**Denosumab Shows Efficacy  
in Relapsed Hypercalcemia of Malignancy**

The RANKL inhibitor denosumab improved responses for patients receiving bisphosphonates in a proof-of-concept study

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February 23, 2015 – A large proportion of patients with hypercalcemia of malignancy (HCM) refractory to the standard-of-care bisphosphonate treatment who received the RANKL inhibitor denosumab experienced a robust clinical response in a single arm proof-of-concept study.

Mimi I. Hu, MD, of the University of Texas MD Anderson Cancer Center in Houston, and colleagues reported the results of their study in the September 18, 2013 issue of the *Journal of the National Cancer Institute*.

As noted by the researchers, denosumab functions as an inhibitor of RANKL, a mediator of bone resorption. Previous studies showed denosumab to be effective at treating HCM when compared with zoledronic acid treatment.

In the present study, Hu and colleagues treated patients refractory to the standard-of-care bisphosphonate treatment with denosumab and monitored these patients for a reduction in disease score.

Enrolled patients received 120 mg of denosumab on days 1, 8, 15 and 29 of the study. Patients received additional doses every 4 weeks, up to day 57.

The primary outcome assessed in the study was the number of patients demonstrating a clinical response to denosumab treatment at 10 days after initial treatment with the antibody, defined as a reduction in albumin-corrected serum calcium (CSC) levels to 11.5 mg/dL or less (a grade of ≤ 1 according to the Common Terminology Criteria for Adverse Events [CTCAE]).

Twelve patients, or 80% (95% exact confidence interval [CI] = 52% to 96%), met the primary outcome criteria.

The researchers also evaluated response duration and proportion of patients demonstrating a complete response to treatment as secondary outcomes. In patients who responded to denosumab, the median duration of response was 26 days. Ten patients, or 67% (95% exact CI = 38% to 88%), responded completely, demonstrating a CSC level ≤10.8 mg/dL by 10 days post initial denosumab treatment.

A number of severe adverse events were reported during the study, although the investigators did not attribute the adverse events to treatment with denosumab. The adverse events most commonly experienced by patients involved in the study were pyrexia (20%), nausea (20%), and additional hypercalcemia associated with progression of the patients' malignancies (20%).

The study reported by Hu and colleagues involved only a small number of patients (15) and did not contain a control arm. However, the authors note that the “response was maintained for a median of 26 days, a clinically meaningful outcome given that patients entered this study with hypercalcemia of grade 3 and greater within a median of only 18 days after receiving the last dose of intravenous bisphosphonate.”

The authors further suggest that denosumab "may offer a new treatment option for HCM in this challenging population" of patients refractory to the standard-of-care bisphosphonate treatment.

*The sponsor of this study, Amgen Inc., participated in the design and interpretation of the study as well as in the preparation of the report.*

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