ORAL BISPHOSPHONATE PREVENTS BONE LOSS IN ANDROGEN DEPRIVATION THERAPY FOR NONMETASTATIC PROSTATE CANCER

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We studied the short-term efficacy of alendronate, an oral bisphosphonates, on bone mineral density (BMD) during androgen deprivation therapy (ADT) in 45 nonmetastatic prostate cancer patients at the beginning of ADT (treatment group). All received alendronate five mg daily from the initiation of ADT. Lumber BMD was evaluated by dual energy X-ray absorptiometry, at baseline and after six months of treatment. Historical data on 24 patients with prostate cancer who received ADT without bisphosphonate administration were studied as controls (control group). BMD decreased in 13.9 and 45.8% of the patients in the treatment and control groups, respectively. Mean BMD changes in the lumber spine were $+1.6\pm3.0\%$ in the treatment group and $-1.1\pm2.7\%$ in the control group ($p=0.006$). No pathological fractures occurred during the study period. No severe adverse effects were observed, but three patients could not continue alendronate treatment because of adverse events. Despite the short-term of this evaluation, our results showed that oral alendronate is an effective and safe treatment for preventing bone loss and increasing BMD in patients receiving ADT for prostate cancer.

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Key words : Prostate neoplasm, Osteoporosis, Bisphosphonate, Bone mineral, Androgen deprivation

INTRODUCTION

Androgen deprivation therapy (ADT) for patients with localized prostate cancer has been reported to be effective with median survival reported as five to ten or more years compared to that of two to five years in patients with metastatic disease[1–3]. Therefore, such patients are more likely to suffer from the long-term side effects of ADT, which is widely recognized as a risk factor for bone loss[4-6], and resultant pathological fractures[7–10]. Studies have shown the efficacy of intravenous[11–12] and intramuscular[13] administration of bisphosphonates for the prevention of bone loss in patients treated with ADT. However, the efficacy and safety of oral bisphosphonates for prostate cancer patients receiving ADT is not reported[14–15]. In a recent study, the administration of alendronate, an oral bisphosphonate, resulted in increased bone mineral density (BMD), decreased loss of height and a decreased incidence of vertebral fractures in men with osteoporosis[16–17].

In this study, we evaluated the efficacy and safety of alendronate on BMD in patients receiving ADT for localized prostate cancer.

MATERIALS AND METHODS

We evaluated 45 consecutive patients (all Japanese) who received ADT for nonmetastatic prostate cancer, as neoadjuvant hormone therapy in most cases, in our hospital from August 2002. Clinical evaluation comprised complete blood counts, serum biochemistry, serum prostate-specific antigen, abdominal computerized tomography, systemic radionuclide bone scintigram and radiogram of the chest and abdomen. Patients were excluded from the study if they had undergone ADT previously, had previous use of drugs interfering with bone metabolism, or renal or liver insufficiency. The study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained in every case.

Patients were treated with five mg alendronate daily given at wakeup with a glass of water for six months from the time they started ADT with a gonadotropin-releasing hormone agonist with or without an antiandrogen (treatment group). Historical data on 24 consecutive patients with prostate cancer who before August 2002 received ADT without bisphosphonate administration were also studied as controls (control group). Control group patients also had no bone metastasis, no ADT before and no previous use of drugs interfering with bone metabolism.

BMD was measured in the treatment and control groups at the lumber spine (L2 – L4) in anterior-posterior projection by a dual energy X-ray absorptiometry densitometer (HOLOGIC QDR2000), at baseline and at six months after starting treatment. BMD measurements were expressed in absolute terms as g/cm^2 and percent changes of the initial value. Longitudinal changes in BMD were expressed as percent

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changes as calculated by subtracting the measured BMD from the initial BMD and dividing this difference by the initial BMD. Percent changes in BMD were calculated for each individual and any decrease in BMD was determined as 1.0% change or greater. Statistical analyses were performed with commercial statistical software. Statistical significance was recognized when $p<0.05$.

RESULTS

Of the 24 patients in the treatment group, nine were excluded from the efficacy analyses because three were lost to follow-up, three failed to undergo post-treatment BMD measurement, and three discontinued alendronate treatment due to adverse events. Thus efficacy in the treatment group was analyzed using data from the remaining 36 patients. All 45 treatment group patients were included in the safety analyses. Baseline demographics were similar between the two groups (Table 1). In the total 69 study patients, serum prostate-specific antigen (PSA) levels showed substantial reductions of at least 30% after 6-month ADT, indicating serum testosterone levels were satisfactory suppressed by our ADT treatment.

Table 1. Baseline demographic characteristics of each group

	Control group	Treatment group	p value*
No. of patients	24	36	
Age	74 (60–84)	78 (58–87)	0.70
Height (m)	1.63 (1.45–1.69)	1.65 (1.45–1.74)	0.50
Weight (kg)	60.5 (47–75)	60.5 (39–76)	0.94
PSA (ng/ml)	7.3 (2.6–69)	12.8 (2.7–540)	0.11
BMD (g/cm^2)	0.984 (0.688–1.281)	0.988 (0.605–1.419)	0.98

Date are expressed as median (range). * Mann-Whitney's U test.

BMD decreased in 13.9 and 45.8% of patients in the treatment and control groups, respectively. The mean percent change in BMD at the lumber spine was $+1.6\pm3.0\%$ and $-1.1\pm2.7\%$ in the treatment and control groups, respectively. The difference in BMD change between the two groups was statistically significant ($p=0.006$ Mann-Whitney's U test, Fig. 1). In the treatment group, the BMD changes from baseline to six months were also statistically significant ($p=0.0018$, Wilcoxon test, Fig. 2), although those of the control group were not ($p=0.836$ Wilcoxon test, Fig. 2). In the treatment group, the BMD changes had no correlation with initial PSA, initial BMD and age (Spearman).

No pathological fractures were observed in either group during the study period. Of the 45 patients who received alendronate, adverse events were observed in seven patients (15.6%). Of these, six complained of gastrointestinal problems including five with a sense of chest burn or stomach discomfort and one with hiccups : two of these patients discontinued alendronate administration. The remaining patient who discontinued taking alendronate had mild drug-induced liver dysfunction. Incidences of adverse events and discontinuation were thus 15.6 and 6.7%, respectively. No patient needed further treatment and the gastrointestinal problems and liver dysfunction improved spontaneously in the three patients who

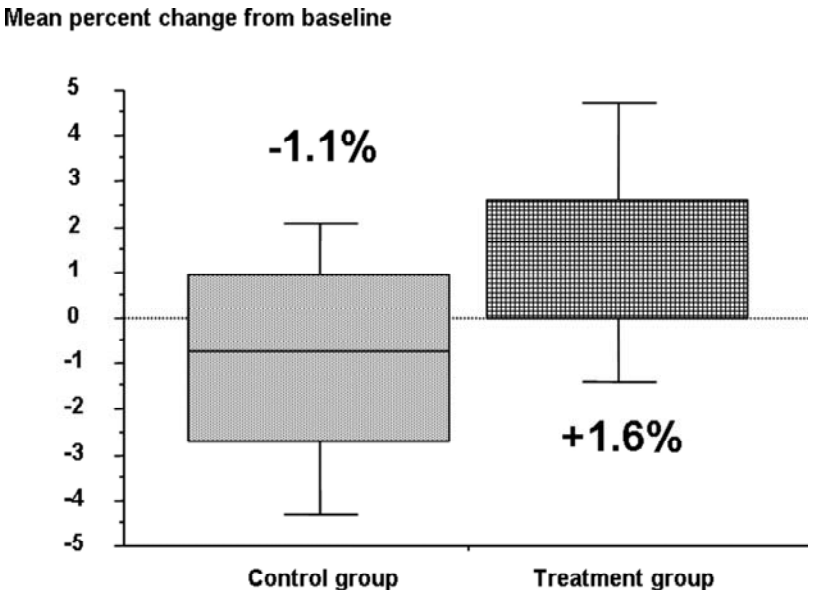

Fig. 1. Changes in BMD of all patients at baseline and at 6 months after starting treatment. BMD decreased in 45.8% of patient in the control group and in 13.9% of men in the treatment group.

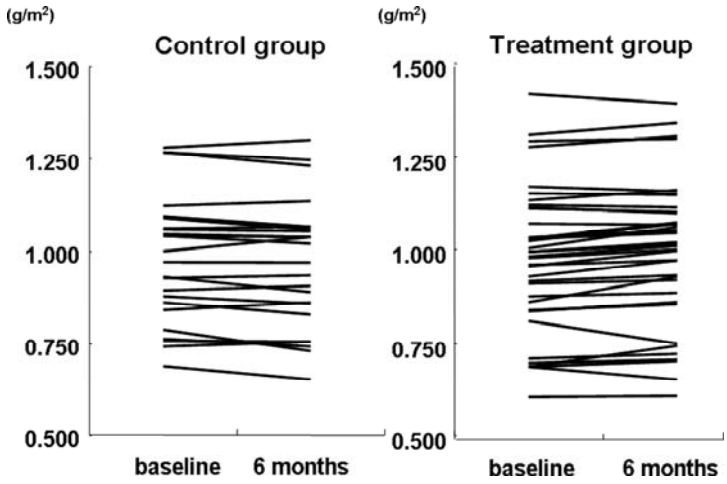

Fig. 2. Mean percent change in BMD at the lumber spine in the control and treatment groups ($p = 0.006$, Mann-Whitney's U test).

discontinued taking alendronate.

DISCUSSION

An important finding of our study is that we confirmed the adverse effects of ADT on BMD in a Japanese population. In the control group, bone loss of 1.0% or greater was observed in 45.8% of the patients despite the relatively short-term follow-up of six months. This reduction rate of 1.0% in six months is greater that the spontaneous physiological reduction from aging, 1.2 percent per year[18]. The results were consistent with previous reports that one year bone mineral losses of 2.4 to 6.6%[4,6]. Based on these previous reports and our own results, the prophylactic use of bisphosphonates for the patients receiving ADT for prostate cancer was considered.

According to our findings from the treatment group, concomitant use of alendronate in prostate cancer patients undergoing ADT showed significant efficacy for preventing bone mineral loss and improving BMD at six months. The number of patients with ADT-induced bone mineral loss in the treatment group was 13.9% which was significantly fewer than the 45.8% in the control group (Fig. 1). BMD changes in the treatment group were significantly better than those of the control group (Fig. 2). Because of small sample size and relatively shot-term follow-up we could not evaluate the efficacy for preventing pathological fractures. However, our results showing improved BMD suggested that alendronate may reduce the risk of bone fractures in patients receiving ADT for nonmetastatic prostate cancer, since BMD is inversely related to fracture risk in men and ADT is now a widely recognized risk factor for bone fractures[7–10].

Studies of intravenous or intramuscular administration of bisphosphonates have shown that they are a promising therapy against ADT-induced osteoporosis. Intravenous administration of zoledronic acid not only prevents treatment-related bone loss, but also increases BMD in men receiving ADT[12]. Intramuscularly administered, netidronate also prevents bone loss[13]. However, there are no reports of oral administration of bisphosphonates for prostate cancer patients receiving ADT. Thus this appears to be the first report on the efficacy of an oral bisphosphonate for preventing ADT-induced osteoporosis. Compared to intravenous or intramuscular administration, oral intake may be more easily accepted by some patients as it is the less invasive, however, oral administration requires both good understanding and compliance by the patients. Our results showed that alendronate,an oral bisphosphonate, is an option available for the treatment to prevent ADT-induced bone loss in nonmetastatic prostate cancer patients receiving ADT.

In our study, adverse events were not severe and compliance with taking alendronate treatment was moderately good. The 15.6% incidence of adverse events in our study was equivalent to those in previous reports : 17% for alendronate[16] and 24% for zoledronic acid[12].

Dietary supplementation with calcium and vitamin D reduces bone loss and decreases fracture risk in elderly men and women[19]. Certain living habits including maintenance of a high body mass index (BMI), weight-bearing physical activity and avoidance of alcohol and smoking also help in maintaining BMD[20]. These findings suggest that not only drugs but also life style and food should be considered for maintaining BMD especially low BMD patients receiving ADT. The synergic effects of vitamin D supplementation or a positive life styles with alendronate administration are unclear, since these factors were not evaluated in the present study.

Our study has several limitations. We evaluated just a small number of patients and only for six months because our study focused on the short-term efficacy and

toxicity of alendronate. This treatment regimen was found to be safe and effective, but was a short-term schedule and not designed as a randomized control study. Further studies will be needed to determine whether long-term alendronate administration can prevent bone complications, especially pathological fractures, and whether it can be tolerated for prostate cancer patients receiving ADT. Studies are also need to determine who are at risk of bone mineral loss by ADT, who would benefit from treatment with oral bisphosphonates and when the administration of bisphosphonate should be initiated and stopped. In our study, we were unable to detect patients who were or were not maintaining their BMD with alendronate. It would be helpful to measure bone metabolism markers including N-terminal telopeptide of type I collagen (NTX), deoxy pyridinoline (DPD), bone alkaline phosphatase (BAP) and osteocalcin, none of which were evaluated in the present study. It has yet to be elucidated whether oral bisphosphonates yield any anti-tumor effects, which has been shown in intravenous bisphosphonates in addition to the preventive effects on bone mineral loss[21]. Our findings suggested that oral alendronate is a promising alternative for preventing ADT-induced osteoporosis and provides important evidence to justify future studies on a large scale and with a randomized control design.

CONCLUSION

Oral alendronate is an effective and safe treatment for preventing treatment-related bone loss in nonmetastatic prostate cancer patients receiving ADT. Our results provide evidence of an alternative prophylactic treatment against ADT-induced osteoporosis using an easily accessible oral bisphosphonate.

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和文抄録

骨転移を有しない前立腺がん患者へのアンドロゲン除去療法による骨粗鬆症に対する経口ビスフォスフォネート製剤の予防効果について

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目的：アンドロゲン除去療法は骨塩減少とそれに伴う病的骨折の潜在的な危険因子である．点滴ビスフォスフォネート製剤はアンドロゲン除去療法を受けている前立腺がん患者に対する骨塩量の減少を予防することが示されているが経口ビスフォスフォネート製剤については評価されていない．今回，われわれは経口ビスフォスフォネート製剤の1つであるアレンドン酸を骨転移を有しない前立腺がん患者に投与して骨塩量を測定し短期間での効果を検討した．

対象と方法：治療群として45人の骨転移を有しない前立腺がん患者について検討した．アレンドロン酸を1日5 mg 経口投与し治療前，治療半年後に腰椎の骨塩量を測定し比較検討した．対照群として24人の骨転移を有しない前立腺がん患者についても同様に検討を行った．

結果：骨塩量の減少は治療群で13.9%，対照群で45.8%に見られた．腰椎における骨塩量の変化は治療群で平均1.6%，対照群で－1.1%であった（p＝0.006）．治療期間内において病的骨折は認められず，有害事象として重篤なものは認めなかったが副作用のため3例が内服継続困難であった．

結語：短期間の検討であるにもかかわらず経口ビスフォスフォネート製剤であるアレンドロン酸は前立腺がん患者に対するアンドロゲン除去療法による骨塩量減少を予防するのに有効で安全な治療法であることが示唆された．

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