RE: Denosumab for Patients With Persistent or Relapsed Hypercalcemia of Malignancy Despite Recent Bisphosphonate Treatment

We read with great interest the article by Hu et al. (1) who reported that denosumab was effective for hypercalcemia of malignancy (HCM) refractory to intravenous bisphosphonate at a dose of 120 mg on days 1, 8, 15, and 28 and every 4 weeks thereafter. We would, however, like to voice our concern regarding the safety of this dosage and schedule, especially for patients with some degree of renal dysfunction, such as in many with HCM. Aside from excluding patients on dialysis, the authors made little mention of renal function for enrolled patients.

Early clinical trial results have indicated that patients with renal dysfunction are at increased risk for severe hypocalcemia after denosumab administration, despite no notable effect of renal function on the pharmacokinetics of denosumab (2). The occurrence of severe hypocalcemia necessitated concurrent calcium supplementation in patients undergoing denosumab treatment, as recommended by the manufacturer. Because fatal hypocalcemic episodes in three initially hypercalcemic patients were reported in the Post-Marketing Pharmacovigilance study in Japan, calcium supplementation should be considered at some point, even for patients with HCM.

In a phase I dose-escalation study, a single dose of denosumab resulted in a dose-dependent increase in serum parathyroid hormone (PTH) levels (from as low as 0.03 to 3.0 mg/kg), suggesting that denosumab decreases serum calcium levels in a dose-dependent manner (3). In randomized phase II dose-finding studies, the 180 mg dose was abandoned because it induced several cases of hypocalcemia, including a case of severe hypophosphatemia with hyperparathyroidism. At 120 mg, the incidence of hypocalcemia was 5% to 13%, but rare at 60 mg. Moreover, all deaths among patients with denosumab-induced hypocalcemia occurred with the 120 mg dose, and none occurred with the 60 mg dose. By contrast, a case report of two children with refractory hypercalcemia proved that small amounts of denosumab (0.13–0.27 mg/kg) can normalize serum calcium levels successfully (4).

We recently treated a 42-year-old woman with HCM refractory to weekly intravenous bisphosphonate. After confirming normal renal function, we administered a single 120-mg dose of denosumab, which immediately and durably normalized serum calcium levels for more than 8 weeks despite no objective tumor response. We monitored pharmacodynamics markers such as PTH, PTH-related protein, and the urinary calcium to creatinine ratio (Ca/Cr), which reflects hypocalcemic effects before serum calcium levels decline. We confirmed the compensatory functions against hypocalcemia; the index of renal calcium reabsorption (Ca/Cr levels) was suppressed immediately, and PTH was elevated 1 month after denosumab administration.

Drug exposure of 120 mg of denosumab weekly seems to be comparable to that of a single 180-mg dose (Figure 1), which is 1.5-fold higher than that clinically recommended (5–7). Furthermore, patients with renal dysfunction have a markedly higher risk of hypocalcemia, which usually occurs within 3 weeks of administration. Considering that the time to maximum concentration of denosumab is approximately 5 to 21 days, it might be prudent to wait at least another few weeks before the second administration. In addition, the dose might need to be reduced in cases of substantial renal dysfunction.

Figure 1. Pharmacokinetics of denosumab according to its dosing and schedule (5–7).
References


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