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CLINICAL CASES

Denosumab increases bone mineral density in a young osteoporotic woman on dialysis after allogeneic stem cell transplantation for hematologic malignancy

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Osteoporosis is a common, long-term skeletal complication of allogeneic stem cell transplantation (allo-SCT). Osteoporosis can lead to increased bone fragility and an increased risk of fractures. Several treatment modalities are currently available to prevent and treat bone loss in patients undergoing allo-SCT, but with some limitations. Bisphosphonates are useful antiresorptive agents used to treat bone loss, but their use in patients with renal impairment is limited. Denosumab, a humanized monoclonal antibody to receptor activator factor-kappa B ligand, might be a therapeutic option for osteoporosis in patients with renal impairment after allo-SCT but has not been well studied in such patients. We present here the case of a young woman who was on dialysis due to renal failure after allo-SCT for acute myeloid leukemia and whose severe osteoporosis was safely and successfully treated with denosumab. To our knowledge, we are the first to report the benefit of denosumab in a patient who underwent allo-SCT and who also had severe renal impairment and was undergoing dialysis. The rapid onset of action, sustained long-term effects and good tolerability of denosumab suggest that this drug should be evaluated in future studies of patients with hematologic malignancies who have renal insufficiency and osteoporosis after allo-SCT.

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Introduction

Allogeneic stem cell transplantation (allo-SCT) for hematologic malignancies has resulted in improved outcomes; however, as more patients survive longer the effect of long-term complications is gaining importance.[1] Skeletal complications such as osteoporosis, a disease characterized by low bone mass and deterioration of bone microarchitecture, are common.[2–4] Osteoporosis increases bone fragility and susceptibility to fracture.[2] Several therapies, such as vitamin D, calcium, bisphosphonates and hormone replacement therapy, are currently used to prevent and treat osteoporosis.[1] Bisphosphonates are potent antiresorptive agents that can be useful in treating patients with bone loss after allo-SCT, but the usefulness of bisphosphonates is limited for patients with renal impairment or for those on dialysis.[5]

Denosumab, a fully human monoclonal antibody directed against receptor activator factor-kappa B ligand (RANKL), inhibits RANK receptor activation, resulting in reduced osteoclast activity and bone resorption.[6,7] Denosumab was approved by the US Food and Drug Administration in 2010 for the treatment of postmenopausal osteoporosis, but its efficacy has not been evaluated in patients after allo-SCT and/or in those on dialysis. The RANK/RANKL pathway is involved in other cell signaling pathways, including immune surveillance, and thus there is a theoretical risk of cancer or infections. In postmenopausal women of the FREEDOM trial an increased rate of cellulitis culminating in hospitalization was observed, but the rates were no different from the placebo group and no increased rates of cancer or other infections were observed.[8]

Osteoporosis treatment strategies in patients with kidney impairment can get complex. In the FREEDOM trial, of the

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7868 patients studied, 2817 had stage 3 chronic kidney disease (CKD) and 73 had stage 4. The stage 3 patients showed a significantly lower risk of both vertebral and non-vertebral fractures. Stage 4 patients also showed an increase in bone mineral density (BMD), but the numbers were too small to show a statistically significant difference and subjects were excluded if they had stage 5 CKD.[8] Published studies on the safety of denosumab in patients on dialysis are limited. A case report of a 61-year-old female on dialysis treated with denosumab revealed severe hypocalcemia, which resolved in 2 months after her first dose of denosumab.[9] Some other small studies suggest hypocalcemia as a side effect of denosumab in hemodialysis patients, but the results are inconclusive.[10]

We report the case of a young woman who had severe renal impairment and was receiving hemodialysis after allo-SCT for a hematologic malignancy and whose osteoporosis was treated successfully with denosumab.

Patient Characteristics

In March 2011, a 29-year-old woman was seen at The University of Texas MD Anderson Cancer Center (Houston, TX, USA); she reported severe pain in her mid and lower back of $\sim$3 months' duration and generalized muscle wasting and weakness with difficulty in standing up from a seated position. The patient's medical history was complicated: she had breast cancer stage 2A at age 24 and was treated with lumpectomy, radiation and chemotherapy. Her cancer was human epidermal growth factor receptor 2 positive and estrogen receptor/progesterone receptor negative. She received trastuzumab treatment for 1 year. She was then put on capecitabine and lapatinib for 1 year, ending in December 2009. She developed an episode of pneumonia and was diagnosed with acute myeloid leukemia (AML) with monosomy 7 in April 2010. She subsequently underwent one antigen-mismatched unrelated donor stem cell transplantation in July 2010. Post transplantation, her treatment course was complicated by steroid-refractory acute graft versus host disease (GVHD), requiring multiple lines of immune suppression and prolonged steroid use. As a consequence of her immune-suppressed state, she also developed multiple episodes of pneumonia requiring intravenous antibiotics. Eventually she developed acute renal failure with serum creatinine levels as high as 5.3 mg dl^{-1} (normal: 0.6–1.0 mg dl^{-1}), and was put on hemodialysis.

Assessment of the patient's history revealed that no one in her family had been diagnosed with osteoporosis or abnormal calcium, parathyroid or thyroid function. As a child, she had consumed moderate amounts of milk and other dairy products. She had regular menstrual cycles until the age of 25 when she experienced chemotherapy-induced early menopause.

In June 2011, a Hologic dual-energy X-ray absorptiometry (DEXA) scan revealed a lumbar spine BMD *T*-score of -1.6 and left femur neck and total hip BMD *T*-scores of -2.4 and -2.5, respectively. An X-ray revealed demineralization as well as a superior endplate fracture of T11, and superior endplate deformities at L1, L2, L4 and L5. Owing to the immobility caused by the vertebral fractures, the patient's muscles atrophied, and she became very sedentary. A serum C-terminal telopeptide (CTX) (Beta-CrossLaps, performed at Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN, USA) level revealed a significantly high bone turnover rate with a serum CTX level of 3371 pg ml^{-1} (normal: 104–1008 pg ml^{-1} in postmenopausal women), serum osteocalcin level of 58 ng ml^{-1} (normal: 9–42 ng ml^{-1}), serum creatinine level of 3.2 mg dl^{-1} (normal: 0.6–1.0 mg dl^{-1}), Vitamin D (25-hydroxy) level of 20 ng ml^{-1} (normal: 20–52 ng ml^{-1}), parathyroid hormone (PTH) level of 58 pg ml^{-1} (normal: 9–80 pg ml^{-1}) and a low ionized calcium level of 1.08 mmol l^{-1} (normal: 1.13–1.32 mmol l^{-1}).

Owing to several comorbidities, the treatment options available to improve her bone health were limited. Bisphosphonates were contraindicated in light of her renal failure and dialysis, and teriparatide given her history of radiation treatment. Starting in June 2011, she was given calcium, 600 mg twice daily, and vitamin D, 2000 IU once a day. This patient's case was discussed at our institutional monthly metabolic bone case conference, and the addition of denosumab (subcutaneous injection, 60 mg once every 6 months) was considered. She received her first dose of denosumab in November 2011 and tolerated the medication well and her overall condition improved. Tacrolimus and steroid treatment was discontinued, and the patient's renal function improved. Within the next 3 months, she no longer required dialysis; her AML was in remission, and she was able to return to her daily life. Her back pain and steroid-induced myopathy were significantly improved.

A Hologic DEXA scan 6 months after initiation of denosumab revealed a 7.3% increase in BMD at her lumbar spine, and a 11.5% increase in her total hip and femur neck BMD. Her serum CTX (Beta-CrossLaps) level was significantly reduced to 2049 pg ml^{-1} (normal 104–1008 pg ml^{-1} in postmenopausal women) 1 year after initiation of denosumab, that is, after receiving 2 doses, 6 months apart. A DEXA scan 2 years after initiation of denosumab showed that the patient's lumbar spine BMD *T*-score was 0.0 and that her femur neck *T*-score was -1.1. A direct comparison of her previous BMD with the 6-month or baseline BMD could not be made because the last scan was conducted using a different machine in her hometown. Nevertheless, we have observed a trend toward continued improvement in her BMD. The patient's serum creatinine has remained in the range of 1.21–1.71 mg dl^{-1}. Serum calcium and Vitamin D levels have remained in the normal reference range. **Table 1** shows the change in laboratory measurements in relation to denosumab administration. The patient has continued to receive denosumab every 6 months, since she responded well to the medication. Clinically, she did not develop any new fractures and is able to function without much pain or muscle weakness.

Discussion

Advances in transplantation methodologies and post-transplantation care have resulted in a growing population of long-term survivors.[1] Bone loss, which can lead to osteoporosis and an increased risk of bone fragility and fractures, occurs in $\sim$24–50% of patients 2–12 months after allo-SCT.[3,4] The incidence of osteoporosis is obviously affected by complications sustained after transplant, such as GVHD, which require long-term steroid exposure. Normal bone remodeling is a dynamic process and is primarily regulated by the RANKL pathway, which is essential in the development and activation of osteoclasts. An alteration in RANKL and osteoprotegerin (which

Table 1 Laboratory values in relation with denosumab administration

Time	*Jun-11*	*Nov-11*	*Jun-12*	*Dec-12*	*Aug-13*	*Reference range*
Denosumab[a]		*1st dose*	*2nd dose*	*3rd dose*	*4th dose*	
Creatinine serum	3.2	3.61	1.71	1.46	1.21	0.6–1.0 mg dl^{-1}
Calcium serum	9.1	10.1	9.2	9.6	8.5	8.4–10.2 mg dl^{-1}
Osteocalcin serum	58	—	107	—	—	9–42 ng ml^{-1}
Parathyroid hormone (PTH)	67	—	58	—	—	9–80 pg ml^{-1}
Vitamin D	21	—	20	—	25	20–52 ng ml^{-1}
Serum CTX	3371	—	2049	—	—	104–1008 pg ml^{-1}[b]

Abbreviation: CTX, C-terminal telopeptide (CTX) (Beta-CrossLaps) level.
[a]Denosumab was administered as subcutaneous injection, 60 mg once every 6 months. [b]Normal 104–1008 pg ml^{-1} in postmenopausal women.

acts as an endogenous soluble receptor antagonist) has been documented in the pathogenesis of osteoporosis. An increase in soluble osteoprotegerin and soluble RANKL has been observed within 3 months post transplantation.[11] Denosumab binds to RANKL, thus preventing its interaction with the RANK receptor resulting in decreased osteoclast formation and potently inhibiting bone resorption.

Denosumab is not nephrotoxic and has a reversible effect on osteoclast formation and bone resorption. A small single-dose study of denosumab suggests that denosumab dose adjustment based on glomerular filtration rates is not indicated. In the same study none of the patients who received adequate calcium and vitamin D experienced hypocalcemia,[10] suggesting that addition of calcium and vitamin D to the recommended dose of denosumab is a useful therapeutic option for patients with impaired kidney function. One side effect of denosumab is a small but significant increase in infections, which is responsible for some reluctance to use it in immunosuppressed cancer patients and stem cell transplant patients.[12] However, in several randomized clinical trials, denosumab increased BMD and decreased the risk of fractures in postmenopausal patients and cancer patients with skeletal metastasis, without causing significantly increased risk of infection.[8,13–15] The reversible effect of denosamab also renders it shorter acting as compared to some of the bisphosphonates. As long as contributing factors for further bone loss exist, loss of effect would be expected if the medication is discontinued.

To our knowledge this is the first reported case of a patient on dialysis following allo-SCT that had a significant improvement in BMD after administration of denosumab without any acute side effects. Although there has been reluctance to use denosumab in immunosuppressed patients with cancer and in those undergoing allo-SCT, a subset of these patients may benefit from this agent. It is not possible to know if the observed improvement in the BMD was attributable to denosumab and/or the improvement in renal function and the withdrawal of corticosteroids; however, the rapid improvement in her BMD and overall condition following denosumab administration suggests that denosumab played at least a partial role in improving this patient's bone health. Further, we would not expect to observe a dramatic improvement in BMD if the change was attributable only to the discontinuation of corticosteroids and the mild improvement of renal function, supporting the role of denosumab in the improvement of BMD. Denosumab's rapid onset of action, sustained effects for several months and good tolerability (especially in patients with renal impairment) are other factors that strongly suggest denosumab's consideration in this setting. Further studies to evaluate the role of denosumab in managing cancer and post-allo-SCT patients are highly warranted.

Conflict of Interest

The authors declare no conflict of interest.

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