Aprepitant Protects Against Cardiac Wall Thinning From Erlotinib

Aprepitant to treat hypomagnesemia and skin lesions during chemotherapy

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Dietary administration of anti-vomiting drug Aprepitant to treat hypomagnesemia resulting from chemotherapy represents a new use for this commercial drug. Progressive hypomagnesemia, characterized by pronounced decrease (22-28%) of blood magnesium levels, occurs after prolonged chemotherapy with EGFR pathway blockers, such as Erlotinib or Cetuximab. Magnesium depletion leads to systemic oxidative distress, inflammation (including skin lesions) and eventual cardiac dysfunction. Other biochemical abnormalities, caused by magnesium depletion, include impaired calcium metabolism as manifested by hypocalcemia, hypoparathyroidism, and parathyroid hormone resistance.

Erlotinib, a tyrosine kinase inhibitor, causes elevation in circulating Substance P (SP). GW researchers established that elevated SP correlates with hypomagnesemia and then predicted that a SP blocker, like Aprepitant, could provide a treatment. The therapeutic approach is a first ever in hypomagnesemia, which is traditionally managed by replenishing magnesium levels with magnesium salts either orally or intravenously. In contrast, the inventors address the underlying molecular cause of magnesium depletion, i.e. elevated SP levels, and treat that with an oral drug already used for humans.

Preclinical validation data in animal models indicated that Aprepitant treatment completely prevented the development of cardiac systolic and diastolic dysfunction. Co-administration of Aprepitant with Erlotinib during chemotherapy could prevent systemic stress and cardiac dysfunction. Additionally, researchers observed an incredible impact on prevention of skin lesions with Aprepitant and envision applying Aprepitant topically as needed for this indication.

Applications

• Treat hypomagnesemia

• Use of NK-1 Receptor blockers to treat complications of EGFR blocking drugs and prolong chemotherapy adherance
Advantages

• Aprepitant (Emend) is already in clinical use
• Targets the underlying cause of hypomagnesemia and skin lesions

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