2)
Sex				
Male	30 (78.9)	21 (77.8)	9 (64.3)	60 (75.9)
Female	8 (21.1)	6 (22.2)	5 (35.7)	19 (24.1)
KRAS status				
Wild-type	27 (71.1)	3 (11.1)	7 (50.0)	37 (46.8)
Mutated	7 (18.4)	0	1 (7.1)	8 (10.1)
Not known	4 (10.5)	24 (88.9)	6 (42.9)	34 (43.1)
Combination partner				
Platinum	3 (7.9)	13 (48.1)	7 (50.0)	23 (29.1)
Nonplatinum	35 (92.1)	14 (51.9)	7 (50.0)	56 (70.9)
Therapy line				
First line	14 (36.8)	15 (55.6)	5 (35.7)	34 (43.0)
Further line	24 (63.2)	12 (44.4)	9 (64.3)	45 (56.9)
(b) Toxicity (NCI CTC AE version 3.0) by cancer type				
Hypomagnesemia				
Grade 0	21 (55.3)	13 (48.1)	6 (42.9)	40 (50.6)
Grade 1	11 (28.9)	6 (22.2)	3 (21.4)	20 (25.3)
Grade 2	2 (5.3)	6 (22.2)	2 (14.3)	10 (12.7)
Grade 3/4	4 (10.5)	2 (7.4)	3 (21.4)	9 (11.4)
Hypocalcemia				
Grade 0	27 (71.1)	22 (81.5)	7 (50.0)	56 (70.9)
Grade 1	8 (21.1)	2 (7.4)	1 (7.1)	11 (13.9)
Grade 2	2 (5.3)	1 (3.7)	3 (21.4)	6 (7.6)
Grade 3/4	1 (2.6)	2 (7.4)	3 (21.4)	6 (7.6)
Acneiform exanthema				
Grade 0–1	7 (18.4)	8 (29.6)	6 (42.9)	21 (26.6)
Grade 2–4	29 (76.3)	17 (62.9)	8 (57.1)	54 (68.4)
Unknown	2 (5.3)	2 (7.4)	0	4 (5.1)
	Nonplatinum-containing regimen (n=56)	Platinum-containing regimen (n=23)	Total (n=79)	
(c) Toxicity (NCI CTC AE version 3.0) by platinum-based chemotherapy				
Hypomagnesemia				
Grade 0	33 (58.9)	7 (30.4)	40 (50.6)	
Grade 1	13 (23.2)	7 (30.4)	20 (25.3)	
Grade 2	6 (10.7)	4 (17.4)	10 (12.7)	
Grade 3/4	4 (7.2)	5 (21.7)	9 (11.4)	
Hypocalcemia				
Grade 0	41 (73.2)	15 (65.2)	56 (70.9)	
Grade 1	11 (19.6)	0	11 (13.9)	
Grade 2	2 (13.6)	4 (17.4)	6 (7.6)	
Grade 3/4	2 (13.6)	4 (17.4)	6 (7.6)	
Acneiform exanthema				
Grade 0–1	11 (19.6)	10 (43.5)	21 (26.6)	
Grade 2–4	42 (75.0)	12 (52.2)	54 (68.4)	
Unknown	3 (5.4)	1 (4.3)	4 (5.1)	

mCRC, metastatic colorectal cancer; SCCHN, squamous cell cancer of the head and neck.
[a]Other refers to: four undifferentiated adenoid tumors of the head and neck, three carcinomas of unknown primary (CUP) with adenoid differentiation, two gastric cancers, one of each: adenocarcinoma of the lung, breast cancer, prostate cancer.

were significantly associated with higher overall response rates (ORR) (OR = 1.52; $P = 0.03$). A similar trend was observed for disease control rate but did not reach significance (OR = 1.34; $P = 0.08$). Calcium was not associated with either ORR or disease control rate (Table 4).

On constructing ROC curves for response in mCRC patients, the area under the curve reached 0.625 and the sum of specificity and sensitivity reached its maximum at a decrease of magnesium on day 14 of cetuximab treatment to 95% of the baseline value.

Using this discrimination, patients with lower magnesium levels had a significantly longer progression-free survival (4.6 vs. 2.5 months; log-rank $P = 0.03$; hazard ratio 0.42) and a trend toward long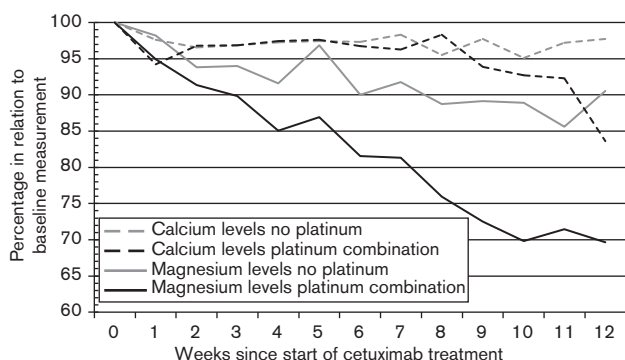er overall survival (20.0 vs. 4.4 months, log-rank $P = 0.12$; hazard ratio 0.45) (Fig. 2). ORR was doubled in patients with lower magnesium levels on day 14, but the difference (33.3 vs. 66.7%) did not reach the level of significance (Fisher's exact $P = 0.053$).

Discussion

Hypomagnesemia has been noted as an adverse event already after the first trials investigating cetuximab [7,14]. Magnesium wasting is supposedly caused by an inhibitory effect of anti-EGFR agents on TRMP6, which is responsible for reabsorption of magnesium in the ascending limp of the loop of Henle [7,9,15]. In most patients, hypomagnesemia remains asymptomatic and does not lead to clinical symptoms such as muscle cramps, fatigue, or general weakness [14]. Therefore,

magnesium serum levels have only been followed in a small fraction of patients participating in clinical trials [1,4,8]. Early changes in magnesium levels have

been described recently as a surrogate parameter for treatment efficacy in the third-line treatment of mCRC [12] with irinotecan and cetuximab. Another study reported a negative prognostic effect when cetuximab was provided as monotherapy [13] in heavily pretreated patients.

Even the present analysis has some limitations because of its retrospective nature and possible selection bias as patients treated for less than 6 weeks were excluded; this indicates a time-dependent, significant decrease in magnesium serum levels in patients treated with cetuximab. Using baseline characteristics for a logistic regression analysis, no risk factor could be established for the decrease in magnesium (Table 2). Risk factors, therefore, may be found in genetic analyses, but to date, no known factor to predict hypomagnesemia has been established from clinical baseline parameters.

Hypocalcemia is a rare event in cetuximab-treated patients [16] and it is unclear whether lower calcium

Fig. 1

Course of calcium and magnesium during cetuximab treatment.

Table 2 Univariate and multivariate logistic regression analysis of baseline factors to predict magnesium decrease on day 14

	OR (univariate) (95% CI)	P	OR (multivariate) (95% CI)	P
Age (continuous) (years)	1.01 (0.99–1.02)	0.30	1.00 (0.99–1.02)	0.68
Sex (female)	1.18 (0.86–1.62)	0.17	1.29 (0.82–2.02)	0.27
SCCHN (mCRC as standard)	1.22 (0.93–1.60)	0.17	1.12 (0.76–1.65)	0.56
Other tumor (mCRC as standard)	0.85 (0.58–1.25)	0.41	0.89 (0.57–1.41)	0.63
Platinum	0.93 (0.70–1.23)	0.60	0.85 (0.58–1.25)	0.42
Creatinine (log) (continuous)	1.09 (0.68–1.75)	0.72	0.60 (0.27–1.31)	0.20
GFR (log) (continuous)	0.44 (0.13–1.47)	0.19	0.31 (0.06–1.64)	0.17
KRAS mutation	1.07 (0.94–1.22)	0.34	1.05 (0.87–1.27)	0.63

CI, confidence interval; GFR, glomerular filtration rate; log, logarithmic values; mCRC, metastatic colorectal cancer; OR, odds ratio; P, logistic regression analysis P; SCCHN, squamous cell cancer of the head and neck.

Table 3 Univariate and multivariate logistic regression analyses of baseline factors to predict calcium decrease on day 14

	OR (univariate) (95% CI)	P	OR (multivariate) (95% CI)	P
Age (continuous) (years)	1.00 (1.00–1.01)	0.29	1.01 (1.00–1.02)	0.12
Sex (female)	1.04 (0.80–1.35)	0.80	1.43 (0.96–1.88)	0.09
SCCHN (mCRC as standard)	1.03 (0.81–1.34)	0.74	0.78 (0.62–1.22)	0.41
Other tumor mCRC as standard)	0.86 (0.63–1.17)	0.33	0.78 (0.57–1.08)	0.14
Platinum	0.97 (0.76–1.24)	0.81	1.02 (0.75–1.37)	0.93
Creatinine (log) (continuous)	0.61 (0.40–0.94)	**0.03**[a]	0.37 (0.19–0.73)	**0.006**[a]
GFR (log) (continuous)	2.66 (0.82–8.62)	0.11	0.85 (0.19–3.90)	0.83
KRAS mutation	1.04 (0.93–1.18)	0.48	1.06 (0.91–1.24)	0.46

CI, confidence interval; log, logarithmic values; mCRC, metastatic colorectal cancer; OR, odds ratio; P, logistic regression analysis P; SCCHN, squamous cell cancer of the head and neck; GFR, glomerular filtration rate.
[a]Statistical significant data are given in bold.

Table 4 Correlation of changes of calcium and magnesium (baseline vs. day 14) with parameters of treatment efficacy

	mCRC (n=38) (95% CI)	P	Database (n=79) (95% CI)	P
ORR				
Magnesium (day 14)	1.52 (1.07–2.15)	**0.03**[a]	1.15 (0.89–1.50)	0.30
Calcium (day 14)	0.95 (0.68–1.32)	0.74	0.88 (0.71–1.11)	0.30
DCR				
Magnesium (day 14)	1.34 (0.98–1.84)	0.08	0.94 (0.74–1.20)	0.64
Calcium (day 14)	0.90 (0.68–1.18)	0.44	0.88 (0.71–1.08)	0.23

CI, confidence interval; DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, overall response rate; P, Fisher's exact test P.
[a]Statistical significant data are given in bold.

Fig. 2
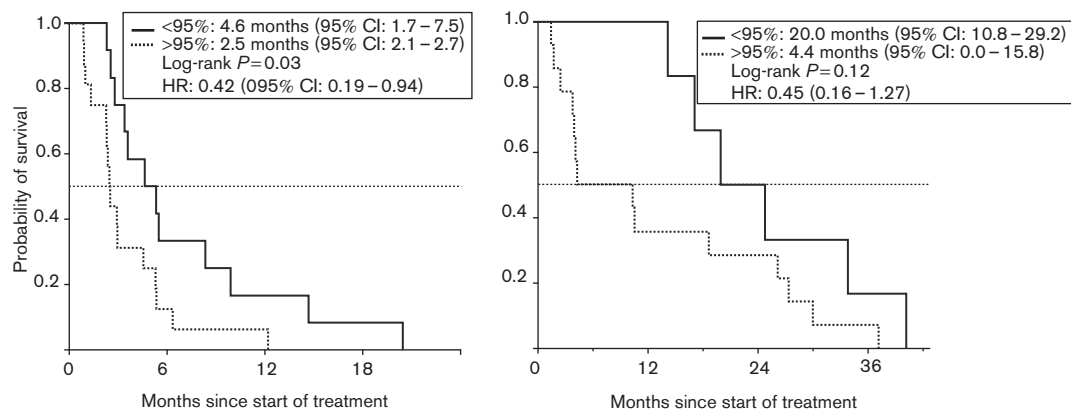
(a) Progression-free survival and (b) overall survival in patients with metastatic colorectal cancer; predictive value of magnesium decrease to day 14. <95%, magnesium serum levels <95% of baseline; >95%, magnesium serum levels >95% of baseline; 95% CI, 95% confidence interval; HR, hazard ratio.

levels are because of changes induced by cetuximab or secondary to changes in the kidney [17]. The phenomenon of hypomagnesemic hypocalcemia is well known [18] and may therefore contribute to the hypocalcemia in cetuximab-treated patients. Hypocalcemia may further be associated with a preexisting impairment of renal function. In univariate and multivariate logistic regression analyses, baseline serum creatinine levels were found to be predictive for hypocalcemia. This indicates that a closer follow-up should be performed of patients with borderline serum creatinine levels for hypocalcemia when treated with cetuximab.

The incidence of grade 3–4 hypomagnesemia in this cohort was 11%, which is somewhat higher than that reported before (3–5%) [7,14]. This may be attributed to the study design as only patients who had received cetuximab for at least 6 weeks were included and because magnesium levels decrease in a time-dependent manner [19]. Hypomagnesemia of any grade could be detected in 49.6% of patients. This rate is higher than that reported by Petrelli *et al.* [8], but it is within the range of another report in which all-grade hypomagnesemia was observed in 56% of patients [16]. The discordant findings may indicate that the lack of routine magnesium determinations is likely to result in an underestimation of the frequency and severity of hypomagnesemia during cetuximab exposure.

The present analysis suggests that patients treated with cetuximab plus platinum derivatives show a faster decrease in magnesium levels that results in markedly lower serum concentrations of magnesium (about 70% of baseline) compared with patients receiving cetuximab with other combinations. This platinum-related difference in the pattern of magnesium kinetics has not been

described before. Previous studies carried out in mCRC comparing oxaliplatin-based regimens with irinotecan-based regimen [20,21] did not compare the frequency or the grade of hypomagnesemia. It may only be speculated that this was in part because of the insignificant effect of hypomagnesemia on clinical symptoms and adverse events.

Recently published analyses recommend routine magnesium measurements for all patients treated with cetuximab [19]. In the present study, it is shown that specifically patients treated with cetuximab plus platinum derivatives should be monitored for clinical symptoms of hypomagnesemia. The reason for the more severe hypomagnesemia in the platinum plus cetuximab-treated cohort may be platinum-induced nephrotoxicity, which is more severe with cisplatin [22], but has also been reported in oxaliplatin-treated patients [23]. If unusual fatigue or muscle weakness or cramps occur and magnesium levels are low, a discontinuation of cetuximab and intravenous magnesium substitution should be considered [7].

As mentioned before, the predictive value of the early decrease in magnesium serum levels is currently under discussion [12,13]. Using ROC analysis, this analysis showed that a decrease in magnesium levels lower than 95% of baseline on day 14 of cetuximab exposure is associated with prolonged survival times in mCRC patients. Although data of Vincenzi *et al.* [12] could be confirmed, the results are in contrast to the report by Vickers *et al.* [13]. This may in part be explained by the different inclusion criteria and regimens used in the studies. In the present analysis, first-line and second-line patients were treated with cetuximab in combination with chemotherapy, which is similar to the more homogeneous group of Vincenzi *et al.* [12], where patients

were treated with irinotecan and cetuximab as the third-line treatment. However, patients in the report by Vickers *et al.* [13] were heavily pretreated and received cetuximab as a monotherapy. Detailed data on patients receiving first-line therapy are still missing. A prospective clinical trial with a closer follow-up of magnesium serum levels to validate the retrospective analyses is clearly required to obtain more information on this issue.

Conclusion

Hypocalcemia is a rare event in cetuximab-treated patients and has no predictive value for efficacy. Patients with impaired renal function as indicated by serum creatinine are more prone to develop hypocalcemia. Therefore, patients with a serum creatinine in the high normal range should be monitored for hypocalcemia when treated with cetuximab. Hypomagnesemia is a common event in cetuximab-treated patients. Data from clinical trials not requiring a close follow-up of magnesium levels probably underestimate the frequency of hypomagnesemia. Because of a greater magnesium waste in patients receiving cetuximab in combination with platinum derivatives, a higher awareness of hypomagnesemia is recommended. If clinical symptoms appear, intravenous magnesium administration and discontinuation of cetuximab are most efficient to restore magnesium levels.

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