The Effect of Bisphosphonates on Bone Mineral Density in Metastatic Prostate Cancer Patients Who Are Treated with Anti-Androgen Drugs and Radiotherapy

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Key Words

Metastatic prostate cancer • Osteoporosis • Radiotherapy • Bisphosphonate therapy

Abstract

Objective: To evaluate the potential effect of bisphosphonates on bone mineral density (BMD) in patients who are treated with anti-androgen drugs and radiotherapy for metastatic prostate cancer. **Materials and Methods:** The data of 31 patients with metastatic prostate cancer who were treated with anti-androgen drugs and radiotherapy during a 1-year period were retrospectively reviewed. Patients were divided in 2 groups, in which 17 patients in group 1 were treated with zoledronic acid (4 mg/month, intravenous) and 14 patients in group 2 who did not receive zoledronic acid. BMD was measured before the treatment and at the end of the 1st year by dual energy X-ray absorptiometry. Statistical analyses were performed with the T test. **Results:** Mean age of the patients was 71.42 ± 6.7 (range 59–85) years. A significant increase was noted for pelvic bone, femoral neck, and lumbar vertebrae t scores when pretreatment and 1st year measurements were compared in group 1 ($p < 0.05$). In group 2 a significant decrease was noted for pelvic bone and

femoral neck t scores at the end of the 1st year ($p < 0.05$). A significant increase was noted for pelvic bone and femoral neck follow-up in BMD values at the end of the 1st year compared to initial measurements in group 1. A significant decrease was noted for lumbar vertebrae follow-up in BMD values at the end of the 1st year when compared to initial values in group 2. **Conclusion:** Zoledronic acid significantly increases BMD and delays unfavorable outcomes for bones in men who are treated with anti-androgen drugs and radiotherapy for metastatic prostate cancer.

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Introduction

Prostate cancer is one of the most common malignancies that cause bone metastasis in older men. Osteoporosis is a frequent finding in patients with prostate cancer. The incidence of osteoporosis increases with various treatment methods including bilateral orchiectomy, gonadotropin releasing hormone (GnRH) agonists, and

combined androgen blockage therapies. These treatment methods decrease bone mineral density (BMD) and increase the risk of bone fracture [1]. Previous studies reported 0.6–4.6% annual loss in BMD for patients with non-metastatic prostate cancer. Pathological fractures caused by osteoporosis cause significant morbidity and mortality in prostate cancer patients and 21–37% of patients with prostate cancer experience pathological fractures [2–5].

Loss in bone tissue due to androgen blockage therapy and bone metastasis can potentially cause unfavorable outcomes in men with prostate cancer, in which 80% of patients with advanced prostate cancer have bone metastasis [3]. The preferred treatment method for bone metastasis is radiotherapy. However radiotherapy provides palliative treatment. Radiotherapy complications include myelo-suppression, pancytopenia, and pneumonia which disrupt patients' quality of life.

Bisphosphonate therapy decreases the pain and prevents possible pathological fractures in men with metastatic prostate cancer. Bisphosphonate, which is a synthetic pyrophosphate analog, suppresses osteoclast activity by binding to hydroxyapatite and concentrating in the bones [6]. Zoledronic acid which is the most powerful bisphosphonate including 3rd generation nitrogen, is the unique approved bisphosphonate for preventing unfavorable outcomes related to bones in patients with prostate cancer and concomitant secondary bone metastasis [7]. Zoledronic acid was proved to prevent BMD decrease when used in combination with androgen blocker drugs [4].

Recently dual energy X-ray absorptiometry (DEXA) is the gold standard method for evaluating BMD. T and Z scores are used in the evaluation of osteoporosis. The T score which is measured by the comparison of BMD of the patient and mean BMD and standard deviation values of the young adult population, is mostly used [8].

In the present study the effect of zoledronic acid on BMD was investigated in metastatic prostate cancer patients who were treated with androgen blocker drugs and radiotherapy.

Materials and Methods

The data of 31 metastatic prostate cancer patients who were treated with androgen blocker drugs and radiotherapy were retrospectively reviewed. Patients were divided in two groups according to zoledronic acid use. Group 1 included 17 patients who were treated with zoledronic acid monohydrate (4mg/month, intravenously). Group 2 included 14 patients who did not received zole-

Table 1. Mean BMD of patients in group 1 and 2

	Total hip	Femoral neck	Lumbar vertebrae
Group 1 (n = 17)			
Initial value	0.79	0.78	1.11
1st year	0.96	0.91	1.21
p value	0.037	0.021	0.062
Group 2 (n = 14)			
Initial value	0.94	0.90	1.16
1st year	0.87	0.77	0.93
p value	0.32	0.42	0.034

dronic acid. DEXA was used to interpret BMD. Total hip, femoral neck, and lumbar vertebrae BMD and t score measurements of all patients were performed initially and at the end of the 1st year with DEXA.

Clinical and laboratory data were analyzed with SPSS version 18.0. Data were displayed as mean $\pm$ SD. Statistical investigations were performed with the independent-t test and paired t test. A 5% level of significance was used for all statistical analyses and a p value of < 0.05 was considered as statistically significant.

Results

The mean age of all patients was 71.42 ± 6.7 (range 59–85) years. It was 73.54 ± 7.6 (range 64–85) years in group 1 and 70.46 ± 6.9 (range 59–82) years in group 2. A significant increase was noted for pelvic bone, femoral neck, and lumbar vertebrae t scores when 1st year follow-up values were compared with initial measurements in group 1 ($p = 0.0001$). In group 2 pelvic bone and femoral neck t scores were significantly decreased at the 1st year compared to initial values ($p = 0.001$ for the pelvic bone and $p = 0.0001$ for the femoral neck). Although lumbar vertebrae t scores increased, this was not statistically significant in group 2 ($p = 0.851$).

In group 1 pelvic bone, femoral neck, and lumbar vertebrae follow-up BMD values increased at the end of the 1st year when compared to initial findings and the increase was statistically significant for pelvic bone and femoral neck BMD ($p = 0.037$ for the pelvic bone and $p = 0.021$ for the femoral neck). The increase in lumbar vertebrae BMD value was not statistically significant ($p = 0.062$). In group 2, a significant decrease was noted for lumbar vertebrae BMD value when 1st year fol-

low-up scores were compared to initial measurements ($p = 0.034$). Although pelvic bone and femoral neck follow-up BMD scores decreased in group 2 at the end of the 1st year, this was not statistically significant ($p = 0.32$ for the pelvic bone and $p = 0.42$ for the femoral neck). Table 1 summarizes mean BMD values of all patients.

In group 1, 3 patients (17.64%) had fever $>38^{\circ}\text{C}$, 2 patients (11.76%) had myalgia, 1 patient (5.88%) had muscle spasms, pins and needles (especially around the mouth), 2 patients (11.76%) had fatigue, and 1 patient (5.88%) had flu-like symptoms.

Discussion

Several skeletal system pathologies including fractures, spinal cord compression and hypercalcemia can be seen in prostate cancer patients that use androgen blocker drugs and radiotherapy, and surgical treatment may be required. In addition the risk of osteoporosis significantly increases in older age patients. The rates of osteopenia and osteoporosis in prostate cancer patients who are not treated with anti-androgen drugs are 37 and 42% respectively. Previous studies demonstrated that androgen blockage therapy significantly increases the risk of osteoporosis in patients with osteopenia [9, 10].

Several studies proved that bisphosphonates, which are synthetic pyrophosphate analogs, prevent cancer cells attaching to the bone matrix and suppress invasion of cancer tissues into the bone matrix [11, 12]. Zoledronic acid, which is the strongest bisphosphonate, is at least 100 times more powerful than clodronate or pamidronate and 1,000 times more powerful than etidronate [7].

Bisphosphonates are an important part of bone metastasis treatment in prostate cancer guidelines. Both European and American Urology guidelines suggest the use of bisphosphonates if the patient has bone metastasis [13, 14]. The National Comprehensive Cancer Network guideline mentioned that the early use of bisphosphonates in metastatic prostate cancer patients treated with androgen blockers has a positive effect on clinical outcome and the patient's quality of life. The guideline suggests the early use of bisphosphonates in metastatic prostate cancer patients to prevent unfavorable bone pathologies [15].

Recent trials showed that intravenous bisphosphonate treatment in non-metastatic prostate cancer patients using androgen blockers significantly decreased the bone loss due to cancer therapy. In a previous study, pamidronate (60 mg/ 2 hours intravenous infusion, once in 12 weeks, for 48 weeks) significantly decreased the rate of

bone loss in prostate cancer patients who were treated with leuprolide (GnRH agonist) compared to a placebo [7, 16].

Early treatment is critical to prevent unfavorable outcomes related to bones. Patients who first experience bone pathology have 2 times the risk of recurring bone disorders [17]. A previous randomized double blinded placebo controlled study showed that zoledronic acid significantly decreased bone pathologies at 15th and 24th months compared to a placebo in 643 patients who had metastatic hormone refractory prostate cancer and delayed the first bone pathology more than 5 months. Asymptomatic patients benefit more from zoledronic acid treatment and this makes early treatment more important [18].

In a previous study zoledronic acid prevented bone pathologies in the presence of both osteolytic and osteoblastic bone metastasis in an experimental rat model injected with prostate cancer cells. In this study it was shown that zoledronic acid is effective in protecting bones both before and after bone metastasis [19]. Previous studies showed that the rate of bone metastasis increases due to bone loss related to androgen blocker therapy in prostate cancer patients. In pre-clinic tumor models it was observed that zoledronic acid suppresses osteolysis stimulated by the tumor, tumor cell proliferation and viability, and metastatic behavior of tumor cells [19, 20]. Prostate cancer patients mostly have vitamin D and calcium deficiencies both of which are significantly associated with increased bone loss [21].

In the present study we found a significant increase for pelvic bone, femoral neck, and lumbar vertebrae t scores when 1st year follow-up values were compared to initial measurements in patients who were treated with zoledronic acid monohydrate. Significant decrease was noted for pelvic bone and femoral neck t scores at the 1st year compared to initial values in patients who did not receive zoledronic acid. Although lumbar vertebrae t scores increased, this was not statistically significant. Pelvic bone, femoral neck, and lumbar vertebrae BMD values increased at the end of the 1st year when compared to initial findings and the increase was statistically significant for pelvic bone and femoral neck BMD in patients who received zoledronic acid. Pelvic bone, femoral neck, and lumbar vertebrae BMD values decreased at the end of the 1st year compared to initial measurements in group 2 and the decrease was statistically significant for the lumbar vertebrae BMD value.

Our findings showed that zoledronic acid prevents bone deterioration and delays unfavorable outcomes in

metastatic prostate cancer patients who are treated with radiotherapy. Limitations of the recent study include its non-randomized retrospective nature, low number of patients, and relatively short follow-up period.

Conclusion

Zoledronic acid significantly increases BMD and prevents unfavorable bone pathologies and has a critical role in metastatic prostate cancer patients who are treated with radiotherapy and anti-androgen drugs which potentially decrease BMD and increase bone fracture risk.

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