Targeting RANK-ligand in the treatment of bone metastasis

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- Bone is the most common site of metastases for many solid malignancies. Roughly 75% of metastatic breast cancer patients will develop bone metastases at some point in the course of their disease (Coleman, 1997).
- Bone metastases can result in skeletal complications, which may include any of the following:
  - pathological fracture
  - spinal cord compression
  - pain requiring radiation or surgery
  - hypercalcemia.
- These four complications are referred to as skeletal related events (SREs).
- Treatment of bone metastases with bisphosphonates in addition to antineoplastic therapy has been shown to reduce and delay the onset of skeletal-related events in this population (Petrut et al., 2008). However, many patients still suffer at least one SRE during the course of their disease (Trinkaus et al., 2010).
- Bisphosphonates are synthetic analogs of pyrophosphate and inhibit osteoclasts. First generation bisphosphonates (clodronate) are 100-fold less potent than second generation (pamidronate) and 10,000-fold less potent than third generation bisphosphonates (zoledronic acid) (Simmons et al., 2009). While there may be some utility to considering a switch to a more potent bisphosphonate at the time of progression of bone disease (Clemons et al., 2006), there is evidence that progressive bone disease still may occur despite low levels of osteoclasts within an area of bone involved with cancer (Trinkaus et al., 2009).
- New developments in the understanding of the role of receptor activator of nuclear factor kappa B ligand (RANKL) in the development of bone metastases have allowed the development of novel targeted therapy in the treatment of bone metastases.
- RANKL is a mediator of osteoclast differentiation, function and survival. It is released from osteoblasts and stromal cells in the bone microenvironment and stimulates precursor and mature osteoclasts to differentiate and induce bone resorption. Factors released from the destruction of bone further stimulate tumour growth. Tumour cells further stimulate osteoblasts and stromal cells to release RANKL and, thus, the vicious cycle continues (Terpos et al., 2009).
- Denosumab is a fully human monoclonal antibody with high affinity and specificity to RANKL. Denosumab subsequently binds to and neutralizes RANKL, thus arresting the vicious cycle of bone metastases (Santini et al., 2009).
- It has been shown to increase bone mineral density and reduce fractures in postmenopausal women with low bone mass (Cummings et al., 2009).
- Results of a large phase III randomized controlled trial of denosumab versus Zometa for the treatment of bone metastases in breast cancer patients has recently been reported, and updated results were presented at the San Antonio Breast Cancer Symposium December 10, 2009 (Stopeck et al., 2009).
  - This study enrolled 2,046 women with breast cancer and bone metastases who had not received IV bisphosphonate therapy. They were randomized in a 1:1 non-inferiority study design to receive SC denosumab at 120mg and IV placebo OR IV zoledronic acid at 4 mg and SC placebo every four weeks.
  - In this way investigators were able to ensure patients, clinicians and investigators were blinded.
  - Daily calcium and vitamin D were encouraged but not mandated.
  - The primary endpoint of this study was time to first on study SRE:
  - This was found to be prolonged in the denosumab arm compared to Zometa with a hazard ratio of 0.82 (95% CI 0.71-0.95, $P < 0.0001$ for non-inferiority)
  - Of note, the statistical analysis was also able to determine superiority of denosumab over zoledronic acid with a $P = 0.01$ for superiority.
  - The secondary endpoints of this study were also met and are summarized in Table 1 (next page).
- Overall, denosumab was superior to zoledronic acid in reducing and delaying the onset of skeletal related events.
- Adverse effects reported higher rates of pyrexia, chills and arthalgia in the zoledronic acid arm of the study compared to denosumab arm. The rate of renal toxicity was found to be 8.5%

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in the zoledronic acid arm compared to 4.9% in the denosumab arm, and the rates of osteonecrosis of the jaw were similarly low in both arms at a rate of 1.4% and 2.0% (p=0.39) in the zoledronic acid and denosumab arms respectively. Denosumab did result in a higher reported rate of toothache and hypocalcemia (Stopeck et al., 2009).

- These results are interesting but, even more importantly, these studies demonstrate the importance of further work on the treatment and prevention of bone metastases, as these lesions can have such a significant impact on a patients' quality of life.

Table 1: Secondary endpoints of Denosumab vs. Zometa study

Endpoint	Result	95% CI	P value
Time to first and subsequent on study SRE	HR 0.77	0.66, 0.89	0.001
Time to first radiation to bone	HR 0.74	0.59, 0.94	0.01
First on study SRE or Hypercalcemia of malignancy	HR 0.82	0.70, 0.95	0.007
Skeletal morbidity rate (number of SREs per year)	SMR 0.45 vs 0.58		0.004
Proportion of patients with at least one SRE	30.7% vs. 36.5%		

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