OPEN

^{223}Ra Therapy in Patients With Advanced Castration-Resistant Prostate Cancer With Bone Metastases

Lessons from Daily Practice

Maarten J. van der Doelen, MD,† Malou C.P. Kuppen, MD,* Marianne A. Jonker, PhD,‡ Niven Mehra, MD, PhD,* Marcel J.R. Janssen, MD, PhD,§ Inge M. van Oort, MD, PhD,† and Winald R. Gerritsen, MD, PhD**

Purpose: To identify pre-therapeutic variables associated with overall survival (OS) in patients treated with ^{223}Ra.

Methods: Data from 45 CRPC patients treated with ^{223}Ra were retrospectively analyzed. All patients who received at least one ^{223}Ra injection were included in the study. Cox proportional hazard regression models were used to estimate hazard ratio's (HR) and to test for association.

Results: Twenty-one patients (47%) received six ^{223}Ra injections and 24 patients (53%) received one to five ^{223}Ra injections. Median OS since start of ^{223}Ra was 13.0 months (95% confidence interval (CI) 8.2–17.8). Patients who completed ^{223}Ra therapy had a median OS of 19.7 months (95% CI 14.9–24.6), while patients who received one to five ^{223}Ra injections had a median OS of 5.9 months (95% CI 3.8–8.1; $P < 0.001$).

Univariable analysis showed poor baseline ECOG performance status (PS), baseline opioid use, lowered baseline hemoglobin, and elevated prostate-specific antigen, alkaline phosphatase and lactate dehydrogenase (LD) levels were significantly associated with OS. Multivariable Cox regression analysis demonstrated that poor baseline ECOG PS (HR 10.6) and high LD levels (HR 7.7) were pre-therapeutic variables that predicted poor OS.

Conclusions: In a multivariable Cox regression model, good baseline ECOG PS and low LD levels were significantly associated with longer OS in patients treated with ^{223}Ra. These variables may be used for stratification of CRPC patients for ^{223}Ra therapy. Prospective studies to evaluate these variables are warranted, to develop a nomogram to select patients properly.

In this retrospective study, predictors of overall survival in 45 metastatic castration-resistant prostate cancer patients treated with ^{223}Ra therapy were evaluated. Baseline ECOG performance status and lactate dehydrogenase levels turned out to be significant in a multivariable prediction model for overall survival.

Key Words: prostate cancer, ^{223}Ra, bone metastases, castration-resistant, radiopharmaceutical

(*Clin Nucl Med* 2018;43: 9–16)

^{223}Ra is a registered palliative therapy for castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases. This radioisotope is very similar to calcium and binds selectively to areas of increased bone turnover in bone metastases. There it emits high-energy alpha particles of short range (<100 μm; 2–10 cell layers), causing double-strand DNA breaks leading to a cytotoxic effect on tumor cells and cells in the tumor microenvironment.[1,2]

In the phase 3 ALSYMPCA trial, CRPC patients were treated with ^{223}Ra or placebo, either before or after docetaxel chemotherapy.[3] The outcome was a significant median overall survival (OS) benefit of 3.6 months in favor of ^{223}Ra over placebo. Subsequent analyses demonstrated survival benefit of ^{223}Ra in chemotherapy-naïve CRPC patients as well as in post-chemotherapy CRPC patients.[4] In addition, ^{223}Ra reduced the risk of symptomatic skeletal events and was accompanied by significant improvement of quality of life.[5,6]

To date, clinical data on ^{223}Ra in daily practice is scarce. In the ALSYMPCA trial, 63% of CRPC patients treated with ^{223}Ra received six injections, whereas only 42% of the Dutch patients received six ^{223}Ra injections in 2016, with a median number of four injections.[3] This may indicate that real-world patients treated with ^{223}Ra differ from those included in the ALSYMPCA trial.[7]

In addition, effect monitoring during ^{223}Ra therapy is challenging. Therefore, optimal patient selection is crucial. It is important to identify pre-therapeutic factors to estimate whether a patient will achieve OS benefit of ^{223}Ra. Knowledge of these factors can lead to better patient selection and might lead to a reduction of health care costs. The objective of this study was to evaluate real-world data of CRPC patients treated with ^{223}Ra, in order to determine pre-therapeutic variables that predict OS and to describe baseline differences between patients who completed and patients who discontinued ^{223}Ra therapy.

PATIENTS AND METHODS

Study Design and Patient Population

CRPC patients treated with ^{223}Ra between September 2013 and March 2016 were retrospectively evaluated. Patients who received at least one ^{223}Ra injection were included in the study. There were no

Received for publication August 31, 2017; revision accepted November 2, 2017.

From the Departments of *Medical Oncology, †Urology, ‡Health Evidence and §Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.

Conflicts of interest and sources of funding: M.J.vdD. has received a research grant from Bayer. N.M. has received research grants from Astellas and Janssen-Cilag. I.M.vO. has received research funding from Astellas, Bayer, Janssen-Cilag and Sanofi. W.R.G. is a member of the advisory boards for Bristol-Myers Squibb, Astellas, Janssen-Cilag, Bayer, Sanofi, Amgen, Morphosys and CureVac, received speaker fees from Bayer and M.S.D., and received research funding from Astellas, Bayer and Janssen-Cilag. The remaining authors declare no conflict of interest. This work was supported by Bayer The Netherlands.

Author contributions: M.J.vdD., M.J.R.J., I.M.vO. and W.R.G. contributed to the design of the study. M.J.vdD. collected and analyzed the data. M.J.vdD. and M.C.P.K drafted the manuscript. M.A.J. contributed to the statistical analysis. N.M., M.J.R.J., I.M.vO. and W.R.G. critically revised the manuscript.

Correspondence to: Maarten J. van der Doelen, MD, Department of Medical Oncology, Radboud University Medical Center, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: Maarten.vanderDoelen@radboudumc.nl.

ISSN: 0363-9762/18/4301–0009
DOI: 10.1097/RLU.0000000000001904

exclusion criteria. All patients continued androgen deprivation therapy and patients were castration-resistant according to the European Association of Urology definition.[8]

The medical records of the patients were reviewed to collect information about demographic characteristics, comorbidity, histology, surgical procedures and medical therapies for prostate cancer, laboratory evaluations, imaging studies, the occurrence of skeletal related events (SREs) and survival. All patients were followed until death or June 1, 2017.

^{223}Ra Therapy Standard of Care

^{223}Ra was injected intravenously every 4 weeks up to six cycles according to standard of care.[9] Institutional criteria for initiation of ^{223}Ra therapy included CRPC patients with bone metastases, no or small (<3 cm in short-axis diameter) lymph node metastases and no visceral metastases. Laboratory requirements were baseline absolute neutrophil count >1.5 × 10^9/L and platelet count >100 × 10^9/L. Laboratory evaluation was carried out within 60 days before ^{223}Ra initiation. Within 3 months prior to start of ^{223}Ra therapy imaging studies were performed, including a bone scintigraphy and computer tomography (CT) of thorax and abdomen. Before every injection, performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG) criteria. Laboratory evaluation before every ^{223}Ra injection included hemoglobin (Hb), platelets, lactate dehydrogenase (LD), alkaline phosphatase (ALP) and prostate specific antigen (PSA) measurements. All eligible patients were discussed in our multidisciplinary team meeting before initiation of ^{223}Ra therapy.

Adverse Events

Adverse events during ^{223}Ra therapy were scored using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. SREs were defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression.[10]

Biochemical and Radiological Response Evaluation

Changes in PSA and ALP were calculated from baseline to week 12 (after three injections), from baseline to end of therapy (approximately 1 month after the last injection) and as maximal percentage change at any time from baseline. Patients who had no baseline level, no follow-up measurements or received concomitant enzalutamide or abiraterone were excluded from biochemical response evaluation. More than 25% decline or increase from baseline of PSA, ALP and LD was considered to be clinically significant, according to Prostate Cancer Working Group 3 criteria.[10] Radiological evaluation was performed in patients who underwent evaluation of soft tissues within 3 months after completion or discontinuation of therapy.

Statistical Methods

Survival time was defined as the time interval from date of first ^{223}Ra injection to the date of death. Cox proportional hazards models were used to assess the prognostic significance of baseline variables in univariable and multivariable analysis. A multivariable Cox regression model was fitted by including variables in the model with a forward selection strategy based on Wald's test at a significance level of 0.10 at every step. In case baseline variables were heavily skewed distributed or the proportional hazard assumption was not likely to hold, log transformation or categorization of variables was performed.

To compare baseline characteristics between patients who completed and discontinued ^{223}Ra therapy, the chi-square test or Fisher exact test was used. Statistical tests were performed two-sided, with P values <0.05 considered statistically significant. Survival curves for patients who completed therapy and patients who discontinued therapy were estimated by the Kaplan–Meier estimator. The Mantel–Cox log rank test was used to compare the survival distributions.

Statistical analyses were performed using SPSS 22.0 (IBM®, Armonk, NY, USA). Figures were created with SPSS and GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA).

Ethics

This study was approved by the medical ethics review committee. The principles of the Helsinki Declaration were followed.

RESULTS

Patient Characteristics

Patient characteristics of the 45 CRPC patients who received ^{223}Ra are shown in Table 1. The median number of prior registered therapies for CRPC was 2 (range 0–4). Twenty-five patients (56%) received prior docetaxel chemotherapy and 35 patients (78%) received prior enzalutamide and/or abiraterone. Baseline laboratory and imaging characteristics are described in Table 2.

Overall Survival

Thirty-eight patients (84%) had died at time of analysis. The median OS since start of ^{223}Ra in the whole study population was 13.0 months (95% CI 8.2–17.8). Univariable analysis showed that baseline ECOG PS, baseline opioid use and baseline hemoglobin, PSA, ALP and LD levels were variables significantly associated with OS (Table 3). With the multivariable analysis we found a model that included baseline ECOG PS and baseline LD levels (Table 4). However, the multivariable analysis was restricted to 32 subjects (71%) due to limited availability of baseline LD levels (complete case analysis). When the baseline LD level variable was left out from analysis, 41 subjects (91%) were included in the analysis and baseline ECOG PS, baseline hemoglobin level and opioid use were selected in multivariable analysis (hazard ratios 2.6 (95% CI 1.1–5.8); 0.8 (95% CI 0.6–1.0) and 2.2 (95% CI 1.0–4.7), respectively).

The Number of Injections

Twenty-one (47%) patients received all six injections. The median number of injections was five. Four patients (9%) received one or two injections, seven patients (16%) received three injections, four patients (9%) received four injections and nine patients (20%) received five injections. We found significant differences between patients who received one to five injections and those who completed therapy regarding baseline LD levels, baseline opioid use and prior use of abiraterone or enzalutamide (Tables 1 and 2). Patients who completed ^{223}Ra therapy had a median OS of 19.7 months (95% CI 14.9–24.6), while patients who received one to five ^{223}Ra injections had a median OS of 5.9 months (95% CI 3.8–8.1; $P < 0.001$) (Fig. 1). This significant finding in survival was substantiated by the OS difference between five (n = 9) and six ^{223}Ra injections (7.3 vs 19.7 months, $P < 0.01$).

Adverse Events

Persistent hematologic toxicity was the reason to discontinue ^{223}Ra therapy in nine of 24 patients (38%; pancytopenia in four patients, thrombocytopenia in three patients, anemia in two patients). No grade 3–4 non-hematologic adverse events occurred during and after therapy.

At baseline, 33 patients (73%) had grade 1 anemia and five patients (11%) had grade 2 anemia. Only one patient with initial grade 2 anemia completed therapy. During therapy, 16 patients

TABLE 1. Baseline Patient Characteristics

	Complete Cohort (N = 45)			Group 1–5 ^{223}Ra Injections (N = 24)			Group 6 ^{223}Ra Injections (N = 21)			
	n	Median [range] or Mean ± SD or n (%†)		n	Median [range] or Mean ± SD or n (%†)		n	Median [range] or Mean ± SD or n (%†)		*P*
Age (years)	45	71	[51–84]	24	71	[51–83]	21	70	[55–84]	0.666
Initial tumor stage										
Localized PCa	45	14	(31.1)	24	7	(29.2)	21	7	(33.3)	0.763
Metastatic PCa	45	31	(68.9)	24	17	(70.8)	21	14	(66.7)	
Gleason score 8–10	45	27	(60.0)	24	16	(66.7)	21	11	(46.7)	0.329
Time diagnosis PCa to CRPC (months)	45	29	[5–200]	24	30	[5–200]	21	26	[12–173]	0.716
Time start ADT to CRPC (months)	45	22	[5–85]	24	20	[5–85]	21	24	[12–75]	0.539
Time CRPC to ^{223}Ra (months)	45	23	[1–80]	24	20	[0–51]	21	30	[6–80]	0.082
Prior therapies for localized PCa										
Radical prostatectomy[1]	45	10	(22.2)	24	4	(16.6)	21	6	(28.6)	0.476‡
Radiotherapy prostate (initial or salvage)	45	17	(37.8)	24	8	(33.3)	21	9	(42.9)	0.511
Pelvic lymph node dissection	45	11	(24.4)	24	6	(25.0)	21	5	(23.8)	1.000‡
Pelvic lymph node irradiation	45	4	(8.9)	24	1	(4.2)	21	3	(14.3)	0.326‡
Prior therapies for CRPC										
Median number of therapies	45	2	[0–4]	24	2	[0–4]	21	2	[0–4]	0.744
None	45	6	(13.3)	24	5	(20.8)	21	1	(4.8)	0.193‡
Abiraterone and/or enzalutamide[2]	45	35	(77.8)	24	17	(70.8)	21	18	(85.7)	0.296‡
Abiraterone	45	31	(68.9)	24	13	(54.2)	21	18	(85.7)	**0.028‡**
Enzalutamide	45	11	(24.4)	24	9	(37.5)	21	2	(9.5)	**0.040‡**
First-line chemotherapy[3]	45	25	(55.6)	24	14	(58.3)	21	11	(52.4)	0.688
Second-line chemotherapy[4]	45	13	(28.9)	24	8	(33.3)	21	5	(23.8)	0.528‡
Radiotherapy to bone metastases[5]	45	27	(60.0)	24	13	(54.2)	21	14	(66.7)	0.393
Concomitant abiraterone or enzalutamide	45	5	(11.1)	24	4	(16.7)	21	1	(4.8)	0.352‡
Body mass index (kg/m^2)	42	26.6	±3.3	21	26.1	±3.3	21	26.8	±3.5	0.782
Opioid use	45	20	(44.4)	24	14	(58.3)	21	6	(28.6)	**0.045**
ECOG performance status										
ECOG 0	44	21	(47.7)	24	8	(33.3)	20	13	(65.0)	0.104
ECOG 1	44	15	(34.1)	24	10	(41.7)	20	5	(25.0)	
ECOG 2-3	44	8	(18.2)	24	6	(25.0)	20	2	(10.0)	

Bold = $P < 0.05$.

[1]Either open (40%) or laparoscopically (10%) or robot assisted (50%).

[2]E.g. abiraterone plus prednisone or enzalutamide.

[3]96% docetaxel, 4% mitoxantrone.

[4]62% cabazitaxel, 38% docetaxel.

[5]At least one time irradiated on metastases (all axial skeleton, one also appendicular skeleton).

†Percentages may not sum to 100 due to rounding.

‡Calculated by two-sided Fisher exact probability test.

ADT indicates androgen deprivation therapy; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; PCa, prostate cancer.

TABLE 2. Baseline Laboratory and Imaging Characteristics

	Complete Cohort (N = 45)			Group 1–5 ^{223}Ra Injections (N = 24)			Group 6 ^{223}Ra Injections (N = 21)			
	n	Median [range] or n (%†)		n	Median [range] or n (%†)		n	Median [range] or n (%†)		*P*
Hemoglobin (g/dL)	45	12.0	[9.3–15.4]	24	11.8	[9.3–14.9]	21	12.6	[9.9–15.4]	0.136
Hb > 10	45	40	(88.9)	24	20	(83.3)	21	20	(95.2)	0.352‡
Hb ≤ 10	45	5	(11.1)	24	4	(16.7)	21	1	(4.8)	
Platelet count ($\times 10^9$/L)	45	240	[140–466]	24	238	[140–461]	21	254	[142–466]	0.794
WBC count ($\times 10^9$/L)	45	7.5	[3.4–12.7]	24			21			
NLR ($\times 10^9$/L)	35	4.20	[0.9–11.8]	19	2.90	[1.0–11.8]	16	4.59	[0.9–9.0]	0.466
NLR ≤ 3.0	35	15	(42.9)	19	10	(52.6)	16	5	(31.3)	0.203
NLR > 3.0	35	20	(57.1)	19	9	(47.4)	16	11	(68.8)	
PSA level (μg/L)	44	130.0	[1–6472]	23	170.0	[9–3000]	21	61.0	[1–6472]	0.142
ALP level (U/L)	43	147	[60–2640]	24	180	[73–1958]	19	125	[60–2640]	0.304
ALP < 115	43	16	(37.2)	24	7	(29.2)	19	9	(47.4)	0.220
ALP ≥ 115	43	27	(62.8)	24	17	(70.8)	19	10	(52.6)	
LD level (U/L)	33	216	[165–1045]	19	288	[175–1045]	14	208	[165–341]	**0.011**
LD < 250	33	20	(60.6)	19	8	(42.1)	14	12	(85.7)	**0.015**‡
LD ≥ 250	33	13	(39.4)	19	11	(57.9)	14	2	(14.3)	
Extent of disease										
6–20 metastases	45	9	(20.0)	24	5	20.8	21	4	19.0	0.912
>20 metastases	45	28	(62.2)	24	14	58.3	21	14	66.7	
Superscan*	45	8	(17.8)	24	5	20.8	21	3	14.3	
Lymph node metastases	41	10	(24.4)	20	5	(25.0)	21	5	(23.8)	0.929
Visceral metastases	41	4	(10.0)	20	2	(10.0)	21	2	(9.5)	1.000‡

Bold = $P < 0.05$.

*Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

†Percentages may not sum to 100 due to rounding.

‡Calculated by two-sided Fisher exact probability test.

ALP indicates alkaline phosphatase; ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group performance score; Hb, hemoglobin; LD, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PSA, prostate-specific antigen; WBC, white blood cell.

TABLE 3. Univariate Analysis of Overall Survival

	n	Median OS (months)	HR	95% CI	*P*
Age (years)	45	13.0	1.01	0.97–1.06	0.59
ECOG, categorical					**<0.01**
ECOG 0	21	19.7	1.00		
ECOG 1	15	5.9	3.35	1.59–7.06	**<0.01**
ECOG 2–3	8	7.3	4.15	1.66–10.33	**<0.01**
Opioid use					
No	25	15.7	1.00		
Yes	20	5.9	2.00	1.05–3.81	**0.03**
Initial tumor Gleason score					
GS ≤7	18	11.0	1.00		
GS 8–10	27	13.6	0.88	0.46–1.69	0.71
Extent of disease					0.16
6–20 metastases	9	17.0	1.00		
>20 metastases	28	13.5	1.32	0.56–3.13	0.52
Superscan*	8	7.9	2.62	0.92–7.49	0.07
Prior chemotherapy					
No	20	15.7	1.00		
Yes	25	8.9	1.77	0.90–3.49	0.10
Prior abiraterone or enzalutamide					
No	10	8.6	1.00		
Yes	35	13.0	1.74	0.72–4.19	0.22
Number of prior CRPC therapies					
0–1	18	14.3	1.00		
≥2	27	10.0	1.47	0.75–2.85	0.26
Number of prior CRPC therapies					0.24
0	6	5.1	1.00		
1	12	14.3	1.24	0.38–4.06	0.72
2	10	8.9	1.10	0.32–3.77	0.88
3	9	11.0	1.80	0.55–5.92	0.33
4	8	6.0	3.07	0.87–10.80	0.08
Hemoglobin (g/dL), continuous	45	13.0	0.74	0.58–0.93	**<0.01**
Hemoglobin (g/dL), dichotomized					
Hb > 10	40	13.6	1.00		
Hb ≤ 10	5	5.7	3.81	1.39–10.38	**<0.01**
Platelet count, continuous	45	13.0	1.00	1.00–1.00	0.21
ANC, continuous	36	11.0	0.98	0.84–1.14	0.78
NLR, continuous	35	11.0	1.08	0.94–1.24	0.30
Log PSA	44	13.0	1.23	1.03–1.48	**0.03**
Log ALP	43	12.2	1.66	1.16–2.35	**<0.01**
ALP, dichotomized (U/L)					
ALP < 115	16	15.7	1.00		
ALP ≥ 115	27	8.6	2.16	1.05–4.44	**0.04**
Log LD (U/L)	33	11.0	7.39	2.54–21.54	**<0.01**
LD, dichotomized (U/L)					
LD < 250	20	15.7	1.00		
LD ≥ 250	13	5.9	2.78	1.23–6.30	**0.01**
Albumin (g/L)	33	13.6	0.96	0.87–1.05	0.34

Bold = $P < 0.05$.

*Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

ALP indicates alkaline phosphatase; ANC, absolute neutrophil count; CI, confidence interval; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score; Hb, hemoglobin; HR, hazard ratio; LD, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PSA, prostate-specific antigen.

received red blood cell transfusion. Seventy-five percent of these patients did not complete therapy and 81% of these patients had received two or more prior CRPC therapies. OS was significantly worse when compared to patients who did not need blood cell transfusion (8 versus 14 months). At any time during therapy, grade 1 thrombocytopenia occurred in 11 patients (24%) and grade 2

TABLE 4. Multivariable Analysis of Overall Survival

	n	HR	95% CI	*P*
Prior abiraterone or enzalutamide	32			
No	9	1.00		
Yes	23	2.38	0.91–6.23	0.08
ECOG, categorical	32			**<0.01**
ECOG 0	17	1.00		
ECOG 1	9	10.62	3.07–36.73	**<0.01**
ECOG 2–3	6	5.67	1.74–18.47	**<0.01**
Log LD	32	7.67	1.75–33.53	**<0.01**

Bold = $P < 0.05$.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LD, lactate dehydrogenase.

(2%) or 3 (2%) occurred in one patient each. Flare-up of pain immediately after ^{223}Ra administration occurred in 16 patients (36%) at any time during therapy.

Physical health deterioration was the reason to stop therapy in six (25%) patients. Five of these six patients had a baseline ECOG PS of 1 (33%) or 2 (50%).

During therapy, 14 SREs were reported in 11 patients (24%). In seven patients spinal cord compression occurred, which was treated by external beam radiotherapy (EBRT) plus dexamethasone. In two patients a pathological fracture occurred; these patients both discontinued therapy. Additionally, three patients underwent EBRT because of increase of pain at a solitary lesion.

Biochemical Response Evaluation

Figure 2 shows PSA and ALP dynamics in patients treated with ^{223}Ra monotherapy. Significant increase of PSA was observed in 65% of patients after three injections. Significant decrease of ALP was found in 53% of patients after three injections. All of the patients with PSA decrease showed remarkable ALP decrease (range 23%–75%). ALP at end of therapy was significantly lower in patients who completed therapy when compared to patients who discontinued therapy ($P < 0.01$).

Radiological Response Evaluation

In retrospect, four patients (10%) had small visceral metastases in either liver (n = 2) or lungs (n = 2) prior to start of ^{223}Ra therapy. The two patients with lung metastases completed ^{223}Ra therapy, while both patients with liver metastases discontinued therapy after the fourth injection.

After ^{223}Ra therapy, 20 patients (44%) underwent evaluation of lymph nodes and soft tissues. Radiological evaluation was mainly performed in patients that completed therapy (90% versus 38%). New lymph node enlargement (≥15 mm in the short axis) was shown in 17% of patients. New visceral metastases to liver, lung, spleen and/or brain were found in 41% of patients. All of these patients were heavily pretreated. Among the 24 patients who discontinued therapy, radiological disease progression was the main reason to stop therapy in five (21%) patients.

Therapies After ^{223}Ra Therapy

In patients who discontinued ^{223}Ra therapy, best supportive care (67%) or a second-generation anti-hormonal agent (33%) was started. In patients who completed ^{223}Ra therapy, subsequent therapy was a second-generation anti-hormonal agent in 15 patients (71%). Two patients (10%) received docetaxel without any toxicity during chemotherapy and three patients (14%) received best supportive care after completion of ^{223}Ra therapy.

DISCUSSION

Overall Survival

Median OS in this cohort was 13.0 months, which is similar to the ALSYMPCA trial.[3] Multivariable analysis selected baseline ECOG PS and LD levels to be significantly associated with OS in this study. The post hoc multivariable analysis of the ALSYMPCA trial also selected baseline ECOG PS and LD were correlated with OS. In addition, that analysis identified albumin level, total ALP, PSA and age to be correlated with OS as well.[11] The analysis of

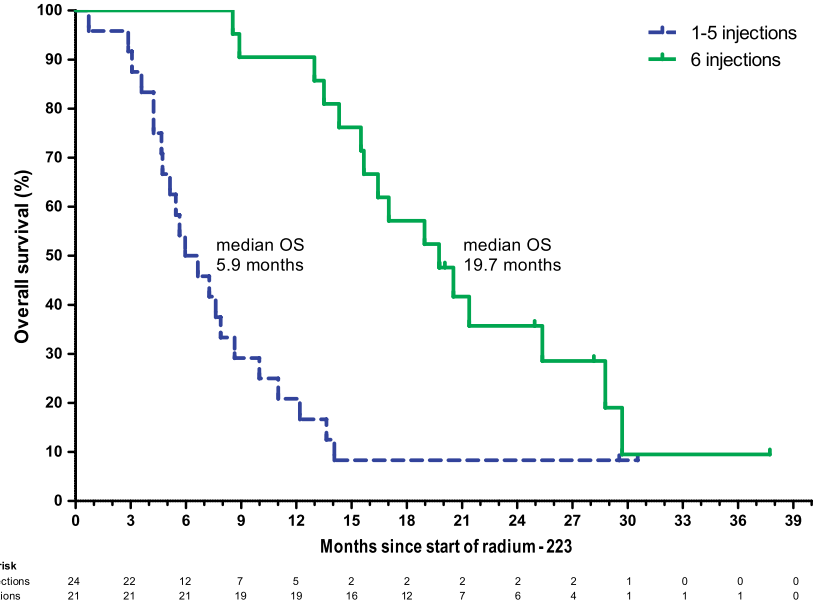

FIGURE 1. Kaplan–Meier curve of overall survival (OS), stratified by number of injections received (1–5 versus 6 injections). Log-rank *P* value < 0.001.

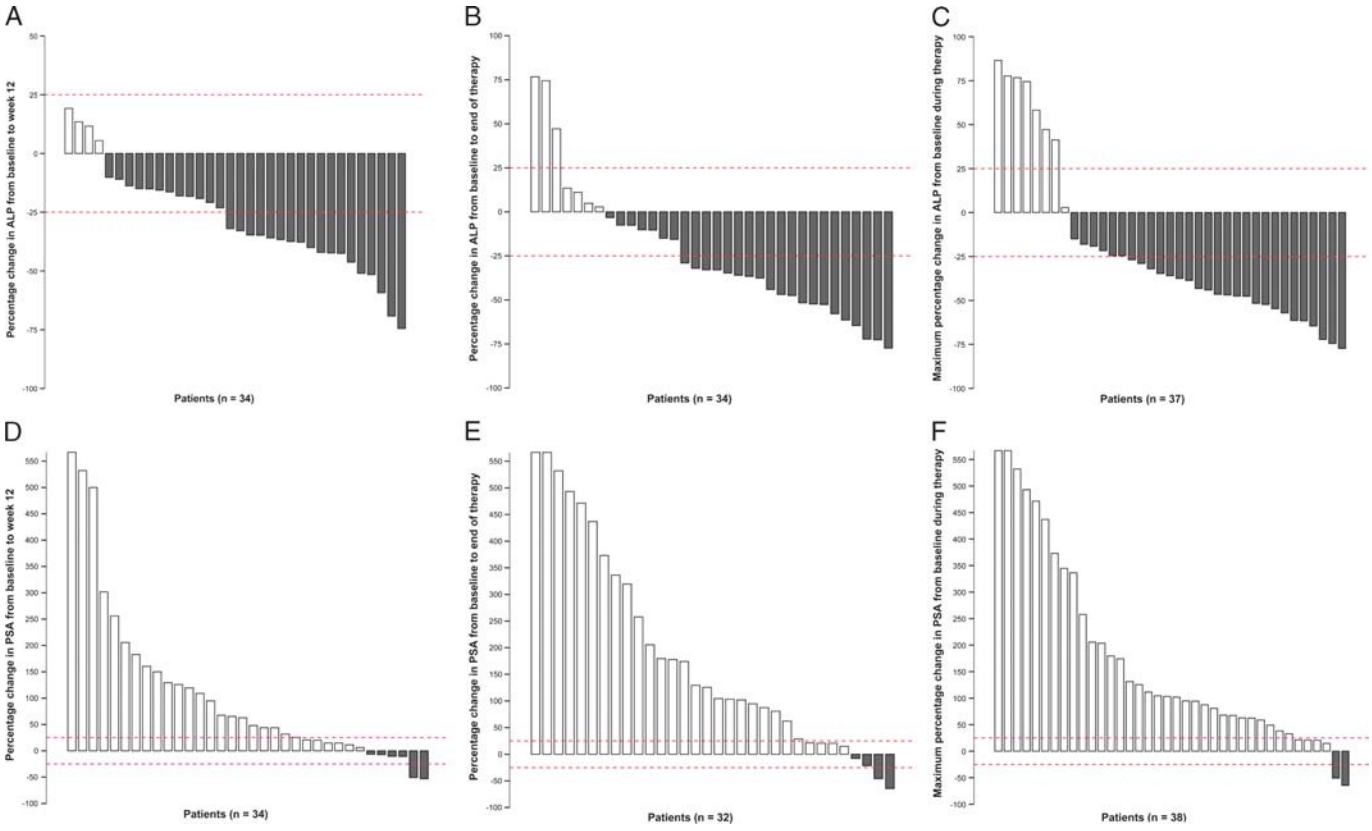

FIGURE 2. Waterfall plots showing percentages change in alkaline phosphatase (ALP) and prostate-specific antigen (PSA). Percentage change in ALP from baseline to week 12, from baseline to end of therapy and maximum percentage change in ALP from baseline during therapy (**A**–**C**). Percentage change in PSA from baseline to week 12, from baseline to end of therapy and maximum percentage change in PSA from baseline during therapy (**D**–**F**).

the early access program demonstrated median OS was longer for patients with low baseline ALP levels, Hb > 10.0 g/dL, ECOG performance score of 0, no reported baseline pain, concomitant use of abiraterone or enzalutamide and concomitant use of denosumab.[12] Recent retrospective analyses stated low baseline ALP levels, no or less prior therapies, and a low number of bone metastases are correlated with better OS.[13–15] In fact, all of these pre-therapeutic variables reflect less advanced disease. These findings, and the fact that the prevalence of visceral metastases increases towards advanced disease stage, seem to underline the need for early application of ^{223}Ra in CRPC patients.[16]

Number of Injections

Remarkable difference in OS between patients who completed and discontinued ^{223}Ra therapy was found. Recently, several retrospective studies described significant associations between the received number of ^{223}Ra injections and OS.[13,14,17] However, these results have to be interpreted with caution, due to immortal time bias.[18] After all, patients must survive sufficiently long to complete ^{223}Ra therapy. In addition, the question remains whether the completion of therapy is the cause of the difference in OS, rather than better patient selection.

Response Evaluation

At week 12 of therapy, ≥25% reduction in PSA was found in 6% of patients. This low PSA response rate is comparable to findings in the ALSYMPCA trial and the early access program.[3,12] According to the proportional treatment effect analysis of the ALSYMPCA trial, ALP decrease at 12 weeks from baseline was found to be the best indicator for risk of death, but accounted only for 34% of the survival benefit from ^{223}Ra treatment.[11] This indicates response evaluation of ^{223}Ra should consist of more than biochemical evaluation alone. There is a clinical need for reliable biomarkers for optimal patient selection and effect monitoring during ^{223}Ra therapy.

In this study, only 44% of patients underwent CT within 3 months after termination of ^{223}Ra therapy. New visceral metastases were found in 41% of the patients. This percentage may be overestimated due to selection of patients for radiological evaluation. However, a recent study described radiological extraskeletal disease progression in even 46% of patients.[19] Advanced imaging techniques, such as ^{68}Ga-PSMA-11 PET/CT, may be helpful to rule out extraskeletal disease prior to ^{223}Ra therapy initiation and was also described to be useful as a gatekeeper during ^{223}Ra therapy.[20–23]

Study Limitations

The impact of this study is limited by its retrospective single-center design and relative small sample size. It is, therefore, susceptible to recall and interpretation bias. The sample size restricted extensive regression analysis. However, this real world study was able to discriminate important baseline variables which are associated with OS. These results were similar to outcomes of other studies.

Learning Curve

Our team experienced a learning curve towards optimal patient selection for ^{223}Ra therapy. In 2014, only 27% of the patients completed therapy. In 2016, 65% of the patients completed therapy.

Nationwide, only 42% of the Dutch patients completed therapy in 2016. According to recent recommendations and our experience, patients should be discussed in a multidisciplinary tumor board with presence of a nuclear physician before start of therapy.[8,24] In addition, all patients must be radiologically evaluated before and after therapy. During therapy, additional imaging may be considered in case of extraordinary elevation of tumor markers, in order to rule out extraskeletal disease.[19]

CONCLUSIONS

In CRPC patients treated with ^{223}Ra, we found a remarkable difference in OS between patients who discontinued and completed therapy. Baseline ECOG PS and LD levels were selected in a multivariable Cox regression model to predict OS. Prospective observational multicenter studies with larger patient populations are needed to confirm our findings and to develop a nomogram to select patients properly.

REFERENCES

1. Henriksen G, Breistol K, Bruland OS, et al. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. *Cancer Res*. 2002;62:3120–3125.
2. Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. *Clin Cancer Res*. 2017;23:4335–4346.
3. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213–223.
4. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*. 2014;15:1397–1406.
5. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol*. 2014;15:738–746.
6. Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol*. 2016;27:868–874.
7. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJ, et al. Differences in trial and real-world populations in the Dutch Castration-resistant Prostate Cancer Registry. *Eur Urol Focus*. 2016; [Epub ahead of print]. DOI: 10.1016/j.euf.2016.09.008.
8. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol*. 2017;71:630–642.
9. Kluetz PG, Pierce W, Maher VE, et al. Radium Ra 223 dichloride injection: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res*. 2014;20:9–14.
10. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34:1402–1418.
11. Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. *Ann Oncol*. 2017;28:1090–1097.
12. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol*. 2016;17:1306–1316.
13. Alva A, Nordquist L, Daignault S, et al. Clinical correlates of benefit from radium-223 therapy in metastatic castration resistant prostate cancer. *Prostate*. 2017;77:479–488.
14. Etchebehere EC, Milton DR, Araujo JC, et al. Factors affecting (223)Ra therapy: clinical experience after 532 cycles from a single institution. *Eur J Nucl Med Mol Imaging*. 2016;43:8–20.
15. Wong WW, Anderson EM, Mohammadi H, et al. Factors associated with survival following radium-223 treatment for metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer*. 2017; [Epub ahead of print]. DOI: 10.1016/j.clgc.2017.04.016.
16. Pezaro CJ, Omlin A, Lorente D, et al. Visceral disease in castration-resistant prostate cancer. *Eur Urol*. 2014;65:270–273.
17. McKay RR, Jacobus S, Fiorillo M, et al. Radium-223 use in clinical practice and variables associated with completion of therapy. *Clin Genitourin Cancer*. 2017;15:e289–e298.
18. Jones M, Fowler R. Immortal time bias in observational studies of time-to-event outcomes. *J Crit Care*. 2016;36:195–199.
19. Keizman D, Fosboel MO, Reichegger H, et al. Imaging response during therapy with radium-223 for castration-resistant prostate cancer with bone metastases—analysis of an international multicenter database. *Prostate Cancer Prostatic Dis*. 2017;20:289–293.
20. Ahmadzadehfar H, Azgomi K, Hauser S, et al. 68Ga-PSMA-11 PET as a gate-keeper for the treatment of metastatic prostate cancer with 223Ra: proof of concept. *J Nucl Med*. 2017;58(3):438–444.
21. Ahmadzadehfar H, Schlenkhoff CD, Rogenhofer S, et al. 68Ga-PSMA-11 PET represents the tumoricidal effect of 223Ra in a patient with castrate-resistant metastatic prostate cancer. *Clin Nucl Med*. 2016;41:695–696.
22. Bräuer A, Rahbar K, Konnert J, et al. Diagnostic value of additional 68Ga-PSMA-PET before 223Ra-dichloride therapy in patients with metastatic prostate carcinoma. *Nuklearmedizin*. 2017;56:14–22.
23. Bode A, Rahbar K, Konnert J, et al. Benefit of 68Ga-PSMA-PET/CT in patients considered for 223Ra-dichloride therapy. *Clin Nucl Med*. 2016;41:951–952.
24. Baldari S, Boni G, Bortolus R, et al. Management of metastatic castration-resistant prostate cancer: a focus on radium-223: Opinions and suggestions from an expert multidisciplinary panel. *Crit Rev Oncol Hematol*. 2017;113:43–51.