Dear Editor,

We recently read with great interest the notable contribution of Wolf et al. [1] and thank the authors for sharing their exciting ideas on hypomagnesae mia in cancer patients with us. Magnesium, the forgotten cation [2], seems get an emerging impact in oncology. But, actually this happens not through its presence, even more by its absence.

Magnesium, the second most abundant intracellular cation of the human body, is an essential cofactor in all biological systems involving bioenergetics, but in clinical medicine, in particular oncological sciences, it seems to be neglected [3, 4].

Hypomagnesemia in oncology is frequently observed after the application tubolotoxic substances, like antineoplastic treatment with cisplatinum [5]. Nephrotoxicity of cisplatin may result in increased magnesium excretion, even before renal function becomes affected [6]. The anticancer activity of cisplatinum has been also linked to its effects on mitochondrial magnesium and to nucleic acid magnesium. Since tumor growth has been enhanced by supplementation with magnesium, preventing or correcting the induced magnesium depletion, it was anticipated that magnesium administration to cancer patients under treatment might diminish the efficacy of the antineoplastic regimen. However, clinical experience has obviated that apprehension: Magnesium supplementation accompanying cisplatinum treatment has not affected tumor growth rates in cancer patients [7].

New aspects of hypomagnesemia resulted from the introduction of the epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer [8]. Surprisingly, both antibodies can cause a significant hypomagnesaemia in about one third of treated patients by an unexpected interaction with the transient receptor potential melastatin TRPM6 [9-11]. More surprisingly, this therapy-associated hypomagnesemia is related to significant better treatment response and progression free and overall survival. This effect was even more pronounced than the development of a severe acne-like skin rash, which is a well-known surrogate parameter for treatment response [12].

As one can clearly see in the contribution of Wolf et al. [1] these results are difficult to interpret: On one hand this phenomenon may only be a surrogate parameter for any kind of sufficient expression of EGFR, like the well described acne-like skin rash, on the other hand it could be an independent prognostic factor and the treatment-induced magnesium deficiency itself will directly contribute to the tumortoxic effect of the EGFR antibodies [10]. As we know from literature magnesium is needed for cancer development, tumor growth and dissemination as well as in different processes involved in DNA repair and regeneration [13, 14]. Hence, hypomagnesaemia generally might amplify the effect of DNA damaging cancer treatments and thereby be a chemo- and radiosensitizer. Therefore, as we postulated before [15], hypomagnesaemia would also be useful in radiotherapy, because the primary tumor effect of irradiation is mediated by the lower ability of tumor cells to repair the so called sublethal DNA damage, hypomagnesemia may increase the therapeutic ratio by inhibiting DNA repair. Therefore, we need more

Oliver Micke1, Robert Hunger2, Jens Büntzel3, Ralph Mücke4, Klaus Kisters5
1 Franziskus Hospital, Department of Radiotherapy and Radiation Oncology, Bielefeld, Germany; 2 Lürlibadstr. 80, Chur, Switzerland; 3 Südharrz Hospital, Department of Otolaryngology, Nordhausen, Germany; 4 Lippe Hospital, Department of Radiotherapy, Lemgo, Germany; 5 St. Anna Hospital, Department of Internal Medicine, Herne, Germany

Correspondence: Dr O. Micke, Klinik für Strahlentherapie und Radioonkologie, Franziskus Hospital, Kiskerstraße 26, 33615 Bielefeld, Germany
<strahlenklinik@web.de>
preclinical and clinical studies to better understand potential underlying mechanism and to evaluate whether the described positive effects of hypomagnesaemia also occurs under other magnesium deficiency inducing agents, like cisplatinum [16].

We must know, whether we should substitute this treatment induced magnesium deficiency in tumor patients, and we may go that far to hypothesize, that inducing hypomagnesaemia, e.g. with diuretics etc., may support the tumor toxic effect of various forms of anticancer treatment. On the other hand we clearly agree with Wolf et al. [1, 17], that low magnesium levels bear several risks for human health, like the well described immuno-inflammatory response, which can clearly counteract the postulated positive effects of hypomagnesaemia [17].

Altogether, these results show that magnesium is a fascinating ion, which is embedded in complex oncological interactions and causes positive or negative results, depending on the special clinical context and high or low serum levels [17]. In any case, these results should prompt us to revisit our understanding of magnesium substitution in tumor patients. When is it necessary, and useful and when should it avoided?

References

14. Cameron IL, Smith NK. Cellular concentration of magnesium and other ions in relation to protein synthesis, cell proliferation and cancer. Magnesium 1989; 8: 31-44.