Prognostic clinical indicators in patients with metastatic castration-resistant prostate cancer treated with radium-223 plus enzalutamide: Data from patients in J-RAP-BSI trial

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Abstract

Objective: To investigate clinical factors associated with prognosis in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases treated with radium-223 dichloride (^{223}Ra) and enzalutamide combination therapy. **Subjects and Methods:** This retrospective study included a cohort of 71 mCRPC patients in Japan who underwent combination therapy with ^{223}Ra and enzalutamide at 14 hospitals and had pretreatment bone scintigraphy findings available for analysis. Associations of overall survival (OS) with clinicopathological factors, including Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), prostate-specific antigen (PSA), PSA doubling time, automated bone scan index (aBSI), and previous chemotherapy history, were assessed using the Cox proportional hazards model and log-rank testing. **Results:** Sixty (84.5%) of the 71 patients enrolled completed six cycles of 223Ra. The mean follow-up period was 21.9 months (range, 3.9-62.9 months), during which 35 patients (49.3%) died. Univariate analysis demonstrated that low hemoglobin (<12g/dL, P<0.0001), high PSA (≥20ng/mL, P<0.0001), ALP above the normal range (P=0.0067), and high aBSI (≥2.0%, P=0.0006) were significantly associated with shorter OS. In multivariable analysis, low hemoglobin [hazard ratio (HR) 5.52, 95% confidence interval (CI) 2.32-14.2, P<0.0001] and high PSA (HR 3.06, 95% CI 1.07-9.78, P=0.037) were identified as significant prognostic factors for OS. **Conclusions:** In patients with mCRPC treated with ^{223}Ra and enzalutamide combination therapy, pretreatment hemoglobin and PSA levels may serve as useful surrogate biomarkers for predicting overall survival.

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Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease with a poor prognosis for most patients [1]. Several treatment options for mCRPC have been shown to improve radiographic progression-free survival (rPFS) and/or overall survival (OS) in patients whose disease has progressed despite androgen deprivation therapy (ADT), including docetaxel, radium-223 dichloride (^{223}Ra), abiraterone/prednisone, enzalutamide alone or in combination with talazoparib, and lutetium-177 (^{177}Lu) vipivotide tetraxetan [2].

Radium-223 is a first-in-class alpha particle-emitting radiopharmaceutical approved for treatment of patients with mCRPC and bone metastasis, and known to have minimal myelosuppressive effects [3]. Because of their relatively large size, high linear energy transfer, and short path length, alpha particles produce highly localized cell destruction (<100μm, approximately 2-10 cell diameters), thereby inducing predominantly irreparable double-stranded DNA breaks. In the randomized phase 3 ALSYMPCA study involving 921 patients with mCRPC, treatment with ^{223}Ra plus best standard of care prolonged median OS by 3.6 months compared with a placebo plus best standard of care (median 14.9 vs 11.3 months; HR=0.70, 95% CI 0.58-0.83; P<0.001) [4]. Furthermore, ^{223}Ra was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (anemia: 13% vs. 13%; neutropenia: 2% vs. 1%; thrombocytopenia: 7% vs. 2% for ^{223}Ra and placebo, respectively).

In most countries, ^{223}Ra monotherapy is regarded as a second- or third-line treatment option following treatment with an androgen-receptor pathway inhibitor (ARPI), such as abiraterone or enzalutamide. However, because ^{223}Ra does not target nodal or visceral metastasis, combination therapy with more broadly active agents, particularly ARPI, to

control disease progression is an attractive therapeutic option. At this time, the combination of ^{223}Ra and abiraterone is not recommended, because of an increased risk of bone fracture and no survival benefit [5]. In contrast, the efficacy of ^{223}Ra and enzalutamide was demonstrated in a recent randomized phase 3 PEACE-3 trial, which compared ^{223}Ra plus enzalutamide with enzalutamide alone as first-line treatment in 446 patients with mCRPC and bone metastasis [6, 7].

Clinical variables predictive of treatment response to ^{223}Ra and survival have yet to be clearly established. A validated prognostic tool that incorporates patient characteristics and biomarkers is needed to predict OS and facilitate selection of patients most likely to benefit from ^{223}Ra therapy. Previously reported prognostic factors include baseline Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), prostate-specific antigen (PSA), PSA doubling time, automated bone scan index (aBSI) derived from bone scintigraphy, and completion of six cycles of ^{223}Ra [8-21]. The aBSI was developed to quantify skeletal tumor burden shown by bone scintigraphy as the percentage of total skeletal weight [22], thus it provides an objective measurement of metastatic bone involvement may be useful for estimating overall skeletal tumor burden in patients with mCRPC. This automated methodology uses artificial intelligence, and has been shown to provide accurate and reproducible measurements [23]. In a recent prospective multi-institutional phase III study with 721 mCRPC patients, aBSI was clinically validated as a prognostic biomarker [24]. Furthermore, several studies have investigated pretreatment aBSI as a prognostic imaging biomarker in mCRPC patients receiving ^{223}Ra treatment and found that baseline aBSI values were significantly associated with OS [9, 10, 12-14, 21].

To the best of our knowledge, prognostic factors that may help select patients most likely to benefit from combination therapy with ^{223}Ra and enzalutamide have not been systematically evaluated. The Japanese ^{223}Ra Therapy in Prostate Cancer Using Bone Scan Index (J-RAP-BSI) multicenter trial was conducted to investigate the utility of aBSI as an imaging biomarker for assessment of bone metastasis in castration-resistant prostate cancer (CRPC) patients in Japan receiving ^{223}Ra therapy [21]. The present multicenter retrospective study was performed as a sub-analysis of results obtained in the J-RAP-BSI trial to evaluate clinical biomarkers, including aBSI, for predicting survival of mCRPC patients with bone metastasis treated with ^{223}Ra and enzalutamide combination therapy.

Subjects and Methods

Patients

This sub-analysis of the retrospective J-RAP-BSI trial, which enrolled patients receiving ^{223}Ra therapy and bone scintigraphy covered by the national health insurance system, was approved by the Ethical Committee of Hyogo College of Medicine, the primary institution for this study, as well as all participating hospitals. Initially, a total of 258 patients with mCRPC and bone metastasis treated at 14 institutions were analyzed. Each underwent bone scintigraphy between July 2016 and August 2020 before initiation of ^{223}Ra therapy as part of the J-RAP-BSI trial. Those who received combined ^{223}Ra and enzalutamide therapy and underwent technetium-99m methylene diphosphonate (^{99m}Tc-MDP; PDRadiopharma, Inc., Tokyo, Japan) bone scintigraphy within two months before the first ^{223}Ra cycle and with results available for analysis were included in the present study. The automated bone scan index was calculated using the dedicated BONENAVI® software package, version 2 (PDRadiopharma, Inc., Tokyo, Japan) (Figure 1) [25]. Radium-223 therapy consisted of six intravenous injections (55kBq/kg body weight) administered every 28 days and was continued unless disease progression, unacceptable toxicity, deterioration in performance status, or patient request for discontinuation occurred. Enzalutamide was administered at a dose of 160mg/day. The study cohort consisted of males >18 years old with bone metastasis, no visceral metastasis, no lymph nodes ≥3cm, hemoglobin >8.1g/dL, a white blood cell count $>1.5\times10^9$, and a platelet count $>100\times10^9$ at the time of the initial ^{223}Ra injection. Androgen deprivation therapy was continued throughout ^{223}Ra therapy, while use of other medications, such as denosumab or bisphosphonates, was left to the discretion of the attending physician. Prior systemic therapy, such as enzalutamide, docetaxel, or cabazitaxel, was permitted, whereas concomitant treatment with abiraterone or chemotherapy was not. Patients who had undergone chemotherapy within the previous four weeks, had impaired renal or liver function, or had inflammatory bowel disease were excluded. As a result, 71 patients who met the study criteria were included in the analysis. The Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, was used to grade adverse events (AE) [26]. Toxicity was assessed at each treatment cycle.

Statistical analysis

Continuous data are presented as the median and range, and categorical data as number and percentage. Overall survival was de-fined as the time interval in months from treatment initiation to death or censoring at the last follow-up. Receiver operating characteristic (ROC) curves and Youden's index were used to determine the optimal cut-off values for hemoglobin, ALP, LDH, PSA, PSA doubling time, and aBSI. The Kaplan-Meier method was used to estimate OS, with differences between groups assessed with a log-rank test. To identify independent prognostic factors, the effects of multiple risk factors considered to have a significant impact on OS were evaluated using a Cox proportional hazards model. Variables with a P value of <0.05 in univariate analysis were included in multivariate analysis. The relationships between ALP and PSA with aBSI were assessed using Spearman's rank correlation coefficient. Correlation strength was categorized using conventional statistical criteria, with 0.00-0.19 regarded as very weak, 0.20-0.39 as weak, 0.40-0.59 as moderate, 0.60-0.79 as strong, and 0.80-1 as very strong. All statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), with two-tailed P values <0.05 considered statistically significant.

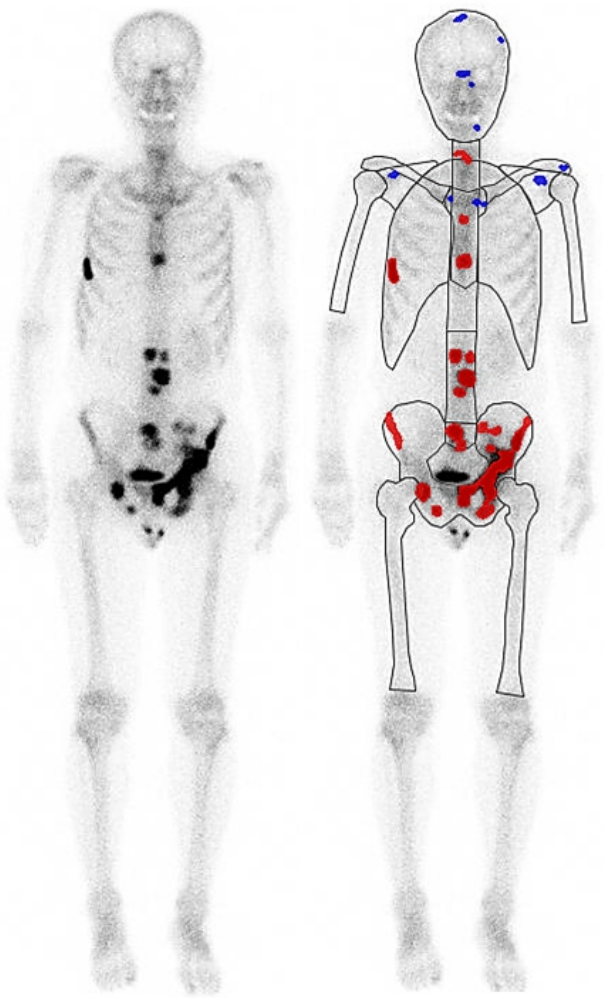

Figure 1. Illustrative aBSI findings on bone scintigraphy in a 68-year-old man before initiation of combined ^{223}Ra and enzalutamide treatment. Red-highlighted areas represent hotspots detected by BONENAVI®, version 2, and were included in the aBSI calculation (5.018%).

Results

Patient characteristics

Baseline patient characteristics are summarized in Table 1. The median age at initiation of ^{223}Ra treatment was 74 years (range, 54-88 years). Before treatment, 27 patients had undergone external beam radiotherapy for bone metastasis, 57 had received novel ARPI therapy with enzalutamide and/or abiraterone, 46 had received taxane-based chemotherapy with docetaxel and/or cabazitaxel, and 52 had received bisphosphonate/denosumab treatment. During combined ^{223}Ra and enzalutamide therapy, 46 continued bisphosphonate or denosumab treatment.

Adverse events occurred in 43 patients (60.6%). The most common AE, regardless of grade, were anemia (27.3%), thrombocytopenia (14.2%), impaired liver function (8.4%), neutropenia (8.0%), and general fatigue (6.5%). Grade 3-4 AE were observed in four patients (5.6%), including bone pain in two, anemia in one, and hyponatremia in one.

Six cycles of ^{223}Ra were completed in 60 patients (84.5%), whereas two (2.8%) completed four, seven (9.9%) completed three, and two (2.8%) completed two cycles. Reasons for early discontinuation included disease progression (n=8), deterioration in performance status (n=2), and hematologic toxicity (n=1).

Survival analysis

Thirty-five of the 71 patients (49.3%) died from prostate cancer during a median follow-up period of 19.0 months (range, 3.9-62.9 months, mean±standard deviation (SD) 21.9±14.5 months) after the initial ^{223}Ra administration.

Receiver operating characteristic analysis identified optimal cut-off values for LDH, ALP, PSA, PSA doubling time, hemoglobin, and aBSI with area under the curve values of 0.739, 0.782, 0.882, 0.679, 0.893, and 0.826, respectively. The corresponding sensitivity and specificity values were 74.1% and 73.9% for LDH, 75.5% and 81.4% for ALP, 87.2% and 76.3% for PSA, 70.8% and 68.3% for PSA doubling time, 88.4% and 80.2% for hemoglobin, and 72.3% and 86.7% for aBSI, respectively. The optimal cut-off values for predicting

Table 1. *Baseline patient characteristics.*

Characteristics	Value (range)	%
Median age (range) in years	74 (54-88)	
Initial stage		
II / III / IV	6/11/54	8.5/15.5/76.1
Initial median PSA (ng/mL)	91.3 (0.91-22412)	
Initial Gleason score		
6/7/8/9/10	1/11/22/28/9	1.4/15.5/31.0/39.4/12.7
Prior external radiotherapy for primary prostate cancer	16	22.5
Prior external radiotherapy for bone metastasis	27	38
Prior androgen-receptor pathway inhibitor	57	80.3
Prior chemotherapy	46	64.8
Prior bisphosphonate/denosumab	52	73.2
ECOG performance status		
0/1/2	49/19/3	69.0/26.8/4.2
Median hemoglobin (g/dL)	12.6 (8.1-15.1)	
Median neutrophil count (×10⁹/L)	4152 (1568-12470)	
Median platelet count (×10⁹/L)	22.9 (10.5-50.1)	
Median tALP (U/L)	316 (108-3494)	
Median LDH (U/L)	197 (128-952)	
Median PSA (ng/mL)	18.9 (0.003-1130)	
Median PSA doubling time (days)	83 (11.7-1202)	
Median aBSI (%)	1.68 (0.03-14.22)	
Number of ^{223}Ra applications		
1/2/3/4/5/6 injections	0/2/7/2/0/60	0/2.8/9.9/2.8/0/84.5
Concomitant use of bisphosphonate/denosumab	46	64.8

ECOG, Eastern Cooperative Oncology Group; tALP, total alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen; aBSI, automated bone scan index.

OS were 20.0ng/mL for PSA, 90 days for PSA doubling time, 12.0g/dL for hemoglobin, and 2.0% for aBSI.

Receiver operating characteristic curve analysis and log-rank testing showed no significant difference in OS between patients with an ECOG performance status of 0 and those with an ECOG performance status of 1 or 2 (P=0.88) (Figure 2a). Patients with prior chemotherapy had a lower OS rate than those without prior chemotherapy (P=0.059) (Figure 2b). Similarly, patients with LDH levels above the normal range tended to have a lower OS rate than those with normal LDH levels (P=0.054) (Figure 2c). In contrast, patients with ALP levels above the normal range had a significantly lower OS rate than those with normal ALP levels (P=0.0067) (Figure 2d). Patients with a PSA level ≥20ng/mL had a significantly lower OS rate than those with a level <20ng/mL (P<0.0001) (Figure 2e). Patients with a PSA doubling time <90 days had a lower OS rate than those with a doubling time ≥90 days (P=0.24) (Figure 2f). A significantly lower OS rate was noted for patients with a hemoglobin level of <12g/dL as compared to those with a level ≥12g/dL (P<0.0001) (Figure 2g). Likewise, patients with an aBSI value ≥2.0% had a significantly lower OS rate than those with an aBSI value <2.0% (P=0.0006) (Figure 2h). Patients receiving concomitant bone-protective agent (BPA) administration tended to have a higher OS rate than those who did not receive concomitant BPA administration, though the difference was not significant (P=0.24) (Figure 2i).

Univariate analysis identified low hemoglobin (<12g/dL, P<0.0001), high PSA (≥20ng/mL, P<0.0001), ALP level above the normal range (P=0.0067), and high aBSI (≥2.0%, P=0.0006) as significant predictors of shorter OS. In contrast, PSA doubling time <90 days, LDH level above the normal range, prior chemotherapy history, and ECOG performance status were not significantly associated with OS (Table 2). Furthermore, multivariable analysis identified low hemoglobin (HR 5.52, 95% CI 2.32-14.2, P<0.0001) and high PSA (HR 3.06, 95% CI 1.07-9.78, P=0.037) as independent prognostic factors for OS (Table 2).

Automated bone scan index showed a strong and significant positive correlation with ALP (r=0.60, P<0.0001) and a weak but significant correlation with PSA (r=0.38, P=0.0016). In addition, ALP and PSA were weakly but significantly correlated (r=0.34, P=0.0043).

Patients with an ECOG performance status of 0, no prior chemotherapy, PSA <20.0ng/mL, hemoglobin ≥12g/dL, aBSI <2.0%, and concomitant use of BPA were significantly more likely to complete all six cycles of ^{223}Ra therapy (Table 3).

Discussion

Bone metastasis is common in patients with mCRPC, whereas visceral metastasis typically occurs later in the disease course. Radium-223 has been approved for treatment of patients with mCRPC and bone metastasis without known visceral metastasis. In addition, enzalutamide demonstrated greater OS benefit in patients without than with visceral metastasis in the AFFIRM [27] and PREVAIL [28] trials. Therefore, the combination of ^{223}Ra and enzalutamide may represent an effective treatment option for patients with mCRPC and bone metastasis. In a phase 2 study conducted to compare ^{223}Ra plus enzalutamide with enzalutamide alone, the combination regimen improved the prespecified secondary endpoints of median OS (30.8 vs. 20.6 months), rPFS (11.5 vs. 7.4 months) and PSA progression-free survival (PSA-PFS) (8.9 vs. 3.4 months), though the between-group differences did not reach statistical significance [29]. Furthermore, a post hoc analysis of that study demonstrated a significant improvement in PSA-PFS with ^{223}Ra plus enzalutamide as compared to enzalutamide alone (18.7 vs. 8.4 months; P=0.033) [30]. The combination regimen also showed promising efficacy (median OS not reached; mean OS 34.8 months) [30] and was associated with improvements in quality of life and pain in a non-comparative study [31]. Two real-world studies [32, 33] that evaluated the efficacy of ^{223}Ra plus enzalutamide found that median OS was longer when the agents were administered concurrently rather than sequentially (22.2 vs. 16.5 months [32]; 19.1 vs. 15.2 months [33]). However, those findings are limited by the small number of patients in the concurrent-treatment groups and absence of a control group. Furthermore, the recent randomized phase 3 PEACE-3 trial compared ^{223}Ra plus enzalutamide with enzalutamide alone as first-line treatment in 446 mCRPC patients with bone metastasis [6, 7]. The HR for rPFS was 0.71, with a median rPFS of 16.4 months in the enzalutamide arm and 19.2 months in the combination arm. The HR for OS was 0.76, with median OS values of 32.6 and 38.2 months, respectively. Furthermore, grade ≥3 treatment-emergent AE increased from 57.6% to 69.3% in the combination arm, as did treatment-related grade ≥3 AE (18.8% vs. 28.9%), with hypertension the most frequent. Collectively, these results support the use of ^{223}Ra plus enzalutamide, together with a BPA, as a first-line treatment option for selected patients with mCRPC and bone metastases.

Several studies have identified clinical factors associated with favorable OS in mCRPC patients treated with ^{223}Ra [8-18]. Frequently reported prognostic factors include good ECOG performance status of 0, no or mild pain, higher hemoglobin levels (≥10g/dL), normal ALP and LDH levels, longer PSA doubling time, lower skeletal tumor burden assessed by aBSI or bone scintigraphy, and fewer prior systemic therapies. In addition, concomitant treatment with enzalutamide or denosumab has been found to be associated with improved outcomes [8]. More specifically, favorable prognostic factors were found to be lower aBSI (<5.0%) and normal LDH in the study by Fosbøl et al. (2018) [10], ECOG performance status of 0 and lower LDH (<250U/L) in the paper presented by van der Doelen et al. (2018) [11], ECOG performance status of 0 and lower aBSI (<3.0%) in the report by Frantellizzi et al. (2019) [12], and lower aBSI (<2.0%) in the study conducted by Nakashima et al. (2019) [13]. Additionally, favorable prognosis was associated with normal ALP and lower aBSI in the study by Anand et al. (2020) [14], with good ECOG performance status (0-1), normal hemoglobin (≥12g/dL), and lower PSA (<20ng/mL) in the study by Frantellizzi et al. (2020) [15], with ECOG performance status of 0, lower PSA (<100ng/mL), longer PSA doubling time (>90 days), and no new progressive bone lesions shown by bone

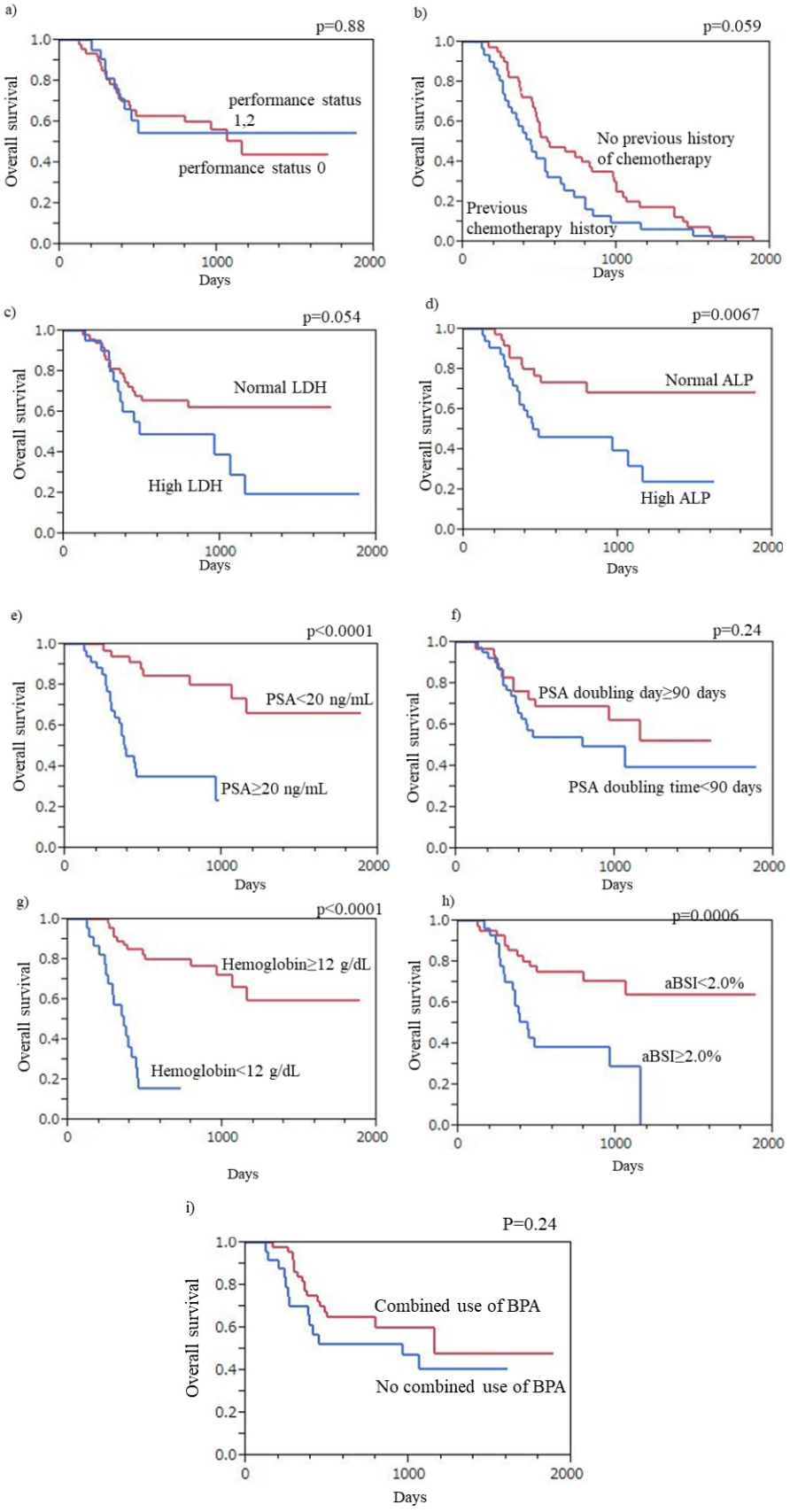

Figure 2. Kaplan-Meier curves for overall survival according to (a) ECOG performance status, (b) prior chemotherapy history, (c) LDH level, (d) ALP level, (e) PSA level, (f) PSA doubling time, (g) hemoglobin level, (h) aBSI, and (i) concomitant use of BPA.

Table 2. *Factors associated with OS in all 71 patients.*

Item	Number of patients	Univariate analysis		Multivariate analysis	
		P (log-rank)	HR (95% CI)	P (log-rank)	HR (95% CI)
ECOG performance status					
0	49	0.88	1.06 (0.46-2.27)		
1, 2	22				
Treatment history of chemotherapy					
No	46	0.059	1.98 (0.96-4.13)		
Yes	25				
LDH					
Normal range	50	0.054	2.01 (0.95-4.12)		
High	21				
ALP					
Normal range	38	0.0067	2.74 (1.31-6.12)	0.55	1.31 (0.55-3.29)
High	33				
PSA					
<20.0ng/mL	36	<0.0001	6.59 (2.79-18.11)	0.037	3.06 (1.07-9.78)
≥20.0ng/mL	35				
PSA doubling time					
≥90 days	30	0.24	1.56 (0.75-3.40)		
<90 days	41				
Hemoglobin					
≥12g/dL	23	<0.0001	8.37 (3.71-20.21)	<0.0001	5.52 (2.32-14.2)
<12g/dL	48				
aBSI					
<2.0%	43	0.0006	3.46 (1.66-7.51)	0.39	1.53 (0.60-4.17)
≥2.0%	28				
Combined use of BPA					
Yes	46	0.24			
No	25				

OS, overall survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; aBSI, automated bone scan index; BPA, bone protecting agent; HR, hazard ratio.

Table 3. *Comparison of clinical factors between patients who completed six cycles of ^{223}Ra therapy and those who did not.*

Clinical factors	Completed six cycles (n=60)	Less than six cycles (n=11)	P value
ECOG performance status (0 vs. 1, 2)	40 pts vs. 20 pts	9 pts vs. 2 pts	0.0044
Prior chemotherapy (No vs. Yes)	41 pts vs. 19 pts.	5 pts. vs. 6 pts.	0.00018
LDH (normal vs. high)	221.4±110.9	263.1±220.7	0.54
ALP (normal vs. high)	407.5±517.9	479.8±135.8	0.36
PSA (<20.0 vs. ≥20.0 ng/mL)	59.4±121.4	284.6±313.2	<0.0001
PSA doubling time (≥90 vs. <90 days)	123.9±158.1	85.0±39.1	0.11
Hemoglobin (≥12 vs. <12g/dL)	12.6±1.7	11.1±1.35	0.0023
aBSI (<2.0% vs. ≥2%)	2.44±3.49	4.24±3.13	0.094
Combined use of BPA (Yes vs. No)	40 pts vs. 20 pts	6 pts vs. 5 pts	0.042

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; aBSI, automated bone scan index; BPA, bone protecting agent; pts, patients

scintigraphy in the study by Hashimoto et al. (2020) [16], with no pain, normal ALP (<328IU/L), and higher hemoglobin (≥ 12.3g/dL) in the report presented by Miyoshi et al. (2021) [17], and with longer PSA doubling time (>90 days), lower number of bone metastases (<20) shown by bone scintigraphy, and fewer previous systemic therapy lines (≤3) in the study by Yamamoto et al. (2021) [18]. Moreover, several investigators have reported that patients with favorable prognostic characteristics are more likely to complete all six cycles of ^{223}Ra therapy [9, 11] and therefore derive greater benefit from the treatment. Alva et al. (2017) [9] demonstrated that completion of six cycles of ^{223}Ra therapy was associated with ECOG performance status of 0-1, no or mild pain, lower PSA, normal ALP, no prior abiraterone or enzalutamide therapy, and lower aBSI (<5.0%). Consistent with these findings, results obtained with the present cohort of patients with CRPC treated with the combination of ^{223}Ra and enzalutamide identified higher hemoglobin (≥12g/dL) and lower PSA (<20ng/mL) as independent prognostic factors for OS.

Several limitations of this study should be acknowledged. First, the retrospective design and inclusion of results obtained at multiple institutions may limit generalization of the findings, while statistical errors are also possible. Additionally, treatment after failure of ^{223}Ra therapy was not standardized, and subsequent therapeutic strategies were selected at the discretion of the attending physician. To further clarify the utility of aBSI as an imaging biomarker for predicting prognosis in patients receiving combined ^{223}Ra and enzalutamide therapy in clinical settings, a prospective multicenter trials involving larger patient cohorts are warranted.

In conclusion, in patients with mCRPC and bone metastasis treated with ^{223}Ra and enzalutamide combination therapy, pretreatment hemoglobin and PSA levels may serve as useful surrogate biomarkers for predicting overall survival.

Disclosure

This report complies with the guidelines for human studies and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The authors have no conflicts of interest to disclose. The requirement for written informed consent was waived due to the retrospective study design. This retrospective study was approved by the Institutional Review Board of Hyogo College of Medicine (No. 3662) as well as the ethics committees of the other 13 participating hospitals.

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