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ORIGINAL ARTICLE

Zoledronic acid combined with androgen-deprivation therapy may prolong time to castration-resistant prostate cancer in hormone-naïve metastatic prostate cancer patients – A propensity scoring approach



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Received 7 April 2015; received in revised form 30 July 2015; accepted 12 October 2015

Available online 31 October 2015

KEYWORDS

Zoledronic acid;

Abstract *Objective:* To clarify the oncological benefit of zoledronic acid for hormone-naïve metastatic prostate cancer, patient outcome of androgen deprivation therapy with zoledronic acid (ADT + Z) and androgen deprivation therapy alone (ADT) was compared.

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Peer review under responsibility of Shanghai Medical Association and SMMU.

<http://dx.doi.org/10.1016/j.ajur.2015.10.003>

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Hormone-naïve prostate cancer; Biochemical recurrence; Propensity score-match analysis

Methods: Fifty-two patients with pathologically confirmed metastatic prostate cancer were prospectively enrolled and treated with combined androgen blockade (goserelin and bicalutamide) with zoledronic acid (4 mg every 4 weeks for 24 months). A propensity score-match with logistic regression analysis was applied to select 50 pair-matched cohorts (both from ADT + Z and from historical control cohorts who had undergone ADT alone), and patient outcomes were compared.

Results: Patients with ADT + Z had significantly longer time to progression (TTP) than those with ADT (median TTP; 24.2 vs. 14.0 months, $p = 0.0092$), while no significant difference of overall survival between two groups ($p = 0.1502$). Multivariate analysis for biochemical recurrence revealed treatment with ADT was the sole independent prognostic factor (HR: 1.724, 95% CI: 1.06–2.86, $p = 0.0297$).

Conclusion: Combination of zoledronic acid with ADT may prolong time to castration resistant prostate cancer.

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1. Introduction

Although androgen deprivation therapy (ADT) is still a mainstay for the treatment of advanced or metastatic prostate cancer, several serious adverse events has been reported including skeletal-related events (SREs) due to decreasing bone mineral density [1]. Zoledronic acid is a potent bisphosphonate that selectively binds to bone mineral surfaces at sites of active bone remodeling, thereby inhibiting osteoclastic bone resorption [2], and is recommended for the prevention of skeletal morbidity in patients with castration-resistant prostate cancer (CRPC) [3]. Pre-clinical studies have also demonstrated anti-proliferative activity against prostate cancer cells *in vitro* and *in vivo* [4,5]. Combination of zoledronic acid therapy with ADT (ADT + Z) is likely to be beneficial not only for the prevention of SREs, but also for anti-tumor effect in patients with hormone-naïve prostate cancer [6–9], while no definite oncological benefit has been drawn due to the comparison with historical control [6–8], or to subgroup analysis [9].

We conducted multi-institutional phase II study to determine the benefits of ADT + Z, and published the data concerning the safety and efficacy preventing SREs [10]. This is a subgroup analysis of the selected cohort from the original study with a primary endpoint of the SRE-free survival at 24 months after treatment [10]. The aim of this study is to study if ADT + Z may have better oncological outcomes than ADT alone with minimizing the potential bias of the background using propensity score analysis [11].

2. Materials and methods

2.1. Patient eligibility

Hormone-naïve patients with pathologically confirmed adenocarcinoma of the prostate and radiologic evidence of bone metastasis were eligible. Detailed patient eligibility and study design were reported elsewhere [10]. In brief, a single-arm open-label multi-institutional phase II study was conducted (clinical trials registry number: UMIN000007548).

All patients provided written informed consent before enrollment in the study. The primary endpoint was the 24-month SRE-free survival rate. The secondary end points were time to the first SRE, time to prostate-specific antigen (PSA) progression, overall survival (OS), decrease in the extent of bone disease, improvement in pain, and safety.

2.2. Treatment and evaluations

ADT consisted of bicalutamide 80 mg administered orally on Day 1 and every day, goserelin acetate 10.8 mg administered subcutaneously on Day 8 and every 12 weeks, and zoledronic acid 4 mg administered intravenously on Day 8 and every 4 weeks. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 were eligible, except for ECOG PS 2 due to bone pain was permitted. Biochemical recurrence (BCR) was defined as the time to a proportional increase of $\geq 25\%$ and an absolute increase of ≥ 2 ng/mL from the nadir, confirmed by a second value obtained ≥ 3 weeks later. If no decline from the baseline value was documented, time to PSA progression was defined from 12 weeks when there was a proportional increase of $\geq 25\%$ and an absolute increase of ≥ 2 ng/mL from the baseline value [10]. Discontinuation of bicalutamide was allowed if BCR was documented, or at the discretion of the physician. Zoledronic acid was continued in principle for 24 months. Drug interruptions were required for any drug-related toxicity of grade 3 or higher, and grade 2 toxicity with patients' wish for withdrawal. Laboratory examinations (routine serum chemistry, hematology, and PSA measurements) and assessments for SREs and adverse events were performed at baseline and every 4 weeks thereafter. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. The end points of the study were BCR and OS.

2.3. Statistical analysis

Baseline PSA at 3 months after initiation of ADT + Z therapy were dichotomized based on the receiver operating characteristic (ROC) for BCR with statistical significant cutoff of 171 ng/mL (area under the curve (AUC): 0.6328,

$p = 0.024$). Case-matching and multivariable regression modeling techniques were used to estimate the association of ADT + Z with oncologic outcomes (BCR and OS) after adjusting for potential treatment selection bias (age, biopsy Gleason score, baseline PSA) using the propensity score [11,12]. A Kaplan–Meier’s plot with log-rank test was used to estimate the statistical difference of time to all cause death, or to BCR. A Cox proportional hazards model was applied for the estimation of factors predicting disease progression in multivariate analysis. All p values are 2-sided. Statistical analysis was performed with SPSS statistics version 21 (IBM, IL, USA), and JMP ver. 9 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Assignment of the propensity score and validation

The propensity score was assigned to 52 cases with ADT + Z and 134 historical control cohorts who had received ADT alone (median PSA: 134 ng/mL, mean age: 73.9 years, percent Gleason score ≥ 8 : 61%), and ranked in order of the score. Approximate values (within 0.03) were regarded as score-match [12], and 50 pair-matched cases were selected from each group. Potential prognostic factors affecting BCR and OS (patient age, baseline PSA, and biopsy Gleason score) were well balanced between ADT and ADT + Z when stratified by quintiles of propensity score. Calculated propensity score was validated as representative of each covariate.

3.2. Overview of the study

Patient background between ADT and ADT + Z was shown in Table 1. Median age and baseline PSA were 73.0 years (range, 55–86) and 241 ng/mL (range, 2.19–19201). Overall death and BCR were 30 and 72 patients, respectively, with a median follow-up of 33.2 months. Median time to PSA progression

was 15.0 months. Overall death and BCR was significantly more in ADT than in ADT + Z ($p = 0.0156$ and 0.0034 , respectively). Thirty-two of the 50 patients (64.0%) had accomplished 24-month treatment of the zoledronic acid with a median duration of 23.2 months ranging 1.8–43.8 months. Sixteen patients have been treated with the drug due to patients’ wish. Reasons of the withdrawal of zoledronic acid were adverse event (4 cases), progressive disease (7 cases), cancer death (3 cases), refusal by the patients (3 cases), and change to another hospital (1 case), respectively.

3.3. Comparison of patient outcomes between ADT and ADT + Z

Patient outcomes were compared between two groups (Fig. 1). Patients with ADT + Z had significantly longer TTP than those with ADT (Fig. 1(A), median TTP; 24.2 vs. 14.0 months, $p = 0.0092$), whereas no significant difference of OS between two groups (Fig. 1(B), $p = 0.1502$). Multivariate analysis revealed ADT + Z was the sole independent predictor for BCR with a 28% risk reduction of the event (Table 2, HR: 1.724, 95%CI: 1.06–2.86, $p = 0.0297$).

3.4. Subgroup analysis of patients with zoledronic acid

Fig. 2 depicted subgroup analyses of 50 patients treated with ADT + Z stratified by Gleason score and baseline PSA. Patients with lower Gleason score (≤ 7) had significantly longer TTP in ADT + Z than that in ADT (Fig. 2(A), median TTP: not reached vs. 15.0 months, $p = 0.0157$), while no significant difference was shown in patients with higher Gleason score (≥ 8) (Fig. 2(B), median TTP: 15.0 vs. 13.0 months, $p = 0.3243$). Likewise, patients with lower PSA (≤ 171 ng/mL) had significantly longer TTP in ADT + Z than that in ADT (Fig. 2(C), median TTP: not reached vs. 15.0 months, $p = 0.0207$), whereas no significant difference in those with higher PSA (>171 ng/mL) (Fig. 2(D), median TTP: 14.8 vs. 14.0 months, $p = 0.1636$).

Table 1 Patient background between ADT and ADT + Z groups adjusted by propensity score-match analysis.

	All cases ($n = 100$)	ADT + Z ($n = 50$)	ADT ($n = 50$)	p -Value
Propensity score ^a	0.3	0.3	0.3	0.93
Age (year) ^b	73.0	71.8	73.7	0.202
PSA (ng/mL) ^b	241	249	207	0.8722
Gleason score				0.5871
≤ 6	6	4	2	
7	28	15	13	
≥ 8	66	31	35	
Follow-up (month) ^b	33.2	31.3	37.0	0.0363
TTP (month) ^b	15.0	24.2	14.0	0.0172
Overall death (n)	30	9	21	0.0156
Cause-specific (n)	25	7	18	
Other cause (n)	5	2	3	
Biochemical recurrence (n)	72	29	43	0.0034

ADT, androgen deprivation therapy; PSA, prostate specific antigen; TTP, time to PSA progression; ADT + Z, androgen deprivation therapy with zoledronic acid.

^a Data presented as mean.

^b Data presented as median.

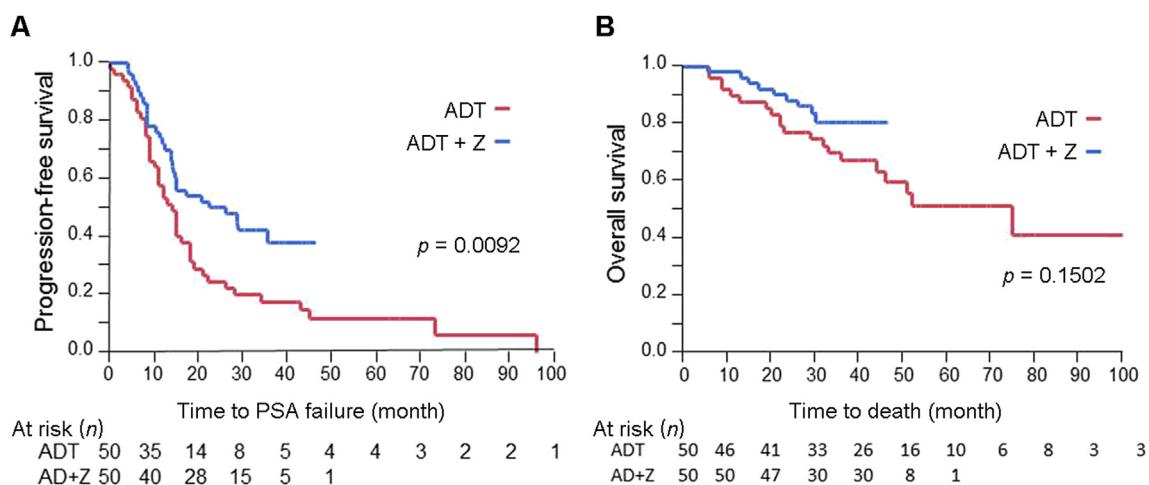


Figure 1 Kaplan–Meier’s plot for (A) progression-free survival and (B) overall survival stratified by androgen deprivation therapy with or without zoledronic acid. ADT, androgen deprivation therapy; ADT + Z, androgen deprivation therapy with zoledronic acid; PSA, prostate specific antigen.

3.5. Adverse events

Adverse events in the ADT + Z were observed in nine (18%), including six cases of grade 3. The grade 3 osteonecrosis of the jaw and renal dysfunction was reported in three (6%) and one (2%) patients. No fetal adverse events was noted in the combination group.

4. Discussion

Several literatures have suggested the anti-tumor effect of zoledronic acid in patients with hormone-naïve prostate cancer [6–9]. Kamiya et al. [6] compared 23 cases with zoledronic acid with ADT to 42 historical control cohorts (ADT alone) regarding the PSA and bone turnover marker declines, and concluded that combination of zoledronic acid with ADT had better PSA and bone turnover marker declines, suggesting the potential anti-tumor effect of zoledronic acid. Okegawa et al. [7] reported that biopsy Gleason score, pre-treatment serum N-telopeptide of type I collagen (NTx), and treatment with zoledronic acid were shown to be independent predictors of PSA failure-free survival time. Uemura et al. [8] reported zoledronic acid with ADT had significantly longer TTP and OS than ADT

alone (historical control) in patients with higher extent of disease (\geq grade 3). Ueno et al. [9] conducted randomized controlled trial comparing the efficacy of progression-free survival of zoledronic acid with ADT to ADT alone. Although no significant difference was noted between two groups, subgroup analysis demonstrated combination treatment improved progression-free survival with 10-month advance in median TTP for patients with high Gleason score. In this study, we applied the propensity score-match analysis which minimizes the selection bias inherent in retrospective cohort studies by creating risk quintiles to match subjects across treatment groups [11–14]. Our results were in good agreement with previous reports regarding the oncological benefit of BCR of zoledronic acid. Although BCR is a surrogate marker for cancer-specific survival, duration of ADT, or time to CRPC was reported to be well correlated with OS in patients with metastatic prostate cancer [15]. Thus, it is worthwhile to extend the median TTP by 10.2 months by adding zoledronic acid. The figure is identical to the data reported by Ueno et al. [9] from patients with high Gleason score. Subgroup analysis of our study, however, were in contrast with the data that zoledronic acid was more effective in higher Gleason score [9]. The discrepancy may result from different patients’ backgrounds. Santini et al. [16] found

Table 2 Proportional hazard model for biochemical recurrence in patients with metastatic hormone naïve prostate cancer.

Factor	Univariate			Multivariate		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age	1.007	0.97–1.04	0.6849	1	0.97–1.04	0.7755
PSA	1	1.00–1.00	0.0453	1	1.00–1.00	0.1305
Treatment ADT vs. ADT + Z	1.8275	1.13–2.99	0.0136	1.724	1.06–2.86	0.0297
Gleason score						
≤6	Baseline		0.0829	Baseline		0.2569
7	0.8506	0.28–3.66		0.6826	0.22–2.99	
≥8	1.549	0.57–6.38		1.09	0.38–4.60	

ADT, androgen deprivation therapy; ADT + Z, androgen deprivation therapy with zoledronic acid; PSA, prostate specific antigen.

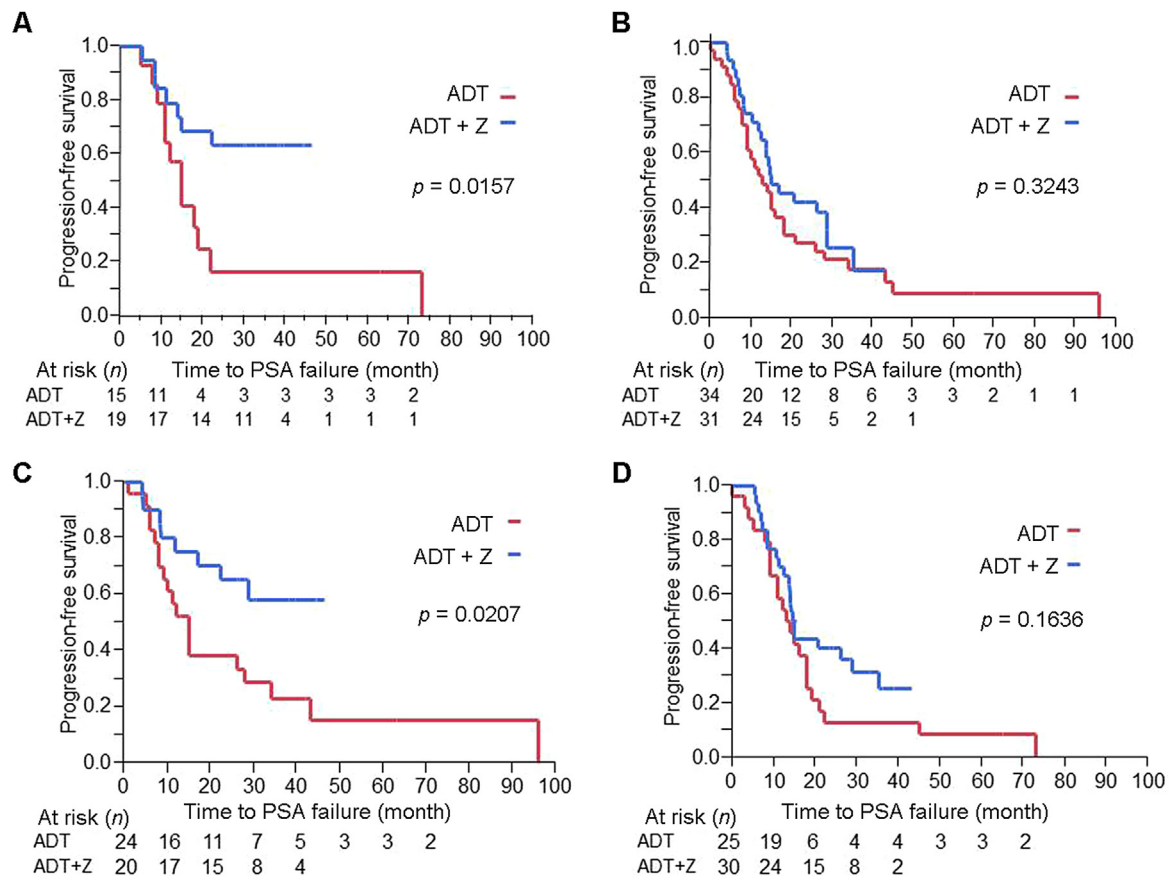


Figure 2 Kaplan–Meier’s plot for progression-free survival by androgen deprivation therapy with or without zoledronic acid in patients who were sub-grouped with dichotomized Gleason score (A) (B), or PSA (C) (D). Gleason score was categorized Gleason score ≤ 7 (A) and Gleason score ≥ 8 (B). PSA level was categorized PSA ≤ 171 ng/ml (C) and > 171 ng/ml (D). PSA cut off (171 ng/mL) was set based on the result of receiver operating characteristic. ADT, androgen deprivation therapy; ADT + Z, androgen deprivation therapy with zoledronic acid; PSA, prostate specific antigen.

repeated low-dose therapy with zoledronic acid (1 mg every week for four times followed by 4 mg with a standard 28-day schedule) could induce an early significant and long-lasting decrease of vascular endothelial epidermal growth factor (VEGF) levels in 26 advanced solid tumor patients. The report may support our hypothesis of direct anti-tumor effect of zoledronic acid. On the other hand, care must be taken for adverse events including osteonecrosis of the jaw or renal dysfunction as found in our study. Baseline status of oral hygiene and potential chronic kidney disease (CKD) should be checked before starting zoledronic acid.

There are several limitations of the study. Retrospective study with relatively small number of cohort, inter-pathologist variation of Gleason score from multiple institutions should be considered for the correct interpretation of the study. These factors are likely to yield discrepancy between our result and other literatures regarding the efficacy of subgroup analysis. It should be noted that the application of propensity-match score analysis is not always a standard one for the prospectively collected cohort because propensity analysis was originally developed for the observation study which was difficult for randomization. Since there are several studies in which authors applied propensity analysis in a similar way, application of this analysis might be acceptable [17,18].

5. Conclusion

Combination therapy of 2-year zoledronic acid treatment with ADT may have better efficacy than ADT alone, and prolong time to castration resistant prostate cancer with a median of 10.2 months in patients who have lower baseline PSA or less than 8 Gleason score.

Conflicts of interest

The authors declare no conflict of interest.

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