Original Article

Effectiveness of Bone Metastases Treatment by Sm-153 Oxabifore in Combination with Monoclonal Antibody Denosumab (Xgeva): First Experience

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Abstract

Breast and prostate cancer have a propensity to metastasize to bones and cause osteolysis and abnormal new bone formation. Metastases locally disrupt normal bone remodeling. Although metastases from prostate cancer have been classified as osteoblastic based on the radiographic appearance of the lesion, data gleaned from a rapid autopsy program indicate that the same prostate cancer patient may have evidence of both osteolytic and osteoblastic disease as shown by histologic examinations. Thus, bone metastases are heterogeneous, requiring combined treatment targeting on both osteolytic and osteoblastic lesions. While Samarium-153 (Sm-153) oxabifore treatment is widely used for the relief of pain in patients with osteoblastic metastatic bone lesions, Xgeva (Denosumab) is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors. It is a fully human monoclonal antibody that has been designed to target receptor activator of nuclear factor-kB ligand (RANKL), a protein that acts as the primary signal to promote bone removal. In many bone loss conditions, RANKL overwhelms the body's natural defense against bone destruction. The main objectives of the current pilot study were to estimate the effectiveness of bone metastases treatment by a combination of Sm-153 oxabifore and Xgeva (Denosumab). Five patients (four female and one male, aged 35-64, mean age 50.8) with multiple skeletal metastases from prostatic carcinoma (1) and breast carcinoma (4) were studied. Their mean objective pain score according to visual analog scoring system on a 1-10 scoring system was 7.8 ± 0.5 (range 6-9). Sm-153 oxabifore was administered at the standard bone palliation dose of 37 MBq/kg body weight. Xgeva (Denosumab) was administered at a dosage of 120 mg every 4 weeks, with the monitoring of calcium level and administration of calcium, magnesium, and vitamin D. Whole body (WB) bone scan was performed before and 3 months after treatment in all patients. After Sm-153 oxabifore administration, pain relief occurred within 4.4 ± 1.25 days (range 2-9 days) and the objective pain score decreased to 0.2 ± 0.2 (range 0-1). There was statistically significant difference found, according to the pain score system, before and after treatment ($P < 0.0001$). WB bone scan showed that in one patient, there was significant reduction in the number and intensity of bone metastases, and in four patients, there was no evidence of bone metastases found. Based on our first experience, combined treatment of bone metastases with Sm-153 oxabifore and Denosumab is effective and safe.

Keywords: Bone metastases, Sm-153 systemic radionuclide therapy, Xgeva (Denosumab)

Introduction

Breast and prostate cancer have an inclination to metastasize to bone tissue, leading to osteolysis and abnormal new bone formation.[1,2] There is a spectrum of factors responsible for tumor growth in bone, which includes tumor stimulation of the osteoclasts, osteoblasts, and response of the bone microenvironment. Breast cancer produces many factors that stimulate osteolysis: Parathyroid hormone-related protein (PTHrP), interleukin (IL)-11, IL-8, IL-6, and receptor activator of nuclear factor-kB ligand (RANKL).[3-8]

Prostate cancer also has propensity to metastasize to bone locally disrupting normal bone remodeling. Tumor produces growth factors such as platelet-derived

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growth factor (PDGF), insulin-like growth factors, adrenomedullin, and vasoactive peptide endothelin A (ET-1) which stimulate the new bone formation.[2,9-15] By secretion of osteoblast-stimulating factors such as Wnt family ligands, bone morphogenetic proteins, PDGF, and endothelin-1, prostate cancer cells stimulate the formation of the hallmark osteoblastic metastases. Tumor-derived signals suppress the ability of osteoblasts to secrete osteoprotegerin, a RANKL antagonist that blocks RANKL–receptor activator of nuclear factor-kappa B (RANK) interaction and resulting osteoclast activation.[16]

Recent clinical evidence indicates that both processes contribute to the metastatic phenotype even in the same patient. Data gleaned from a rapid autopsy program indicate that the same prostate cancer patient often would have evidence of osteolytic and osteoblastic disease as shown by histologic examination.[17] Thus, bone metastases are heterogeneous and would require combined treatment targeting both osteolytic and osteoblastic lesions.

Bone-derived growth factors promote a fertile environment for the survival and proliferation of cancer cells, creating a vicious cycle of bone destruction. RANKL is a key mediator in this process. Within the bone microenvironment, factors secreted by tumor cells stimulate stromal cells and osteoblasts to secrete RANKL, which binds to its RANK on the surface of osteoclasts. RANKL is a critical mediator of osteoclast differentiation, function, and survival.[18]

For prevention of skeletal-related events (SREs) in patients with bone metastases from breast and prostate cancers, recently Xgeva™ (Denosumab) obtained the Food and Drug Administration (FDA) approval.[19] Being a fully human monoclonal antibody, Denosumab is designed to target RANKL, a protein that acts as the primary signal to promote bone removal. In many bone loss conditions, RANKL overwhelms the body's natural defense against bone destruction.

Precursors to osteoclasts, called pre-osteoclasts, express a receptor on their surfaces called RANK. RANK is a member of the tumor necrosis factor receptor superfamily. RANK is activated by RANKL, which is produced by osteoblasts. Activation of RANK promotes the maturation of pre-osteoclasts into osteoclasts.

Denosumab inhibits this maturation of osteoclasts by binding to and inhibiting RANKL. This protects the bone from degradation. The drug, therefore, mimics the endogenous effects of osteoprotegerin, another receptor produced by osteoblasts which can bind RANKL, thus reducing its effect on RANK and helping to modulate bone production.[20]

While Denosumab is a promising medication for prevention of SREs, radionuclide therapy is widely used as an alternate modality for the management of bone pain. Samarium-153 Ethylenediamine tetramethylene phosphonic acid (EDTMP) is a bone-seeking radiopharmaceutical that has an affinity for skeletal tissue and concentrates in areas of increased bone turnover, localizing in active bones, mainly at metastatic lesions, allowing site-directed radiotherapy.[21,22]

In our study, we used Sm-153 oxabifore (oxa-bis (ethylennitrilo) tetramethylphosphoric (ETMP)), in combination with Xgeva (Denosumab) in patients with painful bone metastases and who had disease progression in spite of previous bisphosphonate therapy.

Materials and Methods

Five patients (four female and one male, aged 35–64, mean age 50.8) with multiple bone metastases from prostate ($n = 1$) and breast ($n = 4$) cancers were included in the study. Computed tomography (CT) and magnetic resonance imaging (MRI) studies were performed in all patients to exclude vertebral fracture and/or impending cord compression. Criteria for patient selection included severe bone pain refractory to analgesics and bisphosphonate therapy, intense uptake around painful bone metastases on recent (3-4 weeks before treatment) Tc-99 methylene diphosphonate (MDP) whole body (WB) bone scan, and acceptable hematological parameters (hemoglobin >90 g/L, white blood cell count $>4 \times 10^9$/L, and platelet count of $>100 \times 10^9$/L).

Pain assessment was based on visual analogue scale (VAS), 0 means no pain and 10 means intolerable pain. Mean objective pain score of patients before treatment was 7.8 ± 0.5 (range 6-9). Serum alkaline phosphatase levels were estimated in all cases for assessment of activity of osteoblastic component of bone metastases before treatment and 4 weeks after treatment. According to our laboratory, the normal range of serum alkaline phosphatase level was 38-126 U/L. Mean serum alkaline phosphatase level before treatment was found to be 351.4 ± 35.6 U/L (range 240-424 U/L), which was far more higher than the normal value.

Sm-153 oxabifore therapy

Prior to the administration of radiopharmaceutical, all patients received information both orally and in written brochures about the treatment, including an explanation of the therapeutic procedure, estimated time as to when pain relief may be expected; warning that a transient flare effect of pain may occur, as well as radiation protection guidelines. Sm-153 oxabifore was administered to all patients at the standard bone

palliation dose of 37 MBq/kg body weight. WB bone scan was performed in all patients before treatment and 3-6 months after treatment.

Xgeva (Denosumab) therapy

Xgeva (Denosumab) treatment was started within 1-3 days after Sm-153 oxabifore therapy. A dose of 120 mg Xgeva was administered subcutaneously every 4 weeks in the upper arm, with the serum calcium level monitored. All patients were taking daily calcium and vitamin D (calcium-D3 Nycomed Forte 2) tablets.

Statistical analysis

The acquired results were expressed as the mean + SEM for each index. Comparison of data among various groups was performed with Student's unpaired *t*-test. $P < 0.05$ was considered statistically significant.

Results

Pain relief occurred within 4.4 ± 1.25 days (range 2-9 days) following Sm-153 oxabifore administration. The objective pain score decreased from 7.8 ± 0.5 to 0.2 ± 0.2 (range 0-1) [Figure 1]. This response to therapy was found to be statistically highly significant ($P < 0.0001$).

Four weeks after Sm-153 oxabifore treatment, the mean serum alkaline phosphatase level dropped from 351.4 + 35.6 U/L (range 240-424) to 111.6 + 9.2 U/L (range 89-134). This was found to be highly significant with a $P < 0.0001$.

In one patient, we observed a significant reduction in the number of bone metastases as documented on the Tc-99m MDP WB bone scan, with concomitant reduction in the intensity of radiotracer uptake. Tc-99m MDP WB bone scan showed that in one patient, there was significant reduction in the number of bone metastases and intensity of radiotracer uptake, and in four patients, we observed complete disappearance of osteoblastic bone lesions indicating complete resolution of bone metastases [Figure 2].

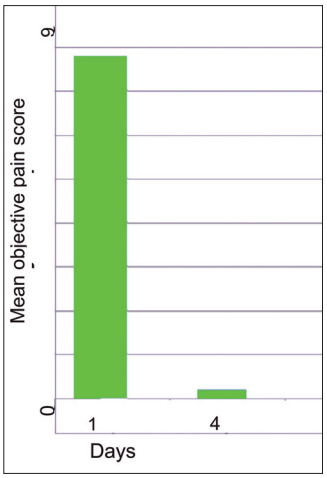

Figure 1: Effectiveness of pain relief following combined radionuclide and Denosumab therapy. Prompt pain relief could be experienced by the patients within 2-9 days following Sm-153 oxabifore administration. Objective pain score was noted to decrease from 7.8+0.5 to 0.2+0.2 ($P < 0.0001$)

Discussion

In patients with bone metastases, there is an imbalance between osteoclast and osteoblast activities that results in local bone destruction. It is estimated that approximately 80% of all patients with diagnosis of breast cancer, prostate cancer, or multiple myeloma will develop bone metastases at some time during the course of the disease. The goal of treating these patients is to reduce the risk of developing an SRE, which normally includes spinal cord compression, pathologic fracture, and hypercalcemia.[23]

The respective phenotypes of dysregulated bone destruction and bone formation represent the two ends of a spectrum, and most patients will have evidence of both.[17] Between breast cancer cells and bone, there is the so-called vicious cycle: Cancer cells, by releasing PTHrP, activate osteoclasts which demineralize bones, causing the release of growth factors from the exposed bone matrix that support cancer cell proliferation and induce further release of PTHrP.[16] Vicious cycle between prostate cancer cells and bone is a bit more complicated. Once the cancer cells arrive in bone, the four major players in this vicious cycle include the cancer cells, osteoblasts, osteoclasts, and mineralized bone matrix, a major source of immobilized growth factors. Prostate cancer cells secrete factors that stimulate osteoblasts to proliferate, differentiate, and secrete growth factors. These factors are deposited into the bone matrix and also enrich the local microenvironment of the tumor cells. Tumor cells secrete osteolytic factors, most of which act via osteoblast production of the osteoclast differentiation factor, RANKL. Growth factors released from the mineralized bone matrix as a consequence of osteoclastic bone resorption further enrich the local milieu. These interactions reinforce each other to accelerate cancer progression through an over-expression of vascular endothelial growth factor (VEGF) and PDGF.[24]

Denosumab, by inhibiting RANKL, prevents maturation of osteoclasts and this interrupts the vicious cycle.[25] Radionuclide therapy targets painful osteoblastic metastases and lead to pain reduction.

We did not find in literature any report on the combined treatment of bone metastases by radionuclides together with Denosumab. However, there are a number of reports which have demonstrated

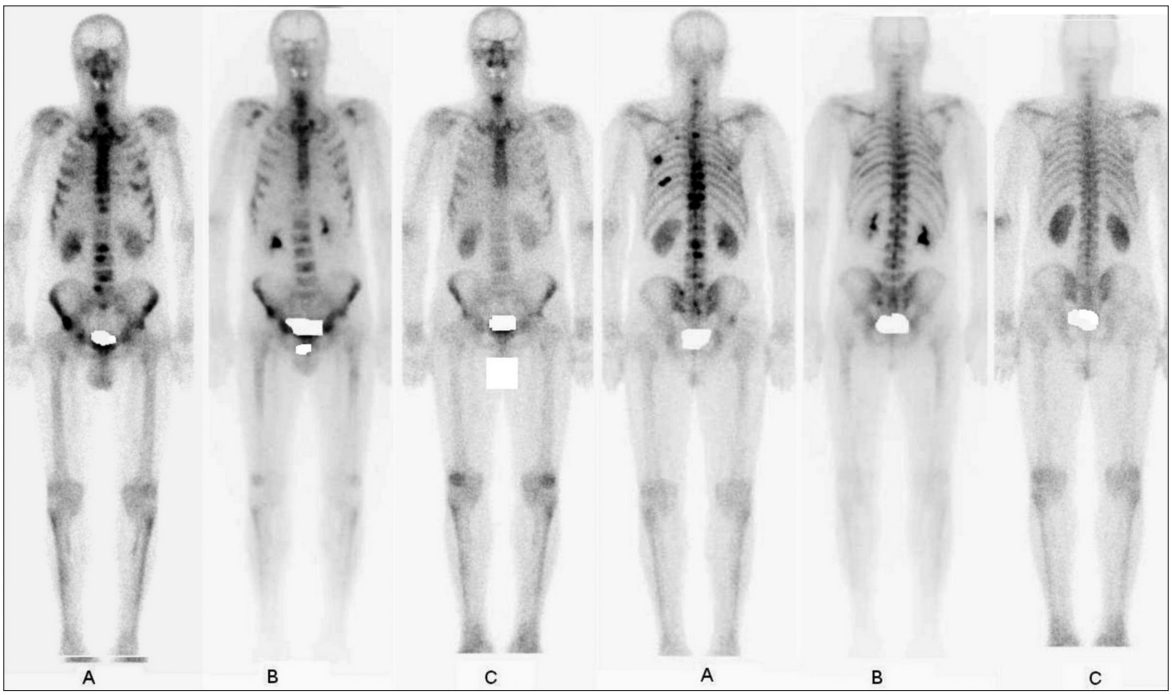

Figure 2: Serial Tc-99m MDP Bone scans in a patient of metastatic bone pain before (A) and at three (B) and six (C) months after combined treatment with Sm-153 Oxabifore and Denosumab. First three panels show anterior views and the last three panels show posterior views of the whole body scans. Multiple osteoblastic bone lesions are evident in the pre-treatment scans (panels 1 and 4). The lesions show a decreasing trend at the three month scan (panels 2 and 5); while complete resolution of the osteoblastic lesions could be noted in the 6 month scan (panels 3 and 6)

a higher effectiveness of Denosumab therapy in comparison to bisphosphonate therapy. In this regard, a placebo-controlled, multicenter, phase III study conducted by Stopeck *et al*. on 2046 patients of breast cancer with bone metastases reported Denosumab to be superior to Zoledronic acid by significantly increasing the time to first on-study SRE.[26]

In another study conducted by Fizazi *et al*.,[27] which was a randomized, placebo-controlled, multicenter, double-blind, non-inferiority trial, the authors compared the results of Denosumab (120 mg monthly) with those of Zoledronic acid (4 mg monthly) therapy. Use of Denosumab resulted in an 18% decrease in the risk of first on-study SRE in this study (P = 0.008), with the median time to first on-study SRE being 20.7 months, compared to 17.1 months in the Zoledronic acid arm. Denosumab also demonstrated superiority in the time to first and subsequent SREs over Zoledronic acid, an 18% risk reduction (P = 0.004).

It is well established that osteoclast-mediated bone resorption can be assessed by measuring urine N-telopeptide and can be inhibited by Denosumab, which, as described earlier, is a fully human antibody against RANKL. In a recent phase II study, Fizzazi *et al*. studied 111 patients having bone metastases from prostate cancer, other solid tumors, or multiple myeloma, with one or more bone lesions and urine N-telopeptide > 50 nM bone collagen equivalents per mM creatinine (urine N-telopeptide > 50) despite the use of intravenous bisphosphonates. In this study, patients were stratified by cancer type and screening urine N-telopeptide, and randomized to continue intravenous bisphosphonates every 4 weeks or receive 180 mg subcutaneous Denosumab every 4 weeks or 180 mg every 12 weeks. The primary endpoint was the proportion of patients with urine N-telopeptide < 50 at week 13. The authors reported the efficacy results for the subset of patients with prostate cancer. Patients with prostate cancer represented 45% (50 of 111) of the study population. At week 13, 22 of 32 (69%) patients in the Denosumab arms had urine N-telopeptide <50 versus 3 of 16 (19%) in the intravenous bisphosphonates cohort. At week 25, 22 of 32 (69%) Denosumab treated patients continued to have urine N-telopeptide <50 versus 5 of 16 (31%) treated with intravenous bisphosphonates. Grade 4, asymptomatic, reversible hypophosphatemia, possibly related to Denosumab, was reported in one patient. The authors concluded that in patients with prostate cancer related bone metastases and increased urine N-telopeptide despite intravenous bisphosphonate treatment, Denosumab normalized urine N-telopeptide levels more frequently than ongoing intravenous bisphosphonates.[28,29]

In our study, we did not estimate uNTx level; however, in all patients, we monitored the serum levels of alkaline phosphatase before and after treatment. According to our results, the serum level of alkaline phosphatase was

reduced significantly at 4 weeks after Sm-153 oxabifore administration, which indirectly reflects the decreasing level of osteoblastic activity of bone metastases. WB bone scans performed concurrently also showed results consistent with the biochemical results.

Conclusion

Overall results in this pilot study, our first experience in the combined treatment of bone metastases with Sm-153 oxabifore and Denosumab, have been promising and effective. However, further studies on a larger number of patients are required to substantiate our findings and to determine the actual role of this novel combined therapeutic modality in the management of patients with bone metastases.

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