Assessment of frequency and severity of hypomagnesemia in patients with metastatic colorectal cancer treated with cetuximab, with a review of the literature

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Abstract. Currently, there are a few systemic treatment options for patients with metastatic colorectal cancer (mCRC). Targeted therapy used in this setting includes the use of monoclonal antibodies, such as cetuximab or panitumumab, directed against epidermal growth factor receptor. The aim of the present study was to estimate the frequency and severity of hypomagnesemia among patients with mCRC treated with cetuximab. The data from the Department of Clinical Oncology, University Hospital of Krakow (Krakow, Poland), concerning 52 patients treated between 2009 and 2013 were collected. Of these, 27 patients fulfilled the inclusion criteria to enter this retrospective study. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 were used to grade the level of hypomagnesemia. In total, 29.6% of all patients experienced hypomagnesemia during treatment, and the majority of cases were grade 1 (22.2%). There was no statistically significant correlation between magnesium (Mg) level and patient age, duration of treatment, localization of primary tumor or metastases, and the number of metastases. However, there was an upward trend in a logistic regression model showing that the risk of developing hypomagnesemia increases with age. Hypomagnesemia is a frequent problem among mCRC patients receiving cetuximab. It is essential to introduce guidelines regarding the monitoring of the Mg level and its supplementation in this group of patients.

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Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein, with an intracellular component that acts as a tyrosine kinase (1). As the EGFR/K-ras pathway is commonly activated in metastatic colorectal cancer (mCRC), it is an attractive target for molecular therapy (1).

CRC is one of the most common malignancies in men and women (2). Cetuximab, a monoclonal antibody (mAb) directed against EGFR, has shown activity in monotherapy and in combination with chemotherapy (chemoimmunotherapy) in various lines of mCRC treatment (3-6). An analysis of Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) phase III and Oxaliplatin and Cetuximab in First-Line Treatment of mCRC (OPUS) phase II randomized clinical trials showed statistically significant improvement in overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) in patients without K-ras mutation receiving cetuximab with first-line chemotherapy (6). The CO.17 trial proved that cetuximab monotherapy administered following progression on chemotherapy lines (oxaliplatin and irinotecan with 5-fluorouracil) also improves OS, PFS and ORR (5). Inhibition of the EGFR/K-ras pathway by cetuximab is connected with numerous side-effects, such as skin toxicity, diarrhea, hypomagnesemia and other dyselectrolytemias or infusion reactions (1,7). A previous study by our group (7) analyzed skin toxicity associated with cetuximab-based therapy; acne-like rash was observed at a frequency of 80% and paronychia at 20%.

Hypomagnesemia may be a result of insufficient magnesium (Mg) supplementation in the diet, hormonal imbalance, antibiotic usage or alcoholism (8,9). The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 are used to grade levels of hypomagnesemia (Table I) (10). The most common symptom of hypomagnesemia is weakness. There are also other problems, including irritability, arrhythmias or metabolic and neuromuscular disorders, which may be revealed in the case

of higher grades of this dyselectrolytemia (8,9). However, the incidence and severity of hypomagnesemia were not assessed in the aforementioned clinical trials.

Cells building the renal tubule are characterized by a high level of EGFR expression. The mechanism of Mg wasting during treatment with cetuximab is associated with the blockage of EGFR-dependent transient receptor potential channel 6 (TRPM6) in the nephron (Fig. 1) (11,12). The blockage of this pathway results in insufficient activation of the TRPM6 epithelial ion channel and Mg wasting (11,12). The process takes place mainly in the distal convoluted tube of the nephron, where the expression of TRPM6 is the greatest (Fig. 2). The other suggested mechanism is via indirect tubular nephrotoxicity (13). The fact that after cessation of therapy with cetuximab the Mg concentration in the plasma returns to normal suggests the reversibility of this process (12,14).

The reason for the present study was to estimate the frequency and severity of hypomagnesemia among patients with mCRC treated with cetuximab. The study also aimed to measure the extent of serum Mg assessment in this group of patients.

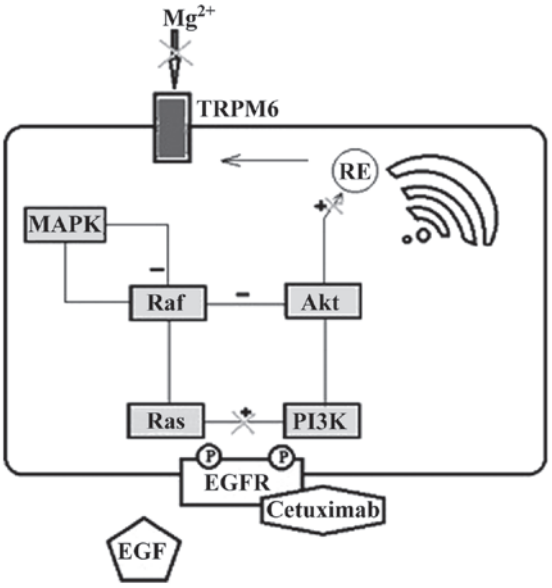

Figure 1. Mechanism of magnesium (Mg) wasting during treatment with cetuximab, associated with the blockage of epidermal growth factor receptor (EGFR)-dependent transient receptor potential channel 6 (TRPM6). Cetuximab blocks EGFR. As a consequence, Ras and mitogen-activated protein kinase (MAPK) signaling pathways are not active and cannot affect TRPM6, which is responsible for magnesium reabsorption in the apical membranes of the cells of the distal convoluted tube. P, phosphorylated tyrosine kinase; PI3K, phosphoinositide 3-kinase; RE, endoplasmatic reticulum.

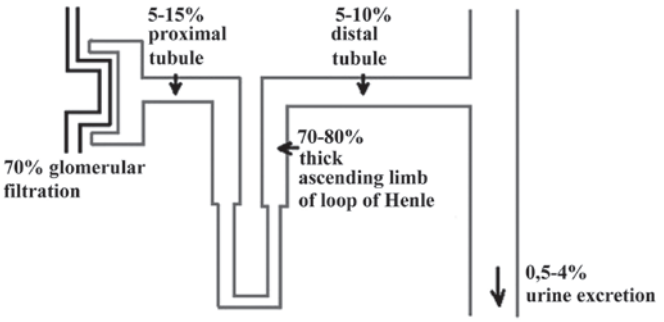

Figure 2. Magnesium reabsorption in the nephron.

Patients and methods

Patients. Between October 2009 and June 2013, a retrospective analysis of the records of 52 patients from the Department of Clinical Oncology, University Hospital, Jagiellonian University Medical College (Kraków, Poland) was performed. The inclusion criteria for the study were as follows: An age of ≥18 years, a diagnosis of CRC confirmed by an available histopathological report, no *K-ras* mutation, presence of metastases on diagnostic imaging (magnetic resonance imaging, computed tomography, positron emission tomography or bone scintigraphy), and receipt of at least 2 doses of cetuximab. The exclusion criteria included: Concurrent malignancies (also in the past), malabsorption or genetic Mg wasting syndromes, a history of hypomagnesemia prior to the treatment, alcoholism, diarrhea (grade 3 or greater according to CTCAE v.4.0) during the 2 months prior to the start of treatment and while on the treatment with cetuximab, concurrent administration of diuretics (thiazide, loop diuretics), and a lack of consent to participate in the study.

The analyzed factors included: Sociodemographic data, localization of the primary tumor and metastases, clinical staging according to the 7th edition of Tumor-Node-Metastasis system (15), type of treatment received (including line of systemic treatment), reason for therapy ending, the presence of hypomagnesemia associated with cetuximab therapy and its intensity. Hypomagnesemia was classified according to the CTCAE v.4.0 (Table I) (10).

Statistical analysis. Statistical evaluation was conducted using computer software Statistica 11.0 PL (StatSoft Poland, Krakow, Poland). Descriptive statistics are used in the form of percentage distribution, range or mean ± standard deviation. When comparing the quantitative variables, Student's t-test was applied; if there was absence of a normal distribution of factors, the Mann-Whitney U test was used. To check the association between quantitative variables, Spearman' test was conducted and the χ^2 test was applied when comparing qualitative variables. Factors potentially associated with the risk of developing hypomagnesemia were also assessed using logistic regression analysis. $P<0.05$ was used to indicate a statistically significant difference.

Ethical approval. The present study was approved by the Jagiellonian University Medical College Ethical Committee (registry number, *KB/254/B/2011*). The data was collected and analyzed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki with its amendments.

Literature search. A literature search of the MEDLINE database (between January 2005 and May 2014; http://www.ncbi.nlm.nih.gov/pubmedhealth/; accessed 1st June 2014) and UpToDate (http://www.uptodate.com/; accessed 1st June 2014) was performed to find an association between treatment with cetuximab and hypomagnesemia. The key words 'anti-EGFR', 'cetuximab', 'hypomagnesemia', 'magnesium', 'metastases',

Table I. Grades of hypomagnesemia according to common terminology criteria for adverse events v.4.0.

Grade	Hypomagnesemia
1	<LLN-1.2 mg/dl, <LLN-0.5 mmol/l
2	<1.2-0.9 mg/dl, <0.5-0.4 mmol/l
3	<0.9-0.7 mg/dl, <0.4-0.3 mmol/l
4	<0.7 mg/dl, <0.3 mmol/l, life-threatening consequences
5	Mortality

LLN, lower limit of normal.

'colorectal cancer', 'colon cancer', 'monoclonal antibody' and 'TRPM6' were used in various combinations.

Results

Of the 52 patients analyzed, 27 patients who fulfilled all the inclusion criteria and none of the exclusion criteria were enrolled into the study. In the excluded cases, 21 lacked a serum Mg level assessment, and the remainder developed grade 3 diarrhea or an anaphylactic reaction.

Table II shows the baseline characteristics of the study population, which was composed of 7 females and 20 males, with a median (± standard deviation) age of 55.0±11.6 years. Cetuximab was administered as a palliative regiment at a standard dose of 400 mg/m^2 as a first dose and at 250 mg/m^2 in each subsequent dose regardless of whether it was administered as monotherapy or in combination with standard chemotherapy. Chemotherapy regimens were based on irinotecan, oxaliplatin or capecytabine alone. The main reason for treatment termination in the patients treated with monotherapy or immunochemotherapy was progression of the disease (92.6%). The median duration of treatment with cetuximab was 98 days (range, 15-546).

In 29.6% of all patients randomly assessed (more than once), the Mg level indicated hypomagnesemia. The majority of cases (22.2%) were grade 1 according to CTCAE v.4.0, while 1 patient of grade 2 and 1 patient of grade 3 was revealed.

There was no statistically significant correlation between the presence of hypomagnesemia (none vs. any) or the grade of hypomagnesemia and patient age (≥55 vs. <55 years; P=0.1 and P=0.1, respectively), duration of treatment (P=0.9 and P=0.3, respectively), type of treatment (monotherapy vs. in combination with chemotherapy; P=0.3 and P=0.6, respectively), line of systemic treatment (P=0.3 and P=0.2, respectively), localization of primary tumor (rectum vs. colon; P=0.6 and P=0.6, respectively) or metastases (liver vs. other localizations; P=0.3 and P=0.3, respectively), and number of metastases (1 vs. >1; P=0.6 and P=0.9, respectively). There was an upward trend in a logistic regression model showing that the risk of developing hypomagnesemia increases with age (odds ratio, 1.10; 95% confidence interval, 0.97-1.25). However, the trend did not reach statistical significance (P=0.1).

None of the patients had the treatment discontinued due to the hypomagnesemia.

Table II. Baseline characteristics of the studied population.

Parameter	Value
Age, years	
Median	55.0
Range	27-72
Gender, n (%)	
Women	7 (25.9)
Men	20 (74.1)
Primary tumor localization, n (%)	
Rectum	13 (48.1)
Colon	14 (51.9)
No. of organs involved with metastases, n (%)	
1	21 (77.8)
>1	6 (22.2)
Location of metastases[a], n (%)	
Liver	18 (66.7)
Other	14 (51.9)
Cetuximab treatment line, n (%)	
1	9 (33.3)
>1	18 (66.7)
Type of therapy, n (%)	
Monotherapy	4 (14.8)
Chemoimmunotherapy	23 (85.2)
Reason for treatment ending, n (%)	
Cancer progression	25 (92.6)
Side-effects	0 (0.0)
Decision of a physician	1 (3.7)
Lack of data	1 (3.7)

[a]In 11 cases patients had more than one site of metastatic disease.

Discussion

Targeted therapy with mAbs has become a widely used treatment option for cancer patients. In comparison with standard chemotherapy, targeted drugs show lower risk of severe systemic adverse effects. First suggestions with regard to the requirement for Mg measurement and supplementation appeared in 2005 (16). The summary of product characteristics produced for Erbitux (cetuximab) estimates the frequency of hypomagnesemia in >10% of patients treated with the drug (17). Table III (17-29) shows the results of other studies regarding hypomagnesemia as a side-effect of cetuximab. In the available results of retrospective studies, the percentage of patients with any grade of hypomagnesemia varied from 6.3-93.3% with grade 3/4 in 0 to 27% (16,25-30). One of the first studies of this dyselectrolytemia associated with cetuximab by Fakih *et al* (14) showed a high incidence of grade 3 and 4 compared with later studies (27%). This may be due to the fact that only patients with both baseline Mg level and level assessed during the treatment were included. As checking the serum Mg concentration was not mandatory at the time of this study, it may be hypothesized that patients with baseline

Table III. Literature data on hypomagnesemia as a side-effect of cetuximab compared with the results of the present study.

First author/s (ref.)	Year	Type of cancer	Hypomagnesemia, %					No. of patients enrolled	Type of study
			G1	G2	G3	G4	Any grade		
Present study	2014	Colorectal	22.2	3.7	3.7	0.0	29.6	27	Retrospective
Chen *et al* (18)	2013	Colorectal	No data		2.9		25.8[a]	2769	Meta-analysis
Cao *et al* (19)	2010	Colorectal, head and neck, non small-cell lung, liver, ovarian, esophageal, gastric	No data		5.6		36.7[b]	3006	Meta-analysis
Price *et al* (20)	2014	Colorectal	15.1		2.0	0.6	17.7	503	Prospective
Lordick (21)	2013	Gastric	19		7	3	29	446	Prospective
Vickers (22)	2013	Colorectal	20.6	2.8	0.9	0.5	24.8	218	Prospective
Weickhardt *et al* (23)	2012	Colorectal	20		18		38	50	Prospective
Vincenzi *et al* (24)	2008	Colorectal	4.4	0.0	0.0	0.0	4.4	68	Prospective
Tejpar *et al* (12)[c]	2007	Colorectal	35	13	3	3	54	98	Prospective
Do Pazo-Oubiña *et al* (25)[d]	2013	Colorectal	31.3	0.0	12.5	0.0	43.8	16	Retrospective
Demizu *et al* (26)[e]	2013	No data	73.3	13.3	6.7	0.0	93.3	15	Retrospective
Melichar *et al* (27)	2012	Colorectal	No data		6	4	56	51	Retrospective
Vincenzi *et al* (28)	2011	Colorectal	5.6	0.7	0.0	0.0	6.3	143	Retrospective
Maliaka and Ledford (29)	2010	Head and neck, colorectal	48	5	2		55	58	Retrospective
Fakih *et al* (30)	2006	Colorectal	No data	8	8	19	No data	48	Retrospective
Schrag *et al* (15)	2005	Colorectal	No data		11.8	2.9	No data	34	Retrospective

[a]Analysis of 1,227 patients' results. [b]Analysis of 1,274 patients' results (availability of data). [c]Study of the effects of cetuximab, matuzumab and panitumumab. [d]Subgroup of patients enrolled in the study treated for CRC. [e]Only abstract available in English.

levels were those more prone to suffer from hypomagnesemia due to other causes or had dyselectrolytemia found in past laboratory tests. The same inclusion criteria were introduced in a study by do Pazo-Oubiña *et al*, however, in this study the incidence was higher for grade 1 and 3, with no patient suffering from grade 4 (25). To omit this potential bias, in the present study, the enrollment of patients without baseline Mg level (but without hypomagnesemia in the history) was also decided upon. Taking into consideration only a sub-group with baseline assessment, the incidence in the present study was slightly higher, but did not reach the levels shown in the two aforementioned studies (data not shown).

Notably, prospective studies also showed significant discrepancies in the assessment of hypomagnesemia incidence, with any grade found in 4.4 to 54% of patients (12,20-24). Even when not taking into consideration the study by Tejpar *et al*, which checked the effects of cetuximab, matuzumab and panitumumab, the differences are significant (4.4 to 38%). The present data are the closest to those obtained by Vickers *et al* (22). Building on their research and conclusions, the huge differences in results [for example when compared with the studies by Vincenzi *et al* (24,28)] may be associated with different baseline serum Mg concentrations or applied types of concomitant and past systemic treatments.

Vickers *et al* (22) performed a sub-group analysis, which found hypomagnesemia to be more commonly presented in patients without K-ras mutation (19 vs. 27%; the difference was not statistically assessed for the significance).

Looking at the two meta-analyses found in the literature search, any grade of hypomagnesemia was observed in 25.8 and 36.7% of patients, and grade 3/4 in 2.9 and 5.6% of patients, respectively (18,19). These results are consistent with the present study observations. Grades 1 and 2 were estimated in none of these meta-analyses (18,19). According to Chen *et al* (18), patients with mCRC have a higher incidence of hypomagnesemia grade 3/4 than patients with other malignancies. Comparing their results obtained for patients with mCRC with an earlier meta-analysis performed by Cao *et al* (19) on a group of patients with various malignancies it can be noted that this incidence was actually higher in the latter study. Additionally, a retrospective study by Maliakal and Ledford that also enrolled patients with head and neck cancer had one of the highest percentages of patients with hypomagnesemia. Table III presents only a sub-group of patients from the study by do Pazo-Oubiña *et al* (mCRC treated with cetuximab) (25). In this study, patients with head and neck carcinoma were also enrolled, and it was concluded that overall hypomagnesemia was less common in mCRC patients than head and neck cancer patients (43.8 vs. 72.2%).

In the present study, no grade 4 hypomagnesemia was observed, which is generally consistent with the majority of other studies where this metabolic complication was a rare event at grade 4. Only one study estimated the level of grade 3/4 hypomagnesemia at 27% (30). Thus, it may be assumed that Mg depletion is a common, but not life-threatening complication in the population of patients treated with EGFR-targeting mAbs. Also, certain other studies indicated that there was no requirement for therapy termination (or reduction) due to hypomagnesemia caused by cetuximab (12). However, it has also been indicated that this metabolic side-effect may influence treatment in severely affected individuals (12).

The main reason for Mg wasting is the blockage of EGFR-dependent TRPM6 in the nephron resulting in impaired renal reabsorption (12,22). There are also suggestions that blocking EGFR by cetuximab may affect the absorption of Mg in the gut (12,16), or that the tubular damage in the kidneys is caused by mAb precipitation (14). Few factors that may predispose to the development and severity of hypomagnesemia during the treatment with cetuximab are taken into consideration. Certain studies propose that concurrent chemotherapy with platinum agents is indicated, as these affect Mg level most significantly (31). Also, the time factor appears to play an important role (30,31). Results of one study showed an increase in hypomagnesemia incidence proportional to the duration of the treatment (30). No such association was observed in the present study.

Tejpar *et al* found an association between an older patient age and Mg wasting (12). This trend was also observed in the present study, although it was not statistically significant. The connection appears to be logical, as ageing is also connected with other conditions leading to Mg loss, such as glomerulosclerosis or deterioration in renal function (32). Notably, higher baseline level may be connected with more prompt Mg reduction (12,22).

Hypomagnesemia resulting from EGFR blockage may be a class effect for all mAbs directed against this receptor. Exact differences between mAbs have not yet been assessed (12).

There are no reliable and precise recommendations concerning Mg measurement and supplementation in patients with mCRC receiving anti-EGFR mAbs. The Erbitux summary of product characteristics claims only that the assessment of serum Mg level (and that of other electrolytes) prior to and periodically during the treatment with cetuximab and, as appropriate, supplementation of electrolytes is recommended (17). Additionally, studies have made suggestions that regular Mg screening should be performed, particularly in patients treated simultaneously with platinum-based agents (25,31). The suggested interval for serum Mg measurement is 4-8 weeks plus the baseline level (25).

As there are no particular recommendations for Mg replacement in this particular group of patients, it appears reasonable to follow general guidelines for Mg supplementation (9). Certain cancer centers have created their own treatment guidelines (26,30). Fakih *et al* (30) administered intravenous Mg sulfate daily or 3 times/week, at 6-10 g per dose, in patients with grade 3 and 4 hypomagnesemia. Also Tejpar *et al* (12) performed daily intravenous Mg supplementation in severely affected individuals. It is notable that oral Mg supplementation in cancer patients may be ineffective due to diarrhea or malabsorption (12,30). Results of the study comparing oral low- and high-dose Mg supplementation in this group of patients are expected to be published (12).

Due to its retrospective character and small population size, the present study is characterized by certain limitations. Data regarding sociodemographic status, as well as information on the treatment and disease were gathered from medical records. Sporadically, the information was incomplete. Only half the patients (27/52; 51.9%) entered the study. The reason

for this was mainly as there was no information on Mg level due to the lack of recommendations suggesting regular Mg measurement. However, previously described studies on cetuximab efficacy have also not carefully assessed the frequency of hypomagnesemia (3-6). In a study performed by Schrag *et al,* only 22.1% of patients (34 patients) entered the retrospective studies assessing Mg level (16,25), while in a recently published study by do Pazo-Oubiña *et al,* 33.8% of patients (68 patients) received mAb anti-EGFR. Currently, all patients in the Department of Clinical Oncology, University Hospital of Krakow, undergo regular Mg level assessment once every 4 weeks, and in the case of any abnormalities, every 2 weeks (prior to every cetuximab infusion), or more often if required.

It would also be interesting to observe the frequency and intensity of Mg decrease from its baseline level prior to the treatment; however, these data were not present in all patient records. One study on 98 patients with mCRC revealed a decrease in serum Mg concentration in 97% of patients during the treatment with mAbs directed against EGFR (12).

Published data on the effect of Mg level on tumor growth are inconclusive (33). There are studies claiming that early hypomagnesemia may work as an inexpensive positive predictive factor for the treatment with cetuximab (24,28). This connection has already been described for the skin-related toxicity caused by this mAb (7). One study has suggested that hypomagnesemia may function in decreasing the proliferation of cells (33). However, other recently published studies suggest an opposite association and a decrease in OS time in patients with hypomagnesemia (22). Vickers *et al* (22) hypothesized that the predictive meaning of hypomagnesemia may be associated with the severity of this side-effect, with lower levels being associated with better treatment outcome and higher levels with worse treatment outcome. However, due to the limited number of patients and a variety of treatment lines, it was not possible to perform statistical analysis of the possible correlations between protocol type/response to the treatment and hypomagnesemia occurrence or grading.

Finally, it should be noted that the prevalence of hypomagnesemia in the healthy population has been estimated as between 2.5 and 15%. A review by Saif suggested an even higher prevalence among cancer patients due to higher urinary and gastrointestinal loss (e.g., diarrhea), malnutrition and poor dietary intake (9). Patients with neoplastic diseases also commonly present with weakness/fatigue, which is the most common symptom of mild hypomagnesemia. It would be extremely difficult to estimate the frequency of this side-effect of cetuximab in a retrospective study, and of other symptoms, such as irritability. For this reason, similar to certain other studies (12), it was decided against collecting data on hypomagnesemia symptoms in the present study.

The results shown in this study and previously published records regarding skin-related toxicity (7) demonstrate that cetuximab-related side-effects present their specific characteristics regardless of whether the drug is used as a monotherapy or in combination with standard chemotherapy. It is essential to know the main symptoms of hypomagnesemia in order to ensure the safety of treatment with cetuximab. Physicians should focus on actively searching for hypomagnesemia and other typical adverse effects in this group of patients. The data regarding this side-effect remain limited, with the hypomagnesemia incidence being assessed at between 4.4 to 93.3%, depending on the study. These metabolic complications are not usually life-threatening, nor do they lead to treatment termination, but require monitoring and treatment. As the extent of Mg monitoring in patients treated with mAbs directed against EGFR is insufficient, it is reasonable to introduce recommendations concerning Mg measurement and supplementation in this population. Physicians should remember that hypomagnesemia may be revealed as a side-effect of cancer treatment, not only as a result of diarrhea or malabsorption.

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