

## CLINICAL VIGNETTE

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# Hypomagnesemia Associated with Pertuzumab Therapy in Breast Cancer Treatment

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### *Case Report*

A 69-year-old woman was diagnosed with stage IIA T2N0, 4-centimeter (cm) high grade invasive ductal carcinoma, Estrogen Receptor (ER) negative, Progesterone Receptor (PR) negative, HER2 positive breast cancer. She was treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) for 6 cycles, followed by mastectomy with residual 2 cm, node negative, ER negative, PR negative, HER2 positive disease remaining at surgery. Subsequently she received 14 cycles of adjuvant therapy with ado-trastuzumab emtansine (Kadcyla). After one cycle of the TCHP neoadjuvant treatment, her blood magnesium level decreased to 1.2, slightly below lower limit of normal of 1.4. She was treated initially with oral magnesium supplementation, but was limited by diarrhea during her neoadjuvant cancer treatment. She also required intravenous magnesium infusions. After evaluation by nephrology, her systemic cancer therapy was the cause of her low magnesium levels. For 15 months after completion of her neoadjuvant therapy, she required oral magnesium replacement therapy in addition to intermittent intravenous magnesium supplementation. Subsequently, her magnesium level remains normal with her continuing oral chronic daily 500 mg of magnesium.

### *Discussion*

We have had a number of patients with significant and at times sustained hypomagnesemia during and after treatment with TCHP. Some patients have been evaluated by nephrology, and the uniform recommendation has been to continue magnesium supplementation.

The two main mechanisms of magnesium loss are renal or gastrointestinal excretion. Some medications used in the TCHP regimen can cause magnesium wasting via renal excretion. Docetaxel can lead to fluid retention. Diuretic therapy with loop and thiazide diuretics can lead to renal magnesium wasting. Loop and thiazide diuretics lower magnesium by inhibiting renal magnesium reabsorption, although this is usually mild.

Platinum agents have been associated with renal magnesium loss, although cisplatin is much more likely to cause this than is Carboplatin. Cisplatin causes urinary magnesium wasting in over half of patients, in a dose related fashion, while Carboplatin is less likely to cause magnesium loss. However, one retrospective study of 144 oncology patients<sup>1</sup> with ovarian, peritoneal, or fallopian cancer treated with carboplatin, most in combination with Taxol, reported 72% of patients had some

decrease of magnesium levels. Hypomagnesemia was increasingly likely with longer duration of cancer therapy; affecting one third of patients with advanced disease. Other medications were also suspected to be contributing to the hypomagnesemia, which was chronic in 14% of patients, possibly in part due to long term chronic nephrotoxicity from carboplatin.

Articles reporting TCHP regimen in the neoadjuvant and adjuvant settings do not report on magnesium levels in the treated patients. However, low magnesium levels following pertuzumab therapy has been reported in a retrospective analysis of 233 patients who received pertuzumab for whom magnesium levels were checked.<sup>2</sup> This study, included patients treated in the neoadjuvant and adjuvant settings: 9% developed hypomagnesemia with median time to onset of 33 days. In the metastatic setting: 14% of patients had low magnesium levels, with a median onset of 216 days. Use of platinum, antibiotics, and diarrhea also contributed to the decline in magnesium.

The Epidermal Growth Factor Receptor (EGFR) inhibitors such as cetuximab panitumumab have been associated with urinary magnesium wasting. The site of active magnesium transcellular absorption in the distal kidney convoluted tubule is under EGFR control. As one of its mechanisms of action, Pertuzumab blocks HER2 dimerization with EGFR. This effect on EGFR may be a mechanism by which pertuzumab contributes to hypomagnesemia.

Gastrointestinal sources of magnesium loss relevant to patients treated with TCHP are diarrhea and protein pump inhibitors (PPI). The magnesium content of the lower GI tract is approximately 15 times higher than the upper GI secretions so hypomagnesemia is much more common with diarrhea than with vomiting. In a large study of over 11,000 patients,<sup>3</sup> PPI use when combined with diuretics was associated with a higher risk of magnesium loss than were diuretics alone, but PPI use alone did not lower magnesium levels.

Even mild loss of magnesium by one or more of these routes, can result in hypomagnesemia as magnesium is stored mainly in bone and cells, with little rapid release of magnesium. Intravenous supplementation of magnesium is inefficient, as up to half is excreted in the urine. Oral magnesium is the preferable route of replacement as the levels tend to be more sustained. Magnesium can cause diarrhea, which is the dose-limiting toxicity. Sustained release magnesium limits renal excretion

due to slow absorption and may also decrease the risk of diarrhea. Due to time needed to replete intracellular stores, magnesium replacement is advised for at least another 1-2 days after the blood level normalizes. Some patients develop hypomagnesemia after TCHP require magnesium replacement chronically.

As hypomagnesemia can be a serious health issue, leading to neuromuscular, cardiac, and metabolic manifestations, we recommend that patients receiving TCHP therapy have their magnesium levels monitored regularly. We have incorporated regular magnesium testing for all patients receiving this regimen.

## REFERENCES

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