Denosumab – a new option for solid tumours metastatic to bone

Philip Saylor

Zoledronic acid is a potent bisphosphonate used as the standard therapy for the prevention of skeletal-related events in patients with solid tumours metastatic to bone. Three phase III studies have reported head-to-head comparisons of zoledronic acid with denosumab, an inhibitor of the RANK signaling pathway.

Skeletal morbidity is a substantial burden in many patients with advanced solid tumours. Pathologic fractures, pain, spinal cord compression and hypercalcaemia are among the potential complications of bone metastases. Osteoclast-mediated bone resorption has an important role in the pathophysiology of bone metastases as it weakens the bone and liberates growth factors that can stimulate both cancer growth and further bone turnover.[1] Therefore, inhibiting osteoclasts is a rational therapeutic strategy and bisphosphonates and denosumab are two available types of osteoclast inhibitors.

Bisphosphonates are analogues of pyrophosphate – a normal component of bone matrix. Once deposited within bone, they inhibit osteoclasts locally. Zoledronic acid is the most potent bisphosphonate available. Since its approval in 2002, it has been the standard bone-targeted treatment for the prevention of skeletal-related events (SREs) in patients with solid tumours that have metastasised to bone.

Denosumab now represents a new class of osteoclast-targeted therapy as it inhibits the receptor activator of nuclear factor κB (RANK) signalling pathway. RANK is present on osteoclasts throughout most of their life cycle and its signalling promotes osteoclast differentiation, activation, and survival.[2] Osteoprotegerin (OPG) is an endogenous decoy receptor to RANK-ligand (RANKL) that negatively regulates this pathway. Denosumab is a monoclonal antibody that functions as an exogenous OPG, suppressing markers of osteoclast activity for several months after a single dose in some settings.[3]

Three randomised phase III studies have recently compared denosumab with zoledronic acid. Fizazi et al.[4] reported that denosumab is superior to zoledronic acid for men with castration-resistant prostate cancer (CRPC) that has metastasised to bone. This phase III study enrolled 1904 men with CRPC who were randomly assigned to treatment with denosumab (120 mg administered subcutaneously every four weeks) or zoledronic acid (4 mg administered intravenously every four weeks). The primary endpoint was time to first on-study SRE (pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression) and the primary objective was to demonstrate noninferiority of denosumab to zoledronic acid. One of the secondary objectives was to demonstrate its superiority. Median time to first on-study SRE was 20.7 months with denosumab and 17.1 months with zoledronic acid (HR=0.82; 95%CI 0.71–0.95; P=0.0002 for noninferiority; P=0.008 for superiority). Time to disease progression and overall survival rates were similar between the two groups.

In another phase III study, Henry and his co-authors reported that denosumab is noninferior to zoledronic acid in patients with metastases due to non-prostate and non-breast cancer.[5] This study enrolled

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1776 patients with advanced cancer or multiple myeloma that had metastasised to bone. Median time to first SRE was 20.6 months with denosumab and 16.3 months with zoledronic acid. Noninferiority, but not superiority, was demonstrated for denosumab. The disease progression and overall survival rates were similar between the two groups.[5]

A third similarly designed study of women with breast cancer metastatic to bone had previously reported superiority of denosumab (HR=0.82; 95%CI 0.71–0.95; *P*=0.01) compared with zoledronic acid in reducing SREs.[6] Taken together, these studies establish denosumab as superior to zoledronic acid in breast cancer and prostate cancer and noninferior to zoledronic acid in other solid tumours. On the strength of these three studies, the FDA approved denosumab in November 2010 for the prevention of SREs among patients with solid tumours that have metastasised to the bone.

Denosumab represents an effective new option for the management of skeletal morbidity, but how is the clinician to choose between denosumab and zoledronic acid? It is worth noting that none of the three trials demonstrated a difference in overall disease progression or overall survival. The choice, therefore, must be driven by consideration of drug toxicities and efficacy in preventing SREs.

In prostate cancer, denosumab is superior to zoledronic acid. Is it superior enough for clinicians to reach for it exclusively? Zoledronic acid became standard of care for bone-metastatic CRPC when it was shown to prolong median time to first SRE from 10.7 months to 16.3 months – a 5.6-month improvement compared with placebo.[7] In the trial reported by Fizazi et al.[4], time to first SRE improved by 3.6 months with denosumab compared with zoledronic acid. Simply put, the magnitude of the additional benefit of denosumab over zoledronic acid is about two-thirds of the benefit of zoledronic acid over placebo. This significant additional benefit should lead us to choose denosumab for men with prostate cancer. The hazard ratio for first on-study SRE was identical in the breast cancer trial, indicating that denosumab should be the standard of care in this population as well.

In non-prostate, non-breast tumours, the difference between denosumab and zoledronic acid is simply too close to call. In the trial by Henry and collaborators, enrolment featured approximately 40% of patients with non-small-cell lung cancer (NSCLC) and 50% with a variety of other non-breast, non-prostate solid tumours. In the absence of any specific contraindications, either drug is a reasonable choice. Denosumab seemed to be inferior to zoledronic acid in the subset of patients with multiple myeloma and hence should not be used for this indication.

In patients with renal dysfunction, denosumab offers a potential advantage. Zoledronic acid is recommended at reduced doses for stable mild renal insufficiency (glomerular filtration rate (GFR) of 30–60 ml/min) and is contraindicated in patients with evolving renal dysfunction or a GFR of <30 ml/min. Denosumab has a long half-life (28 days)[8] and its clearance is not dependent on kidney function. Although denosumab is a rational choice for patients with renal dysfunction, available data are limited because such patients were excluded from the phase III trials that included zoledronic acid arms.

Do the toxicity profiles of the two drugs help in deciding which of the two is preferential? Zoledronic acid often causes a flu-like acute-phase reaction, but this is generally mild and resolves without medical intervention. Inhibiting RANK signalling in cells from the immune system raises the possibility of risk of infection after treatment with denosumab,[9] but the incidence of infectious adverse events did not significantly differ during the 2–3 years of follow up in any of the phase III trials.[4–6]

Hypocalcaemia and osteonecrosis of the jaw (ONJ) are important potential adverse effects of both drugs. Hypocalcaemia can occur with any potent osteoclast inhibitor, although it seems to be more common with denosumab than with zoledronic acid (13% vs 6% in the study by Fizazi et al. and 10.% vs 5.8% in the study by Henry et al.). Because vitamin D deficiency raises the risk for hypocalcaemia, it is important to verify a normal serum vitamin D level before therapy and to encourage calcium and vitamin D supplementation during therapy. ONJ is a rare but important potential toxic effect of both drugs, occurring in 1–2% of the participants in these trials. Appropriate dental care before initiation of therapy is likely the most important preventative measure.[10]

These three phase III trials are practice-changing for patients with solid tumours that are metastatic to bone. Denosumab should be our first choice in men with CRPC and women with breast cancer. For other solid tumours, zoledronic acid and denosumab are equally supported by high-level evidence.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

Three phase III trials establish denosumab as an effective new option to reduce skeletal morbidity in patients with solid tumours that have metastasised to bone. Denosumab is superior to zoledronic acid for patients with prostate or breast cancers and is noninferior for patients with other solid tumours.

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