Hypomagnesaemia in oncologic patients: to treat or not to treat?

Federica I. Wolf¹, Valentina Trapani¹, Achille Cittadini¹, Jeanette A.M. Maier²

¹ Università Cattolica del Sacro Cuore, Istituto di Patologia Generale e Centro di Ricerche Oncologiche Giovanni XXIII, Facoltà di Medicina "A. Gemelli", Roma; ² Università di Milano, Dipartimento di Scienze Precliniche LITA Vialba, Milano, Italy

Correspondence: F.I. Wolf, Università Cattolica del Sacro Cuore, Istituto di Patologia Generale e Centro di Ricerche Oncologiche Giovanni XXIII, Facoltà di Medicina "A. Gemelli", Largo Francesco Vito 1, 00168 Roma, Italy
<fwolf@rm.unicatt.it>

Abstract. Over recent decades there have been several papers that documented hypomagnesaemia*, in cancer patients treated, with cisplatin, with combined chemotherapy and more recently, with cetuximab an antibody against the epidermal growth factor receptor. Recently, however, the clinical read-out of cetuximab-induced hypomagnesaemia has received different interpretations. Some reports called the readers’ attention to the importance of magnesium supplementation in relieving patient’s discomfort or preventing the most severe complications of hypomagnesaemia. Other reports claimed that magnesium deficiency could contribute to the oncologic efficacy of cetuximab. This latter interpretation implies that the decision on magnesium supplementation should consider the pros and cons of returning magnesium to normal levels. Given that decreased magnesium availability inhibits cell proliferation, hypomagnesaemia may slow down tumor growth. Unfortunately, one view does not fit all. We think it important to recapitulate our knowledge on the effects of magnesium on tumor growth, angiogenesis, invasion and metastatization with the aim of providing clinical oncologists with an overview of available data of the potential effects of hypomagnesaemia in tumor growth. Translating these results into clinical settings may help in designing suitable studies to better evaluate the consequences of hypomagnesaemia in cancer patients.

Key words: angiogenesis, cetuximab, chemotherapy, cisplatin, metastasis, tumor growth

Clinical data

In principle, magnesium availability can affect many steps of carcinogenesis and tumor development [1, 2]; in practice, deranged serum magnesium levels may appear during anti-tumor chemotherapy. One of the first available reports on the observation of severe hypomagnesaemia in cancer patients dates from the 1980s. Occasionally, cancer patients treated with high dose or prolonged doses of cisplatin-based chemotherapy developed severe symptomatic hypomagnesaemia [3]. The nephrotoxic effect of cisplatin, leading to renal magnesium wasting, has been well known since that time [4, 5]. In the following years other randomised studies and reviews of the literature investigated the problem of cisplatin-induced hypomagnesaemia [6-9]. Studies of patients treated with cisplatin/5-fluorouracil regimens recommended magnesium supplementation at each cisplatin cycle. Nonetheless, episodes of hypomagnesaemia were shown to occur despite add-on treatments, and an additional magnesium supplementation had to be given to correct for persistent hypomagnesaemia.

Such a pathologic condition can be associated with any drug which causes severe nephrotoxic effects [10]; in oncologic patients, however, the
question concerns the decision as to whether to prescribe add-on therapies, in view of the possible influence of magnesium on tumor development [1].

Around 2005, cetuximab, a monoclonal antibody against the epidermal growth factor (EGF) receptor was introduced in the treatment of several carcinomas and was quickly adopted in combination therapies, especially for metastatic colorectal cancers. Cetuximab-based therapy was found to cause hypomagnesaemia with a severity proportional to the dose and the duration of treatment [11-13]. For cetuximab, as with cisplatin, the depletion of serum magnesium was due to an increased urinary magnesium excretion, probably due to an impaired kidney magnesium re-absorption [14]. Recent findings on the EGF-dependent mechanism regulating transient receptor potential melastatin TRPM within brackets magnesium re-absorption occurring in the kidney distal convoluted tubules provided the molecular foundation for cetuximab-induced hypomagnesaemia [15, 16].

These interesting data, associated with the well-known role of magnesium in sustaining cell proliferation and the possible inhibitory effect of hypomagnesaemia on tumor growth and on neo-angiogenesis [1, 17], lead some clinical oncologists to speculate that reduced serum magnesium might potentiate the chemotherapeutic effects of cetuximab treatments [18]. Indeed, these authors showed that, among patients with metastatic colorectal cancer treated with cetuximab plus irinotecan, those who developed a more modest hypomagnesaemia (~ 37% of patients) showed an improved median time to progression and overall survival time, compared to those who developed a more modest hypomagnesaemia. These results lead to the proposition that hypomagnesaemia might be considered a favourable condition for the efficacy of chemotherapeutic agents such as cetuximab [19].

In the light of these diverging interpretations, we think it important to recapitulate all the controversial aspects of hypomagnesaemia in tumor growth from studies performed in cell cultures, animal models and in the very few clinical data [20]. It follows that the pros and cons of hypomagnesaemia in tumor growth and invasion need an appropriate translation of these data into oncologic human settings.

**Experimental data**

*In vitro*, tumor cells are more independent in their need of extracellular magnesium for growth than normal cells [21, 22]. To study the effect of magnesium availability on tumor growth *in vivo*, mice on a magnesium-deficient diet were xenografted with a variety of solid tumors (Lewis lung carcinoma, 16/C mammary adenocarcinoma, C38 colon carcinoma) [17]. In comparison to magnesium-sufficient controls, the magnesium-deficient mice exhibited an approximate 60% reduction in the growth of primary tumors. Tumors which developed in magnesium-deficient mice were significantly less vascularized than those of controls [23]. We concluded that insufficient angiogenesis contributed to the inhibition of primary tumor growth. Indeed, endothelial cells cultured *in vitro* are among the cells most sensitive to low magnesium availability in terms of impaired proliferation and migration [24], partly because of their reduced sensitivity to angiogenic factors. Altogether, these data clearly showed that magnesium deficiency inhibits primary tumor growth and vascularization *in vivo*; they also support the hypothesis that hypomagnesaemia might potentiate the anti-tumor effect exerted by cetuximab [19]. That said we must emphasise that in this mice model severe hypomagnesaemia was accompanied by a significant leukocytosis [17]. Thus, one cannot precisely define how much primary tumor growth was inhibited by magnesium deficiency or concomitant alterations of the immuno-inflammatory network. Indeed, in rodents, magnesium-deficient diets are associated with a clear-cut, well-described immuno-inflammatory response [25].

In spite of the smaller size of the primary tumor and the low degree of neovascularization, mice on a low-magnesium diet developed far more lung metastases than controls [17]. This occurrence, though unexpected, underlines the intricate aspects of hypomagnesaemia and tumor development. Some data may account for such an effect: in magnesium-deficient mice, as well as in *in vitro* systems, several proteases – metalloproteinases, calpains, and others – which promote tissue remodeling and cell migration, were found to be up-regulated [25]. On the other hand, the exuberant inflammatory response observed in magnesium-deficient mice might be an important determinant of tumor cell extravasation [25, 26]. In this context, the low magnesium-induced up-regulation of vascular cell adhesion molecule (VCAM) by micro- and macro-vascular endothelial cells [27] may favour the binding of tumor cells at metastatic sites [28]. The effects of hypomagnesaemia in tumor growth in the mice model are summarized in figure 1.

In the mouse model of tumor growth under hypomagnesaemic conditions we also found that the re-addition of magnesium in the diet led to a rapid
Figure 1. The effects of hypomagnesaemia on tumor growth in mice. Hypomagnesaemia appears in mice 7 days after solid tumor transplantation. Dietary-induced hypomagnesaemia inhibits primary tumor growth and vascularization (indicated by <), but increases lung metastatic foci (indicated by >). Hypomagnesaemia also induces inflammation, specifically leukocytosis and production of pro-inflammatory cytokines, which contributes to influence tumor growth and invasion.

Figure 2. The effects of hypomagnesaemia on cancer patients. Chemotherapy-induced hypomagnesaemia, by inhibiting tumor growth and vascularization (<), seems to potentiate the effects of chemotherapy on the target tumor (black arrows). Based on the experimental data, however, we do not know whether in oncologic patients hypomagnesaemia induces any inflammation. If this is the case, could the inflammatory response influence tumor growth, invasion and metastatization (grey arrows)?
growth of the primary tumors, which eventually became 40% larger than those grown in control animals [17]. This observation leads to a further question: what happens in oncologic patients who become hypomagnesaemic during the chemotherapeutic treatment, once the magnesaemia, either upon supplementation or spontaneously, returns to normal levels? We do not have any clinical data addressing this issue, and the studies available involved patients who were affected by advanced malignancies (metastatic carcinomas), with limited qualitative and quantitative life expectancies.

Comments and conclusions

Collectively, the information derived from preclinical studies herein briefly summarized reveals a complex scenario in which low magnesium could have both anti- and pro-tumoral effects, such as reversible inhibition of tumor growth at its primary site and facilitation of tumor implantation at its metastatic sites [20]. The immuno-inflammatory response that complicates magnesium deficiency in mice could easily play a role on both sides of this scenario [25, 29].

Clearly, preclinical models of magnesium deficiency need to be adequately translated into clinical facts. First, we should understand whether an immuno-inflammatory response occurs in magnesium-deficient patients and has the same dual effects we described for primary and metastatic tumors in mice. At present, we only know that an inverse relation between magnesium intake, serum levels and markers of systemic inflammation occurs in apparently healthy subjects [30, 31], but we lack information about cancer patients. Maybe more importantly, we need to understand what hypomagnesaemia does first or more vigorously: inhibition of primary tumor growth or facilitation of tumor metastases. In the light of these issues and concerns, more studies are needed before we can conclude that hypomagnesaemia contributes to the activity of cetuximab or other drugs. Figure 2 summarizes the observations and possible questions to be addressed in cancer patients with chemotherapy-induced hypomagnesaemia.

That magnesium deficiency has come to the attention of oncologists denotes how fascinating the biology of this ion is. In practice, however, lacking crucial translational and clinical data, it is recommended that patient evaluation and treatment should be guided by appreciation of multifactorial events rather than perception of just one single event.

Acknowledgments

Supported by MIUR-PRIN 2007 grant number 2007ZT39FN.

References


