Protection of kidneys by magnesium in cisplatin chemotherapy: a fight between two metals

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Cisplatin has been widely used for chemotherapy since the discovery of its anti-cancer property almost five decades ago. It has a broad anti-tumor spectrum and is highly effective in the treatment of ovarian, cervical, breast, testicular, head and neck, lung, colon, and other types of cancer (10). As a platinum-based compound, cisplatin binds to DNA resulting in the formation of intra- and inter-strand cross-links, which, in rapidly dividing cancer cells, induce DNA damage followed by replication stress and cell death (2). Along with its tumor-killing activity, cisplatin has serious side effects in multiple normal tissues, among which nephrotoxicity is particularly notable and remains a major factor that limits the use and efficacy of cisplatin in cancer treatment (6).

Around 30% of patients undergoing cisplatin treatment develop renal problems, including acute kidney injury (AKI) within days and chronic kidney disease (CKD) later (6). The major pathological feature of cisplatin nephrotoxicity is tubular cell death in the forms of apoptosis and necrosis. The proximal tubules and the thick ascending limb of the loop of Henle are particularly sensitive to cisplatin injury, partly attributed to cisplatin uptake and accumulation in these renal tubules at an extremely high concentration via specific transporters (6). Cisplatin activates complex signaling pathways in renal tubules to directly trigger tubular cell death. Meanwhile, a robust inflammatory response is stimulated, further aggravating tubular cell injury. Cisplatin may also induce injury in renal vasculature and result in ischemic tubular cell death (6). During decades of research, a plethora of pharmacological and genetic approaches have been documented to afford protective effects against cisplatin AKI.
However, most of the studies focusing on renoprotection were conducted in cultured cells or tumor-free animals and whether these protective strategies would affect anti-cancer activity of cisplatin was not addressed (6). It is expected that inhibition of some of the cell death signaling pathways that are common to normal and cancer cells, for example the DNA damage response leading to p53 activation, would reduce the efficacy of cisplatin in cancer therapy (6). Therefore, identification of molecular targets and development of normal tissue-specific protective strategies without compromising the anti-cancer effects would significantly improve the therapeutic window and efficacy of cisplatin chemotherapy (6, 7). In this regard, Kumar et al. now further verify an important finding that magnesium supplementation may protect kidneys while enhancing the therapeutic effects of cisplatin in cancer (3).

Magnesium is an important cofactor for numerous enzymes that regulate a variety of cellular processes (4). Magnesium homeostasis is tightly regulated by the kidney. Two-thirds of the total serum magnesium is filtered by glomeruli. The reabsorption of the filtered magnesium takes place primarily in the thick ascending limb of the loop of Henle (70%), with 15% in the proximal tubules and 10% in the distal tubules. Cisplatin injury to renal tubules often impacts magnesium reabsorption, resulting in renal magnesium wasting and hypomagnesemia (4). Earlier studies suggest that cisplatin induces hypomagnesemia in 40-90% of patients receiving the treatment and magnesium loss in turn aggravates cisplatin nephrotoxicity (4, 5). Recent studies further demonstrate that magnesium supplementation attenuates tubular cell injury in experimental models of cisplatin AKI (8, 9). Notably, the
renoprotective role of magnesium supplementation has also been confirmed in cisplatin-treated patients with different types of cancer (1, 11, 12). Unfortunately, most of these clinical data are retrospective and lack follow-up analysis to evaluate the role of magnesium on short- and long-term tumor-related outcomes.

To address this critical question, Kumar et al. examined the effects of magnesium on both cisplatin-induced kidney injury and cisplatin-mediated tumor killing in cultured cells, and more importantly, in immunocompetent BALB/c mice bearing CT26 colon cancer (3). They revealed that cisplatin at a cumulative dose of 20mg/kg induced minimal kidney injury in normal magnesium diet-fed tumor-bearing mice. By contrast, significant renal damage was induced by cisplatin in mice on magnesium-deficient diet. Remarkably, cisplatin-induced AKI in magnesium-deficient diet fed mice was attenuated by magnesium supplementation via a combination of diet, drinking water and subcutaneous injection. Under these conditions, renal function loss was reversed, accompanied with the abrogation of tubular cell injury and death (3).

Kumar et al. further extended the in vivo observations in LLC-PK₁ renal epithelial cell line (3). Compared with the cells cultured in normal media, cells cultured in magnesium-deficient media were more sensitive to cisplatin injury, as indicated by decreased IC₅₀ for cisplatin, reduced cell viability and increased inflammatory response. Again, magnesium supplementation protected LLC-PK₁ cells from cell death, whereas pretreatment of LLC-PK₁ cells with a magnesium transporter inhibitor reduced magnesium uptake and promoted cisplatin-mediated cytotoxicity (3). These in vivo and in vitro findings, together with the authors’ previous work (8, 9), have
provided compelling evidence that magnesium plays a widespread renoprotective role against cisplatin AKI. Mechanistically, the renoprotection of magnesium may be associated with its inhibitory regulation on oxidative stress, inflammation, and cell death signaling pathways that have been shown to contribute to the pathogenesis of cisplatin nephrotoxicity (6).

To further elucidate the effect of magnesium on tumor-killing, Kumar et al. treated CT26 colon cancer cells with cisplatin (3). As expected, CT26 cells cultured in normal media were sensitive to cisplatin injury. In contrast to LLC-PK1 cells, the sensitivity of CT26 cancer cells to cisplatin was not affected by magnesium deficiency or inhibition of magnesium transporter. More importantly, cisplatin-mediated tumor cell killing was not compromised by magnesium supplementation (3). Furthermore, in BALB/c mice bearing CT26 colon cancer cisplatin-mediated chemotherapy was not affected but rather slightly enhanced by magnesium supplementation (3). These findings support the conclusion that magnesium protects kidneys during cisplatin treatment without interfering with the chemotherapy in tumors (3).

The different responses of renal tubular cells and tumor cells to magnesium are of particular interest. What are the underlying mechanisms? Solanki et al. has recently suggested a regulatory role of magnesium on renal accumulation of cisplatin (8, 9). Magnesium deficiency promoted cisplatin accumulation in the kidneys by reducing the renal expression of cisplatin efflux transporters including MRP2, MRP4 and MRP6. Conversely, magnesium supplementation reversed the reduction of cisplatin
efflux and suppressed cisplatin accumulation (8, 9). Notably, magnesium did not
appear to affect the expression of cisplatin transporters and cisplatin accumulation in
tumor cells (3, 9). Further studies need to determine how magnesium specifically
regulates cisplatin transporters in renal tubular cells. Regardless, the current work by
Kumar et al. suggests that magnesium supplementation may represent a clinically
applicable approach for kidney protection during cisplatin chemotherapy.

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