Cisplatin-induced renal toxicity magnified: role of magnesium deficiency in AKI onset

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CISPLATIN IS ONE OF THE MOST common and most effective chemotherapeutic agents used for the treatment of various solid types of cancer (1, 11). Clinically, cisplatin treatment is characterized by a high level of remission: e.g., ~80% in the case of testicular cancer (4). The effectiveness of cisplatin as an antiproliferative agent depends on its ability to form intra- and interstrand cross-links with DNA, effectively blocking cell replication (23). However, cisplatin utilization is severely limited by its toxicity for the myeloid system, the auditory system, the intestine, and the kidney.

In the case of the kidney, following glomerular filtration unbound cisplatin continuously accumulates within renal tubular cells (24), resulting in acute cell injury and cell death (2). Acute kidney injury (AKI) occurs in ~25% of the treated patients (6), and it has been attributed to the altered activity of various signaling pathways, including p53, MAPKs, PKCδ, mitochondrial-dependent apoptotic signaling, and caspase-3 activation, as well as to the increase in reactive oxygen species (ROS) formation and the decrease in cellular glutathione levels (6, 10). Renal injury can be severe as it damages irreversibly both the proximal and distal tubule, ultimately requiring dose reduction or treatment discontinuation (6, 16). Due to the complex pathogenesis of cisplatin-induced nephrotoxicity, no therapy has been consistently shown to reduce or prevent renal damage in patients, sorely limiting the utilization of this chemotherapeutic agent.

Hypomagnesemia is one of the most common complications of cisplatin treatment (3, 8, 18). Although broad variations in incidence have been reported by different studies (3, 8, 18), insufficiency of hypomagnesemia is commonly observed during the treatment period, and it often persists for months or years following its completion or suspension (17). Because of this trend, it is currently recommended that all patients receiving cisplatin should be supplemented routinely with magnesium (40-80 mmol/cycle of cisplatin regimen) (5).

Hypomagnesemia and reduced cellular magnesium levels occur with high incidence independently of treatments with cisplatin or other chemotherapeutic or nephrotoxic agents. In the US, ~40–50% of the population (9, 15), primarily the elderly (21), is estimated to be magnesium deficient to some extent, as a result of a less than optimal dietary intake. The symptoms and signs of hypomagnesemia and tissue magnesium deficiency are largely nongenomic, making the condition difficult to diagnose, especially when circulating magnesium levels are slightly below the physiological concentration of 0.8 mmol/l (14).

The insurgence of a neoplasia represents a confounding factor in that altered magnesium levels are often attributed to the malignancy or its treatment (e.g., cisplatin or anti-EGF monoclonal antibodies) (13). In the case of cisplatin therapeutic regimens, magnesium deficiency is thought to synergistically contribute to the insurgence of AKI (7).

The mechanism(s) responsible for the synergistic effect of magnesium deficiency has remained largely unidentified until recently. In two recent publications (19, 20), one of which is reported in a recent issue of the American Journal of Physiology-Renal Physiology (20), Dr. Metz’s group has started to delineate the modality by which magnesium deficiency contributes to cisplatin-induced AKI. In the first publication (19), Dr. Metz’s group provided evidence that cisplatin accumulation in kidney cells is amplified by magnesium deficiency, and is inhibited or reversed following magnesium replacement. The increase and decrease in cisplatin accumulation observed under magnesium deficiency and replacement, respectively, depended largely on inverse changes in the expression of the cisplatin efflux transporter in renal cells (19). In the present publication (20), Dr. Metz’s group has expanded the initial observation and now provides evidence that magnesium status differently affects tumor cells and renal cells. Magnesium deficiency, in fact, does not affect the ability of cisplatin to exert its antiproliferative effect and limit the progression of a human ovarian tumor in a xenograft model in mice (20). In contrast, magnesium deficiency markedly affects renal function following cisplatin administration, worsening the insurgence and progression of AKI by reducing mRNA expression of the cisplatin efflux transporter Abcc6 in renal cells. Magnesium supplementation after deficiency, on the other hand, improves cisplatin-mediated tumor killing while restoring the transporter expression and activity in renal cells, reducing intracellular storing of cisplatin and attenuation of its negative effects on these cells. Surprisingly, neither magnesium deficiency nor magnesium supplementation impacts the expression and operation of the Abcc6 efflux transporter in tumor cells.

Magnesium homeostasis is known to positively regulate various enzymes and signaling pathways, including ERK1/2, as well as cell cycle progression (12), while inhibiting ROS formation and inflammation in various pathological models (12). Thus it is not surprising that the maintenance (or restoration) of physiological levels of magnesium in the circulation and within cells have major effects on specific cellular functions and transporter expression and operation.

The results of Dr. Metz’s group are important at different levels. First, they indicate that the regulation of Abcc6 expression in tumor cells is different or altered compared with that occurring in renal cells. Second, they confirm that magnesium deficiency negatively affects the host rather than the neoplasia, as already reported (23). Third, they provide a compelling rationale as to why magnesium supplementation should routinely be part of cisplatin regimens to prevent and/or minimize AKI or other complications. At least a couple of key questions are in need of an answer: “Does cisplatin-induced AKI develop...
in predisposed patients who are magnesium deficient based on genetic or dietary bases, possibly compounded by conditions and drugs that affect magnesium homeostasis? and "Is there a threshold for magnesium deficiency below which AKI is more susceptible to develop"? Answering these challenging questions will clearly help in preventing patients at risk of developing a life-threatening renal pathology. 

In conclusion, the data provided by Dr. Metz’s group stress the importance of better understanding how magnesium levels regulate the operation of various transporters in renal cells and how this regulation is altered under magnesium deficient conditions and probably in tumor cells. This information will pave the road to design cisplatin therapeutic regimes that maximize minimizing its negative complications.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: A.M.R. analyzed data; A.M.R. interpreted results of experiments; A.M.R. drafted manuscript; A.M.R. edited and revised manuscript; A.M.R. approved final version of manuscript.

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