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ORIGINAL ARTICLE

# Significance of baseline bone markers on disease progression and survival in hormone-sensitive prostate cancer with bone metastasis

**Masahiro Nozawa · Isao Hara · Hideyasu Matsuyama · Masayuki Iki · Kazuhiro Nagao · Tsukasa Nishioka · Takahiro Komura · Atsunobu Esa · Shigeya Uejima · Masaaki Imanishi · Yasunari Uekado · Takatoshi Ogawa · Hiroshi Kajikawa · Hirotsugu Uemura**

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**Abstract**
*Purpose* This study evaluated the baseline patient characteristics associated with the time to biochemical progression and overall survival in patients who participated in a phase II trial on zoledronic acid combined with the initial androgen-deprivation therapy for treatment-naïve bone-metastatic prostate cancer.
*Methods* Patients received zoledronic acid 4 mg intravenously every 4 weeks for up to 24 months, concomitantly started with bicalutamide 80 mg orally every day and goserelin acetate 10.8 mg subcutaneously every 12 weeks.
*Results* A total of 53 Japanese patients were enrolled between July 2008 and April 2010, and 52 patients were evaluable. Median follow-up period was 41.6 months. Updated median time to biochemical progression was 25.9 months (95 % confidence interval 14.5–49.9). Higher serum bone-specific alkaline phosphatase was an independent risk factor for time to biochemical progression based on multivariate analysis (hazard ratio 6.51; 95 % confidence interval 2.71–15.62; $P < 0.001$). Median time to biochemical progression for patients with serum bone-specific alkaline phosphatase level higher than 26 μg/L was 12.7 months. Multivariate analysis indicated that higher serum C-terminal telopeptide of type I collagen independently increased the risk of death (hazard ratio 9.62; 95 % confidence interval 2.11–43.89; $P = 0.003$). Median overall survival for patients with serum C-terminal telopeptide of type I collagen level higher than 8.0 ng/ml was 31.1 months.

M. Nozawa (✉) · H. Uemura
Department of Urology, Faculty of Medicine, Kinki University, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Japan
e-mail: nozawa06@med.kindai.ac.jp

I. Hara
Department of Urology, Wakayama Medical University, Wakayama, Japan

H. Matsuyama · K. Nagao
Department of Urology, Graduate School of Medicine, Yamaguchi University, Ube, Japan

M. Iki
Department of Public Health, Faculty of Medicine, Kinki University, Osaka-Sayama, Japan

T. Nishioka
Department of Urology, Sakai Hospital, Faculty of Medicine, Kinki University, Sakai, Japan

T. Komura
Department of Urology, Naga Hospital, Kinokawa, Japan

A. Esa
Department of Urology, NTT Osaka Hospital, Osaka, Japan

S. Uejima
Department of Urology, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan

M. Imanishi
Department of Urology, Tondabayashi Hospital, Tondabayashi, Japan

Y. Uekado
Department of Urology, Wakayama Rosai Hospital, Wakayama, Japan

T. Ogawa
Department of Urology, Kainan Municipal Hospital, Kainan, Japan

H. Kajikawa
Department of Urology, Izumiotsu Municipal Hospital, Izumiotsu, Japan

*Conclusions* Baseline bone markers can be useful as predictors for disease progression and survival time in patients with bone metastasis from treatment-naïve prostate cancer treated with upfront zoledronic acid concomitantly started with androgen-deprivation therapy.

**Keywords** Bisphosphonate · Bone marker · Bone metastasis · Predictive marker · Prognostic factor · Prostate cancer

## Introduction

Prostate cancer (PCa) is one of the primary diseases that cause bone metastasis most frequently [1]. Bone metastasis may evoke skeletal-related events (SRE) which lead to not only impaired quality of life, but also poor prognosis [2–4]. Therefore, prevention of SRE plays a very important role in treatment of patients with bony-metastatic PCa.

Zoledronic acid (ZA), a potent bone-modifying agent (BMA) that suppresses osteoclasts, proved its efficacy to prevent SRE compared with placebo in patients with castration-resistant prostate cancer (CRPC) and with bone metastasis based on a phase III trial [5]. However, there can be some patients who benefit from the administration of BMA in the earlier stages before CRPC, or other patients may progress earlier than expected despite adding BMA to the first-line androgen-deprivation therapy (ADT), for whom other treatment modalities may be beneficial, for example, more recent hormone therapy such as abiraterone and enzalutamide or other treatment with distinct mechanism of action like docetaxel or radium-223. It would be beneficial for the future development of novel treatment strategies if biomarkers that predict poor responsiveness to the existing therapy at diagnosis were established.

We previously performed and reported the prospective phase II study on ZA combined with the initial ADT for treatment-naïve bone-metastatic PCa [6]. The SRE-free survival rate at the first 24 months, the primary endpoint, was 84.4 % in the study. Here, we updated the time to prostate-specific antigen (PSA) progression (TPP) and overall survival (OS) and evaluated the baseline patient characteristics associated with early PSA progression or poor survival in patients who participated in the trial.

## Materials and methods

### Patients

This study was performed based on data from a single-arm, open-label, phase II clinical trial of ZA, in which patients with bone metastases from treatment-naïve PCa were enrolled [6]. Key inclusion criteria were as follows: radiologic evidence of bone metastasis; histologically confirmed adenocarcinoma of the prostate; no prior systemic or local therapy for PCa; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; no history of bisphosphonate therapy; and no history of another malignancy within the preceding 5 years [6]. ECOG PS of 2 due to the bone disease was permitted. The study was conducted according to the declaration of Helsinki with approval from ethics committees at each institution. Written informed consent was obtained from all patients consistent with local requirements.

### Study design

Patients received ZA (Zometa; Novartis Pharma, Tokyo, Japan) 4 mg intravenously every 4 weeks for up to 24 months, concomitantly started with ADT of maximum androgen blockade consisting of bicalutamide (Casodex; AstraZeneca, Osaka, Japan) 80 mg orally every day, and goserelin acetate (Zoradex; AstraZeneca, Osaka, Japan) 10.8 mg subcutaneously every 12 weeks [6]. PSA progression and survival were also monitored and updated for the current analyses. Serum PSA levels were assessed every 4 weeks. PSA progression was defined as the date that a 25 % or greater increase and an absolute increase of 2 ng/mL or more from the nadir was documented, which was confirmed by a second value obtained three or more weeks later, or as the date that a 25 % increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment where no decline from baseline was documented [7]. Baseline patient characteristics associated with TPP or OS were analyzed in the current study.

### Bone markers evaluation

Serum bone-specific alkaline phosphatase (BAP) was determined by the chemiluminescent enzyme immunoassay kit (Access OSTASE; Beckman Coulter, Fullerton, CA, USA). Urinary N-terminal cross-linked telopeptide of type I collagen (uNTx) was determined by the enzyme-linked immunosorbent assay kit (Osteomark NTx urine ELIZA; Alere, Waltham, MA, USA). Level of uNTx was adjusted for urinary creatinine. Serum C-terminal telopeptide of type I collagen (ICTP) was determined by the radioimmunoassay kit (UniQ ICTP RIA; Orion Diagnostica, Espoo, Finland).

### Statistical analyses

TPP and OS were estimated using the Kaplan–Meier method. The significance of difference in the

Kaplan–Meier curves was determined using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional-hazard model with step-up procedure for evaluation of baseline patient clinical factors associated with TPP and OS. A level of $P < 0.05$ was accepted as the statistical significance. S-Plus Ver. 6.1 (NTT DATA Mathematical Systems Inc., Tokyo, Japan) was used for the Kaplan–Meier analysis. Data were analyzed with IBM SPSS Statistics ver. 22.0 (IBM, Armonk, NY, USA).

**Table 1** Baseline values of prostate-specific antigen and bone markers ($n = 52$)

| Marker | Median | Range |
|---|---|---|
| PSA (ng/mL) | 249.4 | (2.19–19,201.0) |
| ALP (U/L) | 364 | (43–5,888) |
| BAP (μg/L) | 26.0 | (6.1–1,100) |
| ICTP (ng/mL) | 6.2 | (1.9–34.8) |
| uNTx (nmol/mmol Cr) | 64.4 | (14.2–906.8) |

*ALP* alkaline phosphatase, *BAP* bone-specific alkaline phosphatase, *ICTP* C-terminal telopeptide of type I collagen, *PSA* prostate-specific antigen, *uNTx* urinary N-terminal cross-linked telopeptide of type I collagen

## Results

### Patient demographics

A total of 53 Japanese men with bone metastases from treatment-naïve PCa were enrolled between July 2008 and April 2010, and 52 patients were evaluable. Patient characteristics were described in detail in the previous report

**Table 2** Univariate and multivariate analyses using Cox proportional-hazard model for time to PSA progression

| Variables | Category | Univariate | | | Multivariate (step-up procedure) | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age (years) | ≤72 | Reference | | | | | |
| | >72 | 0.52 | (0.25–1.09) | 0.082 | | | |
| ECOG PS | 0 | Reference | | | | | |
| | 1 or 2 | 1.39 | (0.53–3.63) | 0.498 | | | |
| Pain score | ≤2 | Reference | | | | | |
| | ≥3 | 1.58 | (0.76–3.30) | 0.220 | | | |
| Gleason score | ≤7 | Reference | | | | | |
| | ≥8 | 2.59 | (1.11–6.06) | 0.028 | | | |
| Local stage | ≤T3a | Reference | | | | | |
| | ≥T3b | 1.89 | (0.86–4.14) | 0.111 | | | |
| Lymph-node metastasis | No | Reference | | | | | |
| | Yes | 1.91 | (0.92–3.99) | 0.084 | | | |
| EOD score | ≤2 | Reference | | | | | |
| | ≥3 | 2.98 | (1.40–6.35) | 0.005 | | | |
| PSA (ng/mL) | ≤249.4 | Reference | | | | | |
| | >249.4 | 1.76 | (0.86–3.62) | 0.123 | | | |
| ALP (U/L) | ≤300 | Reference | | | | | |
| | >300 | 2.16 | (0.98–4.77) | 0.057 | | | |
| BAP (μg/L) | ≤26.0 | Reference | | | Reference | | |
| | >26.0 | 6.51 | (2.71–15.62) | <0.001 | 6.51 | (2.71–15.62) | <0.001 |
| ICTP (ng/mL) | ≤5.0 | Reference | | | | | |
| | 5.0< , ≤8.0 | 0.91 | (0.36–2.31) | 0.844 | | | |
| | >8.0 | 2.76 | (1.19–6.41) | 0.018 | | | |
| uNTx (nmol/mmol Cr) | ≤50 | Reference | | | | | |
| | 50<, ≤100 | 3.05 | (1.15–8.12) | 0.025 | | | |
| | >100 | 6.82 | (2.59–17.98) | <0.001 | | | |

*ALP* alkaline phosphatase, *BAP* bone-specific alkaline phosphatase, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EOD* extent of bone disease, *HR* hazard ratio, *ICTP* C-terminal telopeptide of type I collagen, *PSA* prostate-specific antigen, *uNTx* urinary N-terminal cross-linked telopeptide of type I collagen

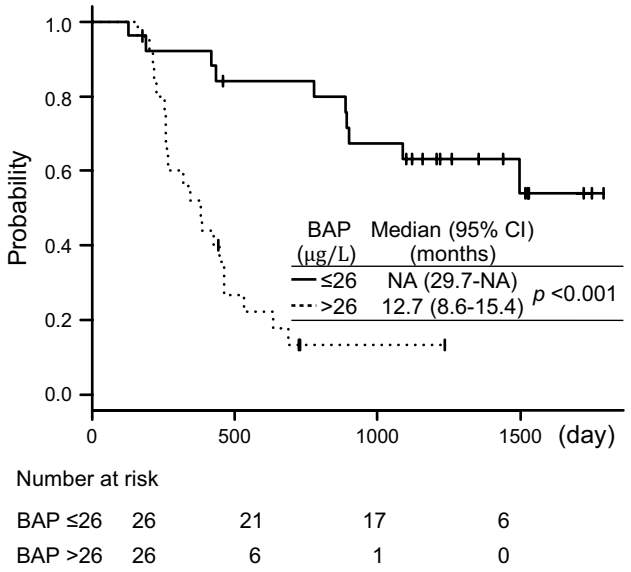


**Fig. 1** Kaplan–Meier curves for time to prostate-specific antigen progression stratified with baseline serum bone-specific alkaline phosphatase (BAP) level

[6]. Median age was 72 years (range 55–86). Most patients (85 %) had an ECOG PS of 0. Majority of patients had Gleason score (GS) of 8 or higher (63 %) and local stage of T3b or greater (56 %). Table 1 shows baseline values of PSA and bone markers.

### Time to prostate-specific antigen progression

At the time of analysis, median follow-up period was 41.6 months (range 5.9–60.0). Updated median TPP was 25.9 months (95 % confidence interval [CI] 14.5–49.9). Univariate analysis revealed that baseline GS, extent of bone disease (EOD), BAP, ICTP, and uNTx had significant impact on TPP (Table 2). Higher BAP was an independent risk factor for TPP based on multivariate analysis (hazard ratio [HR] 6.51; 95 % CI 2.71–15.62; $P < 0.001$). Figure 1 shows that median TPP for patients with BAP level higher than 26 μg/L was 12.7 months (95 % CI 8.6–15.4).

### Overall survival

Median OS was not yet reached at the time of analysis. Univariate analysis revealed that baseline EOD, ALP, BAP, ICTP, and uNTx were significantly associated with OS (Table 3). Multivariate analysis indicated that higher ICTP independently increased the risk of death (HR 9.62; 95 % CI 2.11–43.89; $P = 0.003$). Figure 2 shows that median OS for patients with ICTP levels higher than 8.0 ng/ml was 31.1 months (95 % CI 19.0 to not available).

## Discussion

The current study presents the possible usefulness of baseline bone markers as predictors for biochemical progression and overall survival in patients with bone metastasis from treatment-naïve PCa when they commence treatment with ADT and ZA. The balance between bone resorption and formation is disrupted, and bone metabolism is disorderly upregulated in metastatic bone lesions [8, 9]. The potential prognostic and predictive values of bone markers have been reported in metastatic PCa patients. BAP is indicative of bone formation and has been reported as a possible risk factor for SRE and death in bone-metastatic PCa [10–12]. ICTP, a bone resorption marker, has indicated a correlation with the extent of disease in bone and bone pain in PCa [13]. However, these reports have thus far conveyed their findings based on CRPC. The current study is the first report that addresses hormone-naïve PCa patients.

A notable finding from this study was that GS, local stage, lymph-node metastases, and PSA level were less important than bone markers for predicting disease progression and survival. This result suggests that the extent of deregulated bone metabolism, from the baseline, due to metastatic disease has a greater significance on the responsiveness to treatment and prognosis than the malignant potential and local progression level of the primary lesion even in hormone-sensitive PCa. Thus, it further emphasizes the necessity for early treatment intervention against metastatic bone lesions.

Metastatic bone diseases can provide a favorable environment for the epithelial–mesenchymal transition (EMT) of cancer cells. EMT is a phenomenon in which cancer cells essentially having epithelial characteristics acquire mesenchymal features leading to ability to metastasis, resistance against therapy, or avoidance from apoptosis [14]. Bone marrow contains elevated levels of transforming growth factor-$\beta$ which promotes EMT of cancer cells; thus, EMT may be highly promoted in hyper-metabolic bone lesions [15]. EMT might also contribute to resistance against ADT in PCa. It was reported that ADT induced EMT in PCa in vivo [16]. Moreover, ZA was suggested to reverse EMT of breast cancer cell lines. Therefore, adding ZA to ADT may result in the inhibition of EMT and sustained sensitivity of PCa cells to ADT.

Based on the result from the current study, however, treatment modalities other than ZA might be more beneficial to patients with higher levels of baseline bone markers. Denosumab, a fully human monoclonal antibody against RANKL, has a distinct mechanism of action relative to ZA and demonstrated better performance than ZA for prevention of SRE in CRPC [17]. Radium-223, an alpha emitter, selectively targets bone metastases with alpha particles and

**Table 3** Univariate and multivariate analyses using Cox proportional-hazard model for overall survival

| Variables | Category | Univariate | | | Multivariate (step-up procedure) | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age (years) | ≤72 | Reference | | | | | |
| | >72 | 0.94 | (0.34–2.61) | 0.910 | | | |
| ECOG PS | 0 | Reference | | | | | |
| | 1 or 2 | 2.25 | (0.72–7.08) | 0.165 | | | |
| Pain score | ≤2 | Reference | | | | | |
| | ≥3 | 1.34 | (0.47–3.82) | 0.584 | | | |
| Gleason score | ≤7 | Reference | | | | | |
| | ≥8 | 1.67 | (0.53–5.24) | 0.383 | | | |
| Local stage | ≤T3a | Reference | | | | | |
| | ≥T3b | 0.56 | (0.20–1.55) | 0.268 | | | |
| Lymph-node metastasis | No | Reference | | | | | |
| | Yes | 0.99 | (0.33–2.96) | 0.983 | | | |
| EOD score | ≤2 | Reference | | | | | |
| | ≥3 | 6.67 | (2.26–19.71) | 0.001 | | | |
| PSA (ng/mL) | ≤249.4 | Reference | | | | | |
| | >249.4 | 1.21 | (0.43–3.34) | 0.721 | | | |
| ALP (U/L) | ≤300 | Reference | | | | | |
| | >300 | 4.78 | (1.07–21.25) | 0.040 | | | |
| BAP (μg/L) | ≤26.0 | Reference | | | | | |
| | >26.0 | 3.38 | (1.07–10.63) | 0.037 | | | |
| ICTP (ng/mL) | ≤5.0 | Reference | | | Reference | | |
| | 5.0<, ≤8.0 | 1.01 | (0.14–7.19) | 0.990 | 1.01 | (0.14–7.18) | 0.991 |
| | >8.0 | 8.59 | (1.89–39.07) | 0.005 | 9.62 | (2.11–43.89) | 0.003 |
| uNTx (nmol/mmol Cr) | ≤100 | Reference | | | | | |
| | >100 | 5.24 | (1.77–15.47) | 0.003 | | | |

*ALP* alkaline phosphatase, *BAP* bone-specific alkaline phosphatase, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EOD* extent of bone disease, *HR* hazard ratio, *ICTP* C-terminal telopeptide of type I collagen, *PSA* prostate-specific antigen, *uNTx* urinary N-terminal cross-linked telopeptide of type I collagen

improved OS compared with placebo in metastatic CRPC [18]. Cabozantinib, a tyrosine kinase inhibitor with activity against MET and vascular endothelial growth factor receptor 2, indicated improvement on bone scan in 68 % of patients with CRPC, including complete resolution in 12 % based on a phase II trial [19]. The efficacy of these new treatments against metastatic bone diseases should be theoretically promising not only for CRPC, but also for hormone-naïve PCa.

There are some limitations to the current study, namely being that findings from the study are based on the data from a non-randomized single-arm phase II trial with a small number of subjects. In addition, the markers used are well known. Although no direct clinical impact can be derived because of the absence of a control arm, this study provides proof of principle that baseline bone markers may serve as predictors for biochemical progression and overall survival. We did not evaluate the association between the transition of bone markers during treatment and clinical outcomes. In CRPC, the association between bone marker levels and clinical outcomes were stronger for on-study bone marker levels compared with baseline levels although the statistical heterogeneity in the strength of these correlations has not been reported [20]. We did not investigate the effect of treatments after disease progression with the initial ADT on OS. Docetaxel, abiraterone, enzalutamide, radium-223, and cabazitaxel can influence OS. The landscape for the treatment of hormone-naïve PCa has changed since the conception of the present study; docetaxel with ADT can improve overall survival compared with ADT alone [21], and abiraterone or enzalutamide may prove their value in this setting in the future (NCT01715285, NCT01957436) [22].

In conclusion, baseline bone markers may be useful as predictors for disease progression and survival in patients with bone metastases from treatment-naïve PCa who start treatment with ZA concomitant with ADT. Development of

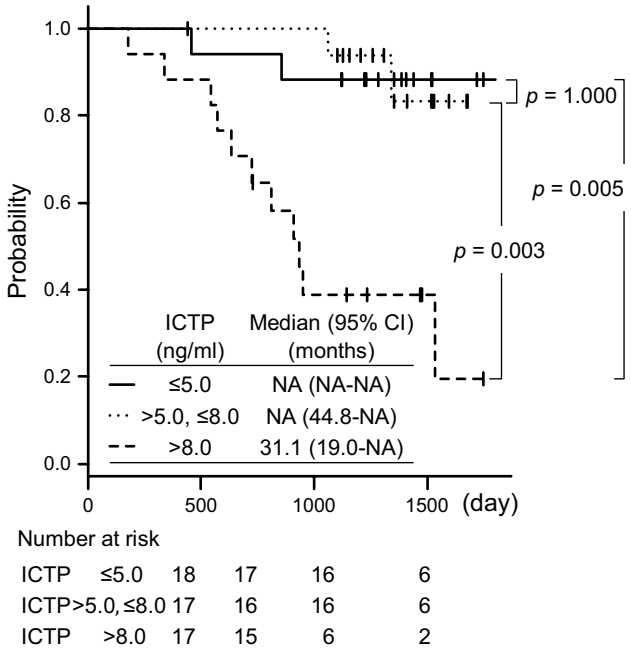


**Fig. 2** Kaplan–Meier curves for overall survival stratified with baseline serum C-terminal telopeptide of type I collagen (ICTP) level

novel treatment strategies against metastatic bone diseases may improve the prognosis even in patients with hormone-sensitive PCa.

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**Conflict of interest** The authors have no conflict of interest.

**Ethical standard** The study was conducted according to the Declaration of Helsinki with approval from ethics committees at each institution. Written informed consent was obtained from all patients consistent with local requirements.

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