Managing Myeloma

# New option in the prevention of bone complications in patients with multiple myeloma

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Bone disease in multiple myeloma continues to be a fairly important problem. Despite all of the new agents we have, we still see patients with bone disease. The incidence of those problems has decreased quite a lot, but given that our patients are living a lot longer now with all of these new drugs, the risk of developing bone disease continues to be cumulative over the course of the patient's lifetime. Up until recently, we only had one drug, which was zoledronic acid and pamidronate, for the treatment of myeloma related bone disease complications. Earlier this year, we had denosumab approved, which is a monoclonal antibody directed against RANK ligand. This was approved after one of the largest clinical trials conducted in the history of myeloma; it was a 1700 patient strong study. The way the study was designed was to demonstrate that this monoclonal antibody would show just as good an efficacy as the zoledronic acid would. It was a head-to-head, double blind, randomized trial comparing zoledronic acid to denosumab. Our primary endpoint here was to look at first skeletal-related event (SRE) on-study and time to first SRE, and we saw that there was really no difference between zoledronic acid and denosumab, suggesting the denosumab was just as good as zoledronic acid. When we did a landmark analysis, we did see the denosumab was a little bit better, but that was more of a post-hoc analysis. What was quite interesting to me was there was always this concern with denosumab that we may be increasing toxicity and causing more mortality, and that had been seen in some of the older studies. However, in this study we saw absolutely no overall survival difference. What was striking in this trial was that all things were equal. We had stratified these patients for the kind of myeloma therapy they were receiving; the regions from where they had arrived for their myeloma treatment; as well as stage of myeloma disease; whether they got a transplant versus not; and when we looked at progression free survival (PFS) of these patients, the PFS really favored the denosumab arm. That favoring of the denosumab arm was as much as by about 10.8 months; I have never seen that kind of a progression free survival benefit even in some of the large randomized trials that we are doing routinely in myeloma. To me, that speaks to the fact that using a target which actually might have a very significant role in the micro-environment may be of some importance. The other thing which was instructive to all of us from that clinical trial was the fact that denosumab, being a monoclonal antibody, is not impacted by kidney

function. That is actually quite critical for patients with multiple myeloma because over the course of a patient's lifetime with myeloma, a lot of them will develop myeloma related kidney problems. If you can use a safer, effective dose instead of zoledronic acid and pamidronate – which are essentially somewhat cleared by the kidneys – you now have a safer option in denosumab which can be given subcutaneously to patients.