Denosumab, anti-RANKL monoclonal antibody, an additional weapon against myeloma bone disease; accumulating evidence

Denosumab (Amgen) is a fully humanised monoclonal antibody against RANKL and has been in development over the last decade as an alternative to bisphosphonates as an anti-resorptive strategy in myeloma bone disease, other tumours that metastasize to bone (eg breast, prostate) and in osteoporosis. Recently, certain key trials have reported evidence to suggest superiority of denosumab over zoledronic acid (Novartis) in a variety of settings. A debate is thus ongoing between Amgen sponsored trials showing superiority, or at least non-inferiority of denosumab and other Novartis sponsored studies which suggest that denosumab is not cost effective. Administration of denosumab does have some attractive features including lack of renal toxicity and monthly sub-cutaneous administration likely to facilitate easier, quicker and possibly domicilliary administration.

What is the role of Denosumab in myeloma bone disease; NICE due to consider in June 2012

NICE has previously recommended its usage as primary and secondary prevention of fracture in postmenopausal, osteoporotic women at increased risk of fracture (at a six monthly dosage of 60mg sc)(NICE Oct 2010; http://guidance.nice.org.uk/TA204/Guidance/pdf/English) but withheld approval of its use in non-metastatic prostate cancer (NICE July 2010; http://guidance.nice.org.uk/TA194/Guidance/pdf/English). Now, prompted by accumulating evidence, NICE is considering the use of denosumab in myeloma and other metastatic cancers and is due to report in June 2012. Furthermore, they will deliberate the circumstances in which they would sanction the use of denosumab including primary prevention of skeletal events, secondary prevention after fracture in patients on bisphosphonates or use limited to those with renal failiure or otherwise intolerant of bisphosphonates. So what of the evidence?

Markers of bone resorption are suppressed for longer in patients on denosumab

Although this may not sound very impressive (as those who have scrutinised the large scale bisphosphonate trials will know) demonstration of efficacy in terms of clear reduction in skeletal related events is difficult and requires large numbers and long follow-up (Djulbegovic, Wheatley et al. 2002). Serial assays of biomarkers give sequential information about bone remodelling and commonly include standard biomarkers of bone resorption (urinary N-terminal telopeptide of collagen 1 (Ntx), serum C-terminal telopeptide of collagen 1 (1CTP), urinary deoxypyridinoline (Dpyr) and urinary pyridinoline (Pyr)) and bone formation (serum C-terminal propeptide of procollagen 1 (PICP), serum bone specific and total alkaline phosphatase and serum osteocalcin)(Abildgaard,

Glerup et al. 2000). These biomarkers have commonly been used as surrogate markers of efficacy for bone protective agents including anti-resorptive strategies and more latterly bone anabolic approaches. Hence, an important study reported in 2006 that in patients with myeloma and those with metatstatic breast cancer treated with a single dose of sc denosumab, the levels of urinary and serum N-telopeptide, a key marker of bone resorption, were reduced for at least 84 days. The reduction in this marker was similar in magnitude to that seen in patients treated with a single dose of iv pamidronate but was considerably more sustained (Body, Facon et al. 2006).

Denosumab more effective than iv bisphosphonates after previous treatment with iv bisphosphonates

Following on from this and reporting in the Journal of Clinical Oncology in 2009, Fizazi et al studied patients with bone metastases from prostate, breast cancer or other neoplasms who had persistently elevated levels of urinary N-telopeptide (uNTX) after iv bisphosphonates. This group reported that sc denosumab normalised uNTX more frequently than in those receiving iv bisphosphonates and furthermore, the denosumab group experienced fewer skeletal related events (Fizazi, Lipton et al. 2009).

Denosumab effective in men with prostate cancer receiving androgen-deprivation therapy

Similarly, in August 2009, Smith et al reported in the New England Journal of Medicine the results of a randomised study of men with prostate cancer receiving androgen-deprivation therapy that compared a six monthly dose of sc denosumab (60mg) or placebo (734 pts in each group). Those in the denosumab arm had a 5.6% increase in lumbar spine density compared with a loss of 1% in the placebo group plus a reduction in the incidence of new vertebral fractures was seen in the denosumab group (Smith, Egerdie et al. 2009). Although this was a comparison with placebo rather than iv bisphosphonate, the results are impressive especially given the six monthly administration (ie the same regimen (six monthly dose of sc denosumab (60mg)) recommended by NICE for the prevention of fracture in post-menopausal women).

Denosumab superior to zolendronic acid in the reduction of skeletal related events in the treatment of patients with advanced breast cancer with bone metastases

In December 2010, a direct head to head, randomised, double blinded study of denosumab versus zolendronic acid in patients with advanced metastatic breast cancer was published in the Journal of Clinical Oncology. Patients were randomised to receive either 120 mg denosumab sc or 4mg of

zolendronic acid iv every 4 weeks. Denosumab was superior to zolendronic acid in delaying the time to first skeletal related event. Denosumab also led to greater reduction in bone turn over markers. Renal toxicity was more commonly seen in the zolendronic acid group although denosumab was associated with more episodes of hypocalcaemia. There was no difference between denosumab and zolendronic acid in terms of overall survival, disease progression or adverse events and the incidence of osteonecrosis of the jaw was similar in both groups (2.0%, denosumab; 1.4%, zoledronic acid)(Stopeck, Lipton et al. 2010).

Subsequent study reports non-inferiority of denosumab versus zolendronic acid in patients with myeloma and other advanced cancer (excluding breast and prostate)

Hot on the heels of the last study, a second direct head to head study between denosumab and zolendronic acid in patients with myeloma or advanced metastatic cancer (excluding breast and prostate cancer) was reported in the Journal of Clinical Oncology in March 2011. Although this study did not show superiority of denosumab in terms or increase in time to first skeletal related event, non-inferiority was demonstrated 'trending towards superiority'. Ease of subcutaneous administration and lack of renal toxicity were heralded as clinically important (Henry, Costa et al. 2011).

No anti-tumour effect evident in myeloma patients treated with denosumab

Given the emerging evidence to suggest anti tumour effects of bisphosphonates and other bone protective strategies, Vij et al trialled monthly denosumab in the treatment of relapsed or plateau-phase multiple myeloma. Primary tumour endpoint considered was reduction in serum M-protein. No patients experienced complete or partial response. Markers of bone resorption were reduced as expected but in this study, no anti tumour effect was demonstrated. Although results of this initial study are disappointing, as with other bone protective agents, further studies exploring anti tumour effects are being considered (Vij, Horvath et al. 2009).

Denosumab superior to zolendronic acid in the prevention of skeletal-related events in men with bone metastases from castration resistant prostate cancer

In March 2011, Fizazi et al have reported in the Lancet a Phase III trial a comparison between monthly denosumab 120mg sc, zolendronic acid 4mg iv and placebo every 4 weeks in patients with bone metasatases from castration resistant prostate cancer. Denosumab was modestly superior to

zolendronic acid in delaying the time to first skeletal related event (20.7 months vs 17.1 months). Adverse effects frequency was similar in both groups although again, hypocalcaemia was more frequent in the denosumab group suggesting that the co-administration of oral calcium and vitamin D is desirable, as is actually currently recommended in UK Myeloma Guidelines as an adjunct to the use of bisphosphonates (Bird, Owen et al. 2010). Osteonecrosis of the jaw occurred infrequently in both groups although the incidence was higher in the denosumab arm (2% vs 1%)(Fizazi, Carducci et al. 2011).

Denosumab may have a cost effective role in patients with myeloma

Thus given the accumulating evidence from large, multi-centre trials the rationale for denosumab is gathering momentum. Drs Lipton and Jacobs, in their September 2011 review suggest that due to its efficacy, ease of administration and favourable side effect profile, denosumab offers an important treatment option for those with cancer induced bone disease (Lipton and Jacobs 2011). Unless subsequent studies demonstrate clear superiority, the rationale for its use in myeloma rest with evidence of non-inferiority, lack of renal toxicity and ease of administration via the sub cutaneous route. As such, when NICE issue their guidance, due June 2012, if the recommendation is favourable, the indication for denosumab use may well be limited to those intolerant of bisphosphonates usually due to renal impairment, a small but significant minority.

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