Risedronate prevents persistent bone loss in prostate cancer patients treated with androgen deprivation therapy: Results of a 2-year follow-up study

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Risedronate Prevents Persistent Bone Loss in Prostate Cancer Patients Treated with Androgen Deprivation Therapy: results of a 2-year follow-up study

Running Title: Risedronate Prevents Bone Loss in Prostate Cancer Patients

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ABSTRACT

Androgen deprivation therapy for prostate cancer causes bone loss. Although we reported previously that risedronate significantly recovers bone mineral density for up to 12 months, there have been no reports with longer follow-up periods to date. The present study extended our earlier series extending the follow-up period to 24 months. Eligible patients had histologically confirmed prostate cancer without lumbar spine metastasis and underwent androgen deprivation therapy. Lumbar spine bone mineral density, urinary deoxypyridinoline, and serum bone alkaline phosphatase were measured at 6, 12, and 24 months. Among the total of 96 patients, we analyzed 26 and 18 patients in risedronate administration and control groups, respectively. Bone mineral density relative to the young adult mean ratio, urinary deoxypyridinoline, and serum bone alkaline phosphatase of the risedronate administration group recovered significantly after 24 months compared with the control group ($P<0.0001$, $P=0.0001$, and $P<0.0001$, respectively). Transient blurred vision, malaise, and vertigo were observed in 1 patient each among the 46 patients treated with risedronate within 28 days after first administration. Oral administration of risedronate is safe and effective for recovery of androgen deprivation therapy-induced bone loss in prostate cancer patients even at 24 months after commencement of treatment.

Key words: Prostate cancer; Androgen deprivation therapy; Bone loss; Risedronate

INTRODUCTION

Prostate cancer (PCa) is the most frequent malignancy in men. In Europe, about 382,000 men (11.9% of all cancers) were diagnosed with prostate cancer in 2008 [1]. In the USA, about 192,280 men (25.1% of male cancers) were diagnosed with prostate cancer in 2009, and this disease is the second most frequent cause of cancer-related death in men [2]. Androgen deprivation therapy (ADT) is usually performed in patients with locally advanced prostate cancer or metastasis. Although ADT is not supported by high level evidence for localized disease, not only in Japan but also in the USA, the frequency of ADT being chosen to treat localized disease is also increasing in clinical practice, especially in elderly patients with multiple comorbidities [3, 4]. Over 600,000 men with PCa in the USA are treated annually with ADT [5]. Osteoporosis is a serious complication of long-term ADT [6]. Bisphosphonates are agents that inhibit proliferation and differentiation of osteoclasts and repress bone resorption by osteoclasts, and have already been used for treatment of primary osteoporosis. Risedronate is a third-generation oral bisphosphonate. We reported previously that bone mineral density (BMD) of the risedronate administration group recovered significantly after 12 months compared with the control group [7]. Although long-term and continuous ADT was shown to be highly efficacious in localized PCa [8], there have been no reports regarding treatment with risedronate over periods longer than 12 months. The present study extended our earlier series to prolong follow-up, and allowed evaluation of whether risedronate recovered decreases in BMD of the lumbar spine caused by ADT through 24 months.

PATIENTS AND METHODS

Study population

All studies were performed after receiving approval from the Institutional Review Board of the Graduate School of Medical Science, Kanazawa University. This prospective observational study was performed with the same patient selection criteria as used previously [7]. However, some patients did not complete 24 months of the study, and 44 of 96 patients initially enrolled were available for analysis. Patients diagnosed with histologically proven PCa and treated with ADT (combination of luteinizing hormone-releasing hormone agonist and antiandrogens or monotherapy of luteinizing hormone-releasing hormone agonist) or newly diagnosed with PCa and scheduled for treatment with ADT were enrolled in this study. The patients with lumbar bone metastasis diagnosed with bone scintigraphy or who were previously treated with drugs that interfere with bone metabolism (bisphosphonates, calcitonin, vitamin D) were excluded from the study. After obtaining written informed consent from the patients, BMD of the lumbar spine was measured by dual-energy X-ray absorptiometry (DXA). We evaluated BMD relative to the young adult mean (YAM) because osteoporosis is diagnosed when BMD falls below 70% of YAM in Japan [9], and then divided patients into 2 groups. If the BMD/YAM ratio was less than 90%, we recommended patients take risedronate with ADT (risedronate administration group); if not, we recommended they be enrolled only for ADT (control group). However, we also took the patient's

wishes into consideration regarding enrolling in the study. A dose of 2.5 mg/day of risedronate was administered orally for 24 months in the risedronate administration group.

Measurement of bone mineral density and bone-related values

BMD was measured in all patients by DXA at baseline and after 6, 12, and 24 months at the lumbar spine (L2 to L4), and BMD/YAM ratio was calculated as a percentage. Serum testosterone (T, normal range 3.3–7.4 ng/mL) and prostate-specific antigen (PSA, normal range 0–4.0 ng/mL) were measured at baseline. Urinary deoxypyridinoline (uDPD, normal range 2.1–5.4 nmol/mmol urinary creatinine) and serum bone alkaline phosphatase (BAP, normal range 7.9–29.0 U/L) were measured at baseline and after 6, 12, and 24 months. Both urine and serum samples for measurement of these bone turnover markers were obtained between 8:30 am and 11:00 am.

Statistical analysis

Statistical analyses were performed using commercially available software (Prism). Endpoint values after 6, 12, and 24 months of treatment were compared with baseline values on enrollment by paired *t* test. Comparison of changes between groups after 6, 12, and 24 months of treatment was performed by unpaired two-sided *t* test at the 0.05 significance level. All data are presented as the mean±SD unless otherwise specified.

RESULTS

Patient population

Of the total of 96 patients (risedronate administration group, *n*=46; control group, *n*=50) initially enrolled in this study, 52 patients (risedronate administration group, *n*=20; control group, *n*=32 patients) were excluded from the analyses for several reasons as follows.

Risedronate administration group: lost to follow-up, *n*=5; changed hospital, *n*=1; withdrawal of ADT, *n*=4; commencement of zoledronate, *n*=1; commencement of alendronate, *n*=1; exodontia, *n*=1; follow-up did not reach 24 months, *n*=4; adverse events, *n*=3.

Control group: lost to follow-up, *n*=4; changed hospital, *n*=3; withdrawal of ADT, *n*=11; commencement of risedronate, *n*=3; commencement of alendronate, *n*=1; commencement of minodronate, *n*=1; commencement of vitamin D, *n*=1; external beam radiation therapy, *n*=1; follow-up did not reach 24 months, *n*=7.

In 44 patients, the mean age was 73.6 years (range, 58–88) and median ADT duration was 15.0 months (range, 0–57). Twenty-six patients were assigned to the risedronate administration group, and 18 patients were assigned to the control group. At baseline, age, T, PSA, uDPD, and BAP were not different between the risedronate administration group and the control group. However, T of 3 patients in the control group was not measured. On the other hand, BMD and BMD/YAM ratio of the risedronate administration group were significantly lower than those of the

control group (mean BMD/YAM ratio: 83.6% *vs.* 99.7%, respectively). ADT duration of the risedronate administration group was also significantly longer than that of the control group (median ADT duration: 18 months *vs.*10 months) (Table 1). These significant differences were expected because patients were divided on the basis of BMD/YAM ratio at enrollment.

Changes in bone mineral density and bone turnover markers

BMD/YAM ratio of the lumbar spine increased significantly from the baseline in patients in the risedronate administration group after 12 and 24 months (12 months, +2.55%±3.29%, P=0.0005; 24 months, +5.79%±6.37%, P<0.0001) although ADT decreased BMD/YAM ratio in the control group after 6, 12, and 24 months (6 months, –1.31%±2.6%, P=0.0478; 12 months, –2.56%±3.37%, P=0.0050; 24 months, –4.34%±6.21%, P=0.0087). BMD/YAM ratio of the risedronate administration group recovered significantly after 12 and 24 months compared with the control group (12 months, P<0.0001; 24 months, P<0.0001) (Table 2 and Fig. 1). The bone resorption marker uDPD was significantly decreased after 12 and 24 months from the baseline in the risedronate administration group (12 months, –14.5%±25.6%, P=0.0080; 24 months, –24.4%±25.5%, P= 0.0001). In addition, uDPD was significantly decreased after 12 and 24 months in the risedronate administration group compared with the control group (12 months, P=0.0217; 24 months, P=0.0001) (Table 2 and Fig. 2). However, uDPD was not measured in 3 patients at 24 months in the risedronate administration group, and they were excluded from the

analysis. The osteogenic marker BAP was significantly decreased after 6, 12, and 24 months from the baseline in the risedronate administration group (6 months, –13.5%±20.4%, P=0.0331; 12 months, –22.6%±23.2%, P<0.0001; 24 months, –32.5%±23.5%, P<0.0001). BAP was significantly increased after 12 months from the baseline in the control group (+25.6%±27.5%, P=0.0011). In addition, BAP was significantly decreased after 6, 12, and 24 months in the risedronate administration group as compared with the control group (6 months, P=0.0260; 12 months, P<0.0001; 24 months, P<0.0001) (Table 2 and Fig. 3).

Adverse events

Transient blurred vision, malaise, and vertigo (Grade 1 of National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0) were observed in 1 patient each among the 46 patients treated with risedronate within 28 days after the first administration. The symptoms in these patients improved immediately after risedronate was discontinued.

DISCUSSION

Continuous ADT decreases BMD and increases the risk of bone fracture [10–12]. Bisphosphonates have already been used for treatment of primary osteoporosis and were also reported to prevent bone loss caused by ADT [13]. Smith *et al.* reported that patients undergoing ADT who received 60 mg of pamidronate intravenously every 12 weeks exhibited no significant changes from baseline BMD at the lumbar spine, total hip, and trochanter, in contrast, placebo group had significant decreases from baseline BMD [14]. They also reported that mean BMD in the lumbar spine increased by 5.6% in patients undergoing ADT who received 4 mg zoledronate intravenously every 3 months for 1 year, and decreased by 2.2% in those given placebo [15]. After this report, there have been reported to show zoledronate consistently increase BMD beyond baseline levels in several studies [16]. On the other hand, oral bisphosphonates including risedronate also have been developed for their convenient administration. Ishizaki *et al.* reported that risedronate prevented bone loss of the femoral neck and can reverse bone loss of the lumbar spine in men receiving ADT for PCa [17]. This was the first report confirming the effect of risedronate on bone loss in PCa patients treated with ADT. A major limitation of their study was a lack of a placebo control group. Moreover, the follow-up period of 6 months may have been too short, because long-term and continuous ADT may be needed for PCa [8]. In our previous study, the follow-up period was 12 months and the risedronate administration group gained a mean of 2.6% in BMD/YAM ratio at the lumbar spine, while the control group lost 2.8% ($P<0.001$). The

control group was set but not randomized [7]. Taxel *et al.* recently reported the results of a randomized, double-blind, placebo-controlled trial [18]. In their study, 40 men receiving luteinizing hormone-releasing hormone agonist for 6 months for locally advanced PCa were randomized in the risedronate administration group and the control group. Although the control group showed a decline in BMD at the lumbar spine and the hip, the risedronate administration group had no bone loss at the hip and an increase at the lumbar spine (1.7%, P=0.04). In addition, bone turnover markers including N-telopeptide, serum C-telopeptide, and procollagen peptide, and 25-OH vitamin D and intact parathyroid hormone were increased significantly in the control group but remained unchanged in the risedronate administration group. Although their report was very important as the first randomized trial of risedronate, the follow-up period was only 6 months and dose of weekly 35 mg risedronate was double that in our setting. In the present study, bone mineral density of the lumbar spine at 24 months increased by 5.79% in the risedronate administration group as compared with a loss of 4.38% in the control group (P<0.0001). A marginally significant difference was seen between the 2 groups at 6 months. At 12 months, a significant difference was seen between the 2 groups, which was sustained through 24 months. To our knowledge, this is the first report to clarify the effect of risedronate for bone loss in PCa patients treated with ADT with a 24-month follow-up. Although Greenspan *et al.* reported that PCa patients treated with ADT receiving alendronate for 24 months showed a mean 6.7% increase at the lumbar spine, the control group also received alendronate for at least 12 months [19]. In addition, their patients received calcium and vitamin D. In the present study, significant differences in bone turnover markers,

including BAP and uDPD, between the risedronate administration group and the control group were also seen at 12 months and sustained through 24 months. The difference in percent change of the BMD/YAM ratio between the 2 groups at 24 months in the present study was >10%, and our results provide preliminary evidence in support of continuing oral bisphosphonate therapy for 24 months.

In general, bisphosphonates are well tolerated [20], and the most common adverse events associated with oral bisphosphonates are mild nausea and arthralgia [21, 22]. There have been recent reports of osteonecrosis of the jaw occurring in cancer patients treated with intravenous bisphosphonates, although it was reported that the prevalence of osteonecrosis of the jaw in patients receiving oral bisphosphonate for treatment of osteoporosis was low [23]. Consistent with these previously reported studies, minor adverse events were observed in only 3 patients in the risedronate administration group in the present study.

Our study had a number of limitations. The study design did not determine the incidence of fracture, although the risk of skeletal fractures is positively correlated with low BMD in healthy men and fragility fractures occur as often or more frequently in men with osteopenia as in those with osteoporosis [24, 25]. Moreover, short follow-up may have prevented determination of the precise statistical significance and incidence of adverse events, and patients were not randomized when they were assigned to each group. Small sample size may also result in incorrect statistical significance and incidence of adverse events. Actually, only 44 of 96 initially enrolled patients could be analyzed. All patients were Japanese, so risedronate may not have the same effects in

patients from other ethnic backgrounds, especially with regard to dose. Larger prospective studies with longer follow-up period are needed to confirm our findings.

Finally, our study provided evidence that daily oral administration of risedronate was effective in preventing bone loss in PCa patients treated with ADT at 24 months. Currently, higher doses of risedronate (17.5 mg–150 mg) are available, and monthly administration has been shown to have equivalent efficacy and tolerability to weekly dosing [26, 27]. This may improve compliance in aging men who comprise the majority of PCa patients. Our data show that PCa patients treated with ADT may prevent further bone loss for 24 months if they received risedronate administration.

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Conflict of Interest

All authors declare no conflict of interest.

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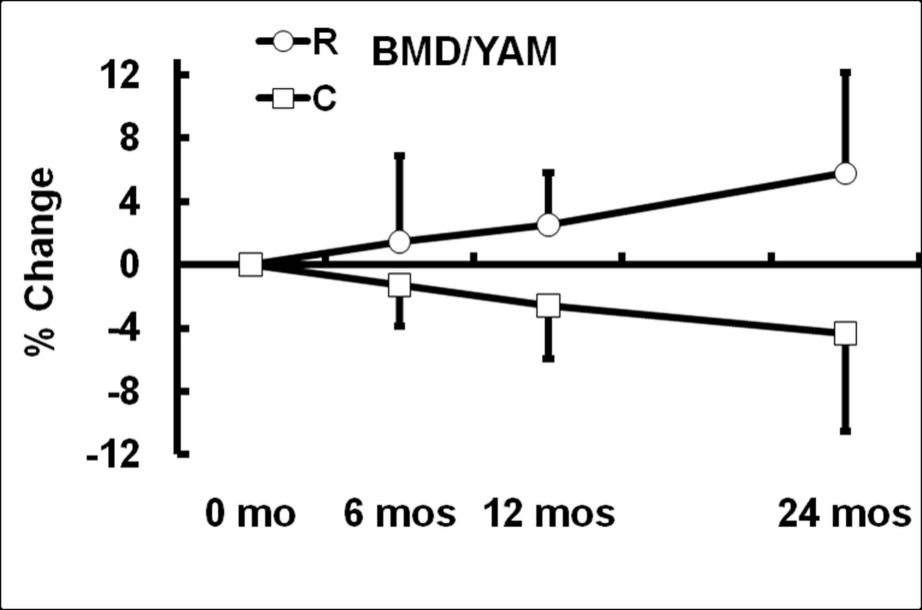
Legends to figures

Fig. 1 – Mean % changes in BMD/YAM ratio. BMD/YAM ratio of risedronate administration group showed significant recovery not only after 12 months but also after 24 months compared with the control group. R: risedronate administration, C: control.

Fig. 2 – Mean % changes in uDPD. uDPD was significantly decreased not only after 12 months but also after 24 months in the risedronate administration group compared with the control group. R: risedronate administration, C: control.

Fig. 3 – Mean % changes in BAP. BAP was significantly decreased not only after 6 and 12 months but also after 24 months in the risedronate administration group compared with the control group. R: risedronate administration, C: control.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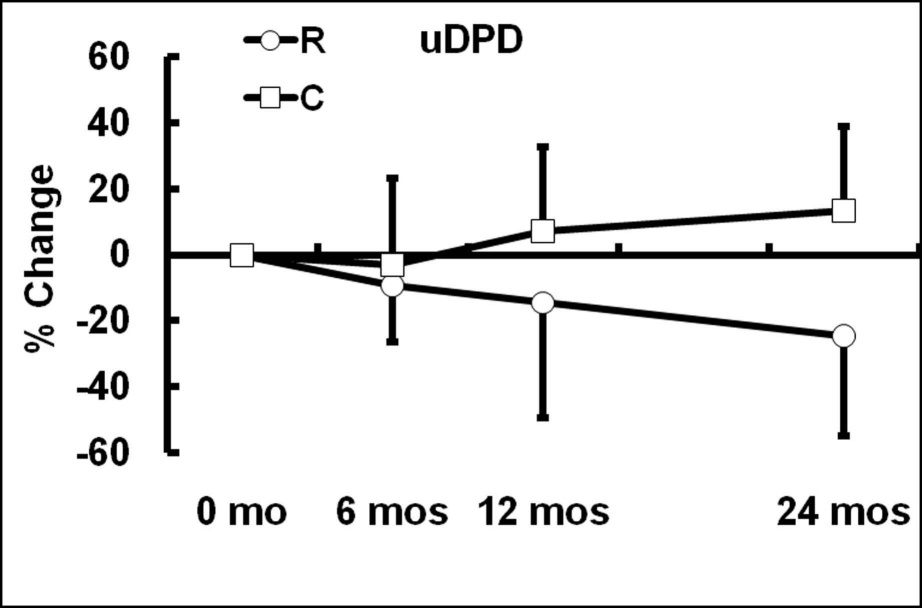
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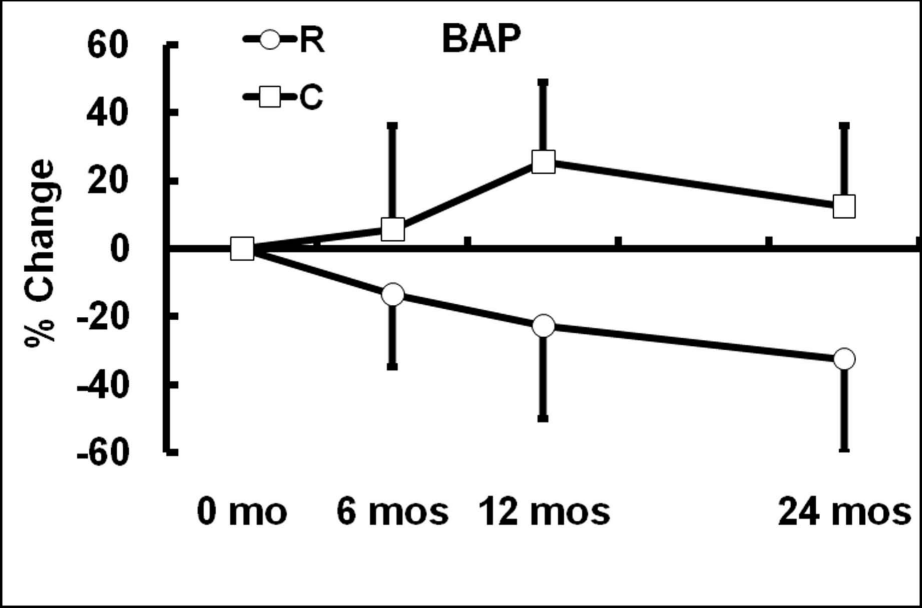
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Table 1. Patient characteristics at baseline

Variables	Risedronate (range)	Control (range)	*p* value
Case	26	18	
Mean Age (year)	73.3 (58-88)	73.9 (59-83)	0.7890
Median T (ng/mL)	0.06 (0.02-0.25)	0.12 (0.02-5.58)	0.0559
Median PSA (ng/mL)	0.042 (0.008-0.576)	0.056 (0.008-177.5)	0.1404
Median ADT duration (months)	18 (2-57)	10 (0-26)	0.0152
Mean BMD (g/cm^2)	0.992 (0.74-1.40)	1.18 (0.97-1.80)	0.0020
Mean BMD/YAM ratio (%)	83.6 (65-117)	99.7 (84-152)	0.0016
Mean uDPD (nmol/mmol Creatinine)	6.87 (4.1-10.0)	6.48 (4.1-12.2)	0.4918
Mean BAP (U/L)	30.3 (16.8-75.2)	28.4 (11.1-48.8)	0.5678

ADT, Androgen-deprivation therapy; T, Testosterone; PSA, Prostate specific antigen; BMD, Bone mineral density; YAM, Young adult mean; uDPD, Urinary deoxypyridinoline; BAP, Bone alkaline phosphatase.

Table 2. % changes in bone mineral density and bone turnover markers

		6 months			12 months			24 months		
		mean (SD)	*p* value[a]	*p* value[b]	mean (SD)	*p* value[a]	*p* value[b]	mean (SD)	*p* value[a]	*p* value[b]
BMD/YAM ratio	Risedronate	+1.48 (5.44)	0.1869	0.0512	+2.55 (3.29)	0.0005	<0.0001	+5.79 (6.37)	<0.0001	<0.0001
	Control	-1.31 (2.6)	0.0478		-2.56 (3.37)	0.0050		-4.34 (6.21)	0.0087	
uDPD	Risedronate	-9.19 (26.2)	0.0857	0.3810	-14.5 (25.6)	0.0080	0.0217	-24.4 (25.5)	0.0001	0.0001
	Control	-2.94 (17.4)	0.4826		+7.18 (34.7)	0.3921		+13.2 (30.2)	0.0806	
BAP	Risedronate	-13.5 (20.4)	0.0331	0.0260	-22.6 (23.2)	<0.0001	<0.0001	-32.5 (23.5)	<0.0001	<0.0001
	Control	+5.70 (21.2)	0.2696		+25.6 (27.5)	0.0011		+20.0 (27.4)	0.0703	

ADT, Androgen-deprivation therapy; BMD, Bone mineral density; YAM, Young adult mean; uDPD, Urinary deoxypyridinoline; BAP, Bone alkaline phosphatase; [a] Comparison with basal values, [b] Comparison between risedronate-administrated group and control group