THERAPY

Bisphosphonate-independent reduction of bone resorption in patients with bone metastases

The human monoclonal antibody denosumab decreases bone resorption independently of previous treatment with bisphosphonates in patients with bone metastases.

> "Denosumab has a unique mechanism of action distinct from that of bisphosphonates"

Bone metastases increase osteoclast activity, which results in elevated levels of bone turnover markers that are associated with skeletal-related events and death in such patients. Previous studies have shown that tumor-induced osteolysis is essentially due to an increased expression and secretion of receptor activator of nuclear factor κB ligand (RANKL).

The current standard of care for the prevention of skeletal-related events, such as fractures, spinal cord compression and the need for radiation or surgery to bone, is to administer intravenous bisphosphonates, which are potent inhibitors of osteoclast activity. Nevertheless, not all patients achieve a reduction of the levels of bone turnover markers, notably urinary N-telopeptide, and renal toxicity associated with bisphosphonates can limit their use.

To address the need for alternative therapies, Body *et al.* measured the effects of denosumab, which has a very high affinity and specificity for RANKL, on the suppression of bone turnover markers and the delay or prevention of skeletal-related events in two phase II trials. The first study included 255 women with breast cancer and bone metastases who had not previously received bisphosphonates, and the second trial enrolled 111 patients with solid tumors and bone metastases or multiple myeloma and elevated urinary N-telopeptide levels despite previous bisphosphonate treatment ≥8 weeks. Patients were randomly assigned to receive either intravenous bisphosphonates every 4 weeks or different doses of denosumab in the same interval or every 12 weeks.

The study revealed that denosumab was as efficient as bisphosphonates in the suppression of bone turnover and delay or prevention of skeletal-related events in patients with bone metastases. The effects of denosumab were consistent, regardless of the type of tumor, history of skeletal-related events and previous bisphosphonate treatment.

"Denosumab has a unique mechanism of action distinct from that of bisphosphonates," says lead author Jean-Jacques Body (Brugmann University Hospital, Brussels, Belgium). This notion

is supported by the finding that a decrease in tartrate-resistant acid phosphatase type 5 levels, a specific marker of osteoclast number, can be detected after denosumab but not after bisphosphonate treatment.

"With its rapid and sustained effects, denosumab administered as a monthly subcutaneous injection represents a potential treatment option for the management of bone metastases," concludes Body.

Linda Koch

Original article Body, J. J. *et al.* Effects of denosumab in patients with bone metastases, with and without previous bisphosphonate exposure. *J. Bone Miner. Res.* doi:10.1359/jbmr.090810