Magnesium in Head and Neck Cancer

Is it a possible Biomarker for Tumor Treatment?

Oliver Micke
Department of Radiotherapy and Radiation Oncology
Franziskus Hospital
Bielefeld, Germany
strahlenklinik@web.de

Ralph Mücke
Department of Radiotherapy
Lippe Hospital
Lemgo, Germany
Ralph.Muecke@klinikum-lippe.de

Klaus Kisters
Department of Internal Medicine
St. Anna Hospital
Herne, Germany
kisters@annahospital.de

Jens Büntzel
Department of Otolaryngology
Südharz Hospital
Nordhausen, Germany
jens.buentzel@shk-ndh.de

Abstract—We investigated the hypothesis that patients with advanced head and neck cancer exhibit a decreased serum concentration of magnesium compared to the normal population. In July 2013 we measured the magnesium serum concentration of 18 patients with squamous cell carcinoma of the head and neck region. The control group consisted of 17 patients received tonsillectomy during the same period. Overall 14/18 patients with cancer have had Magnesium serum concentrations < 0.80 mmol/l (78%). The control group showed only two patients (12%) with serum levels below the cut off. This small controlled study supports the hypothesis that decreased Magnesium serum concentrations are typical for patients with advanced head and neck cancer. We could not show, that hypomagnesaemia is prognostic biomarker in head and neck cancer treatment.

Index Terms—Magnesium, head and neck cancer, hypomagnesaemia, cetuximab, chemotherapy, biomarker

I. Introduction

Several clinical studies suggested that patients with advanced head and neck cancer exhibit a decreased serum concentration of magnesium compared to the normal population [1, 2, 3, 4, 5], and it may be interesting because hypomagnesaemia is discussed as an independent prognostic factor regarding the effectivity of antibody treatment with the epidermal growth factor receptor (EGFR) antibody cetuximab [3, 4, 5, 6].

It seems to interact with the transient receptor potential cation channel TRPM6 an causes in the majority of patients a clinical hypomagnesaemia and in up to 10% to 36% of cases a severe Grad III/IV hypomagnesaemias [4, 5, 6]. Thereby, interestingly it appeared that there is a significant positive correlation between hypomagnesaemia and clinical response to the antibody therapy as well was to a significantly better survival [4, 5, 6]. The underlying mechanism is nearly unknown, but it may be similar factors, as we postulated in hypomagnesaemia and radiotherapy, for example the inhibition of DNA repair in tumor cells [6].

II. Material and Methods

We investigated the hypothesis that patients with advanced head and neck cancer exhibit a decreased serum concentration of magnesium compared to the normal population.

In July 2013 we measured the magnesium serum concentration of 18 patients with squamous cell carcinoma of the head and neck region. The control group consisted of 17 patients received tonsillectomy during the same period. Table 1 summarizes the biometric data of both groups. Table 2 shows the important clinical key points of the tumor patients (localization, status, stage). It is possible to compare both groups because the age is the only imbalance and has no relevant impact on the serum concentration. All patients of the control group were without any serious secondary diseases. They had tonsillitis as their main diagnosis. The patients of the tumor group suffered from cancer for at least 4 month.

TABLE 1 BIOMETRIC DATA OF PATIENTS

	Tumor patients	Tonsillectomy patients
Total number	18	17
Male	13	10
Female	5	7
Median age (range)	62.5 (47-72)	36.5 (7-80)

IJRS

TABLE 2 KEY DATA OF TUMOUR PATIENTS

	total n=19	remarks
tumor localization		squamous cell carcinomas
- oropharynx	6	
- larynx	6	
- salivary glands	2	
- mouth	2	
- esophagus	1	
- hypopharynx	1	
tumor status		
- active tumor tissue	13	
- tumor-free	5	
tumor stage		
- stadium I	0	
- stadium II	2	glottic carcinomas
- stadium III	0	
- stadium IV	16	

III. RESULTS

Overall 14/18 patients with cancer have had Magnesium serum concentrations < 0.80 mmol/l (78%). The control group showed only two patients (12%) with serum levels below the cut off. The mean serum concentration was 0.78 mmol/l in the tumor group.

The control group had a mean value of 0.86 mmol/l. The Student's t-test documents a significant difference (p=0.003, 2 sided, different variance).

This small controlled study supports the hypothesis that decreased Magnesium serum concentrations are typical for patients with advanced head and neck cancer [1]. 5/18 patients have received Cetuximab.

Table 3 concluded the case histories of these patients.

IV. DISCUSSION

The part of patients with decreased serum Magnesium is too high that it is not possible to use hypomagnesaemia as a biomarker of the effectivity of cetuximab [1].

Furthermore, hypomagnesaemia is typical and our patients start with this characteristic symptom into the antibody therapy for recurrent or residual head and neck cancer.

In particular, in oncological therapies negatively influencing renal function, as cisplatinum, severe hypomagnesaemias can occur, as shown by own studies, which often requiring treatment [3]. A new aspect arose from the introduction of the epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab in the oncological therapy, particularly in colorectal cancers [3]. These lead by an interaction with the transient receptor potential cation channel TRPM6 [2, 5] in the majority of patients to a clinical significant hypomagnesaemia and in up to 10% to 36% of cases to severe Grad III/IV hypomagnesaemias. Thereby, interestingly it appeared that there is a significant positive correlation between hypomagnesaemia and clinical response to the antibody therapy as well was to a significantly better survival. Unfortunately a recent randomized study by Vickers et al. (2013) did not confirm these results and underlined the disadvantageous effects of hypomagnesaemia.

The underlying pathophysiological mechanisms are nearly unknown, but maybe similar factors, as we postulated in hypomagnesaemia and radiotherapy [7], for example the inhibition of DNA repair in tumor cells. If this phenomenon also appears in others types of EGFR-inhibition, e.g. in targeted therapy with tyrosinkinase inhibitors, can be postulated, but is not well examined yet [2].

Clearly, the transient receptor potential cation channel TRPM6 and TRMP7 plays a key role in magnesium metabolism. The TRPM7 channel appears to be a main actor in the process of tumor growth and development by affecting proliferation, migration and metastasis mediating the role of magnesium in this process [6, 7]. This may also lead to several potential diagnostic and therapeutic implications [6, 7]. Figure 1 delineates the interdigitation of magnesium deficiency and tumorigenesis.

Overall, on the background of the above mentioned findings the substitution of magnesium deficiency is still and newly recommended.

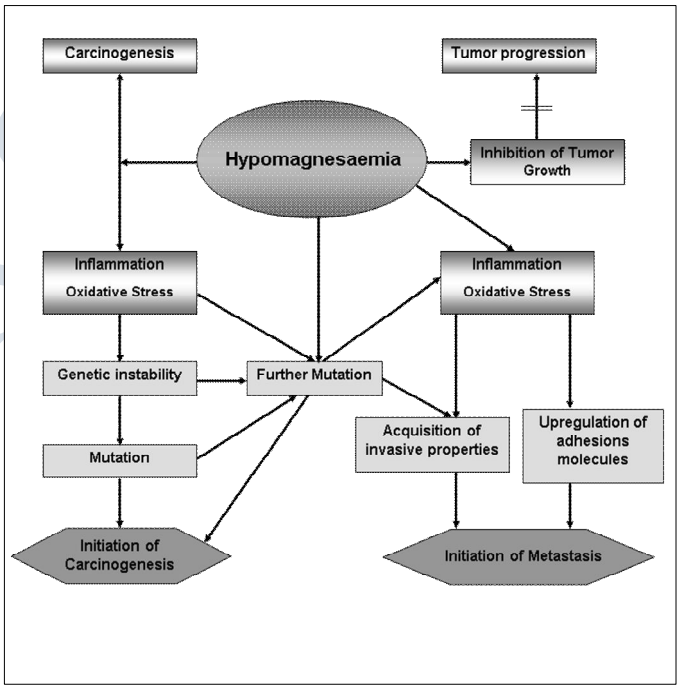


Fig. 1. Magnesium deficiency and cancer

V. CONCLUSION

Hypomagnesaemia is a typical phenomenon in head and neck cancer patients. This study supports the hypothesis that decreased magnesium serum concentrations are typical for patients with advanced head and neck cancer, but we could not show, that hypomagnesaemia is prognostic biomarker in head and neck cancer treatment.

In the light of the recent study data, magnesium remains an ion of high interest for oncology, whose different facets should be more and more enlightened.

REFERENCES

[1] J. Büntzel, M. Glatzel, R. Hunger, R. Mücke, K. Kisters, and O. Micke, "Magnesium in patients with head and neck cancer," Trace Elem. Electrolytes, vol. 30, p 78, 2013.

[2] D. H. Liebscher and U. Liebscher, "Personalized medicine and magnesium deficiency," Trace Elem. Electrolytes, vol. 30, p 81, 2013.

[3] O. Micke, J. Büntzel, R. Mücke, M. Glatzel, U. Schäfer, R, Hunger, K. Kisters, "Trace Elements and water in Grisons," Trace Elem. Electrolytes, vol. 28, pp 178-180, 2011.

[4] B. Vincenzi, S. Galluzzo, D Santini, L Rocci, F. Loupakis, P. Correale, 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., vol. 22, pp 1141-1146, 2011.

[5] O. Micke, J. Büntzel, R. Hunger, R. Mücke, K. Kisters, "Magnesium in oncology: New aspects of a forgotten cation," Trace Elem. Electrolytes, vol. 30, p 80, 2013.

[6] F. I, Wolf, V. Trapani, A. Cittadini, J. A. Maier, "Hypomagnesaemia in oncologic patients: to treat or not to treat?" Magnes. Res., vol. 22, pp 5-9, 2009.

IJRS