Refractory Hypercalcemia of Malignancy: Responsiveness to Denosumab and Zoledronate

D. Giri\textsuperscript{1}, R. Ramakrishnan\textsuperscript{1}, J. Hayden\textsuperscript{2}, L. Brook\textsuperscript{2}, U. Das\textsuperscript{1}, M. Zulf Mughal\textsuperscript{1}, P. Selby\textsuperscript{1}, P. Dharmaraj\textsuperscript{1}, S. Senniappan\textsuperscript{1}

\textsuperscript{1}Department of Paediatric Endocrinology, Alder Hey Children's Hospital, \textsuperscript{2}Department of Paediatric Oncology, Alder Hey Children's Hospital, \textsuperscript{3}Department of Paediatric Palliative Care, Alder Hey Children's Hospital, \textsuperscript{4}Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, \textsuperscript{5}Department of Medicine, Manchester Royal Infirmary

Background
Hypercalcaemia secondary to malignancy is rare in children and adolescents. PTH-rP (Parathyroid hormone related peptide) secreted by malignant cells is an important humoral factor that increases bone resorption and renal calcium retention causing hypercalcaemia. We report 2 cases of hypercalcaemia of malignancy refractory to treatment with pamidronate and corticosteroids but responsive to treatment with Denosumab and Zoledronic acid.

Case 1
A 17-year-old boy with epidermolysis bullosa presented with advanced squamous cell carcinoma of the left leg and symptomatic hypercalcaemia (serum adjusted calcium, 4.2mmol/l). PTH was suppressed at 0.7pmol/l. Serum 25 hydroxy vitamin D level was 31nmol/l (normal range > 50nmol/l). PTH-rP and 1, 25 dihydroxy vitamin D levels were elevated at 2.1pmol/l (0.0-1.8) and 173pmol/l (43 – 143) respectively. The management is shown below(Figures 1,2,3).

Figure 1: Initial management of Hypercalcaemia (Week 1)

HH denotes hyper hydration

Figure 2: Management of Hypercalcaemia (week 2)

Case 2
A 17-year-old girl with pelvic rhabdomyosarcoma was hypercalcemic (serum adjusted calcium, 3.19mmol/l) with suppressed PTH of 0.3pmol/l and serum phosphate of 2.2 mmol/l. Serum 25 hydroxy Vitamin D was 28nmol/l and renal profile was normal. The management is as shown in the graph below(Figure 4).

Figure 4: Management of Hypercalcaemia. HH denotes Hyper Hydration

Discussion
Denosumab is a monoclonal antibody which neutralises RANKL (receptor activator of nuclear factor kappa-B ligand), inhibiting the function of osteoclasts thereby preventing generalized bone resorption. Zoledronic acid blocks osteoclast resorption and has a more potent calcium-lowering effect than pamidronate. These two drugs widen the treatment options for patients with refractory hypercalcaemia of malignancy.

Reference