Denosumab Lowers Calcium in Patients With Patients with Refractory Hypercalcemia of Malignancy.

Drug that binds RANKL effective in patients with hyperglycemia of malignancy refractory to standard therapy with bisphosphonates.

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November 13, 2014 – Denosumab effective lowers calcium levels in patients with hypercalcemia of malignancy (HCM) that is non responsive to bisphosphonates, according to a small, proof-of-concept study.

In patients with advanced solid tumor and hematologic cancers, HCM is a grave complication and sign of poor prognosis. The current standard of care for HCM is intravenous (IV) bisphosphonates such as zoledronic acid or pamidronate.

According to the study finding, for the subset of patients with HCM failing to respond or relapse despite bisphosphonate treatment, the human monoclonal antibody denosumab may be an effective alternative. Denosumab binds the bone resorption mediator RANKL and phase III studies have shown it helps prevent skeletal-related events or HCM.

Mimi I. Hu, MD, and colleagues at the University of Texas MD Anderson Texas Center performed an open-label, single-arm, proof-of-concept study from November 2009 through June 2011. Patients included in the study had received IV bisphosphonates 7 to 30 days before screening, had albumin-corrected serum calcium (CSC) levels greater than 12.5mg/dL and Common Terminology Criteria for Adverse Events (CTCAE) grades > 3.

Study participants (15 total) received subcutaneous denosumab 120 mg on days 1, 8, 15 and 29 and then every four weeks. CSC levels were checked several times in the first 29 days and then weekly until day 57.

The primary endpoint was the proportion of patients who achieved a CSC ≤ 11.5mg/dL (CTCAE grade <1) within 10 days of their first dose of denosumab. Twelve patients (80%; 95% CI) reached this endpoint, with the median response time actually being 8 days (95% CI = 5 days to not estimable).

Secondary endpoints included response duration (number of days from the first to the last continuous value of CSC level ≤ 11.5mg/dL). The median duration of response was 26 days (95% CI = 5 days to not estimable). Also studied was the percentage of patients achieving a complete response (CSC ≤ 10.8mg/dL by day 10). Eleven patients (73%) had a complete response at a median time of 9 days (95% CI = 5-35 days), consistent with previous studies.

Adverse events (AE) most commonly were nausea, pyrexia and hypercalcemia secondary to cancer progression. Most serious and fatal AE were not thought to be related to denosumab treatment.

Investigators acknowledged the limitations of their study noting the narrow study population however “it would not have been clinically appropriate to conduct a randomized controlled trial to compare denosumab with a treatment that had already proved ineffective for these patients”.

The authors note that the sample size was small, but they concluded that these “interim results suggest that denosumab may offer a new treatment option for HCM in this challenging population.”

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