Denosumab for bone lesions in multiple myeloma – what is its value?

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In June 2017 the Food and Drug Administration (FDA) accepted a supplemental biologics license application seeking to expand the currently approved indication of denosumab to patients with bone lesions from multiple myeloma. The FDA set a prescription drug user act (PDUFA) action date of February 3, 2018. Denosumab is an inhibitor of receptor activator of nuclear factor κ-B ligand (RANKL) and was previously approved for postmenopausal women at risk of osteoporosis in addition to patients at risk of skeletal-related events due to bone metastases from solid tumors and giant cell tumors of the bone. The application for use in patients with myeloma is based on the findings of the recently presented '482 trial.[1] This commentary seeks to understand the value of this therapy for patients with multiple myeloma.

Denosumab is a monoclonal antibody and uses a novel mechanism to decrease bone resorption. RANKL is a protein expressed on osteoblastic stromal cells. It binds to receptor activator of nuclear factor-κB (RANK) and thus mediates osteoclastic differentiation, activation, and survival. RANKL therefore controls osteoclast-mediated bone resorption. Osteoprotegerin is a soluble RANKL decoy receptor which binds RANKL and is the key regulator of the RANKL–RANK pathway. Denosumab binds to RANKL thus blocking the interaction of RANKL with RANK, mimicking the endogenous effects of osteoprotegerin. This agent has been shown to lead to a decrease in bone resorption, based on changes in serum and urinary N-telopeptide, which are markers of osteoclastic bone resorption.[2]

Until recently bisphosphonates had been the standard therapy for strengthening bone in a variety of conditions such as osteoporosis and cancer. Bisphosphonates essentially bind to bone mineral and inhibit the activity of mature osteoclasts. Non-nitrogen containing bisphosphonates achieve this goal by being metabolized to ATP analogs that block osteoclast function and induce osteoclast apoptosis. Nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase, thus preventing the post-translational modification of guanosine triphosphate binding proteins which are essential for osteoclast function and survival.[3] The essential difference between bisphosphonates and denosumab is that bisphosphonates inhibit mature osteoclasts while denosumab inhibits osteoclastic precursors.

Denosumab has already gained FDA approval for multiple indications based on advanced phase clinical trials. In postmenopausal women with low bone mineral density, it was found to lead to a 3.0% to 6.7% increase in bone mineral density of the lumbar spine.[2] Multiple trials have compared zoledronic acid and denosumab in patients with solid tumors. In patients with bone metastases from breast cancer, denosumab was superior to zoledronic acid in delaying or preventing first on-study skeletal-related event [hazard ratio (HR)=0.82; 95% confidence interval (95% CI): 0.71- 0.95; *P*= 0.01).[4] Likewise, denosumab was superior in terms of time to first skeletal-related event in patients with bone metastases from prostate cancer. The median time to first on-study skeletal-related event was 20.7 months (95% CI: 18.8-24.9) with denosumab compared to 17.1 months (95% CI: 15.0-19.4) with zoledronic acid (HR=0.82, 95% CI: 0.71-0.95; *P*=0.008 for superiority).[5] Despite the reduction in skeletal-related events with denosumab, there was no associated improvement in overall survival in patients with either breast or prostate cancer.[4,5] In patients with giant cell tumors of the bone, an open label study with denosumab demonstrated a high level of efficacy: 96% of patients with surgically unsalvageable giant cell tumors of the bone did not have disease progression after a median follow-up of 13 months.[6]

The '482 trial was an international phase 3, randomized, double-blind trial comparing the safety and efficacy of monthly denosumab to monthly zoledronic acid in patients with multiple myeloma.[1] The trial enrolled 1718 patients and the primary endpoint was the time to first on-study skeletal-related event, and was powered to demonstrate non-inferiority. Secondary endpoints were time to first skeletal-related event (powered to superiority), time to first and subsequent skeletal-related events (powered to superiority), and overall survival. The study met the primary endpoint and demonstrated that denosumab was non-inferior to zoledronic acid in terms of skeletal-related events (HR=0.98; 95% CI: 0.85-1.14; *P*=0.01). The trial failed to meet the secondary endpoints of demonstrating superiority in terms of time to first skeletal-related event or overall survival. The authors performed an unplanned exploratory analysis to evaluate progression-free survival as an endpoint and found a prolonged progression-free survival in the denosumab group (HR=0.82; 95% CI: 0.68-0.99; *P*=0.036). Although the trial was well conducted with double-blind randomization, this finding should be considered only as hypothesis-generating, as it was an unplanned endpoint analysis and such analyses are known to have a lack of statistical reliability.[7]

There were no significant differences between the two groups in terms of adverse events apart from hypocalcemia and renal toxicity. In patients with baseline creatinine clearance ≤60 mL/minute, 13% of patients in the denosumab group developed renal toxicity, compared to 26% of patients in the zoledronic acid group (*P*<0.01). The rate of creatinine doubling from baseline in the zoledronic acid group was nearly twice as high as in the denosumab group (6.5 *versus* 3.3%). Conversely, there were higher rates of hypocalcemia in patients receiving deno-

sumab (17%) compared to those receiving zoledronic acid (12%) (*P*=0.009).

In the USA we can calculate the cost of the drugs to Medicare by using the average sales price (*www.cms.gov*). This accounts for discounts and rebates and is a close estimate of the cost to Medicare. The patent for zoledronic acid expired in 2013, at which point the reimbursement cost decreased. The average sales price for 4 mg of zoledronic acid is $48 and that for 120 mg of denosumab is $2044. The annual cost is therefore $576 for zoledronic acid, and $24,528 for denosumab – a difference of almost $24,000. In addition to this cost there is a mark-up of 4.3% that Medicare reimburses to providers. It should be noted that this mark-up may provide a financial incentive to the physician to prescribe the more expensive medication, despite the higher cost to the patient and insurer. Finally, treatment centers also charge an infusion cost of approximately $140, billed with code 96413 (www.cms.gov). While these are the costs to Medicare, we must also recognize that the patient often shares a significant proportion of the cost. In 2015, the average annual Medicare beneficiary cost share was $527 for denosumab and $68 for zoledronic acid (www.cms.gov - 2015 Medicare drug spending data). The price of drugs is different in other countries around the world; however, it is clear that everywhere in the world zoledronic acid is significantly cheaper than denosumab. This commentary is not intended to assess what was the most appropriate launch price of these drugs at the very different times of their being launched. The purpose is to discuss the most appropriate choice of therapy in 2018, when the prices are significantly different, due to one of the options being available in the significantly cheaper, generic form.

There is some additional convenience from using denosumab. Firstly, denosumab can be given subcutaneously which may be preferable to the intravenous administration of zoledronic acid. Secondly, denosumab is dosed the same for all patients, and no adjustment is needed according to renal function, whereas dose adjustments are necessary for zoledronic acid. It is doubtful however, that this additional convenience justifies the additional annual cost in the USA of $24,000 per patient.

Recent data for zoledronic acid demonstrate equivalent efficacy in patients with bone metastases secondary to breast cancer, irrespective of whether the drug is given monthly or every 3 months.[8] Could these data perhaps be extrapolated to patients with multiple myeloma? There are currently no good quality data regarding the use of denosumab every 3 months in patients with neoplastic bone disease.

In an era of financial challenges for healthcare, we, as physicians, must be careful stewards of finite healthcare resources. There appears to be no benefit from using denosumab instead of zoledronic acid in terms of overall survival or skeletal events. In addition, the safety profile is very similar. There appears to be slightly more renal toxicity with zoledronic acid; however, this is balanced by the higher rates of hypocalcemia with denosumab. Although there was a demonstration of benefit in terms of progression-free survival, this finding should be treated with caution, as it emerged from a *post hoc* exploratory analysis. There are, however, significant differences in costs – both to society and to patients. Denosumab costs approximately $24,000 more per patient per year in the USA. Zoledronic acid is also considerably cheaper than denosumab in Europe as well. Perhaps the most appropriate management would be for all patients to receive zoledronic acid, except those with a contraindication due to a low creatinine clearance. The reason for the high cost of new cancer drugs is complex. Without doubt, one of the many reasons is that the cost of drug development is high, partially related to the many regulatory requirements. However, while cancer is still often an incurable disease, we must strive towards bringing forward new therapies that provide clinically meaningful benefits to our patients.[9] In an era of medical bancruptcies and increasing healthcare costs, we owe it to both our patients and society to incorporate costs into clinical decision-making.

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