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

Lessons from Daily Practice

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

Methods: Data from 45 CRPC patients treated with ²²³Ra were retrospectively analyzed. All patients who received at least one ²²³Ra 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 ²²³Ra injections and 24 patients (53%) received one to five ²²³Ra injections. Median OS since start of ²²³Ra was 13.0 months (95% confidence interval (CI) 8.2–17.8). Patients who completed ²²³Ra therapy had a median OS of 19.7 months (95% CI 14.9–24.6), while patients who received one to five ²²³Ra 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 ²²³Ra. These variables may be used for stratification of CRPC patients for ²²³Ra 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 ²²³Ra 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, ²²³Ra, bone metastases, castration-resistant, radiopharmaceutical

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²²³Ra 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 μ m; 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 ²²³Ra 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 ²²³Ra over placebo. Subsequent analyses demonstrated survival benefit of ²²³Ra in chemotherapy-naïve CRPC patients as well as in post-chemotherapy CRPC patients.⁴ In addition, ²²³Ra reduced the risk of symptomatic skeletal events and was accompanied by significant improvement of quality of life.^{5,6}

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

In addition, effect monitoring during ²²³Ra 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 ²²³Ra. 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 ²²³Ra, in order to determine pre-therapeutic variables that predict OS and to describe baseline differences between patients who completed and patients who discontinued ²²³Ra therapy.

PATIENTS AND METHODS

Study Design and Patient Population

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

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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.

²²³Ra Therapy Standard of Care

²²³Ra was injected intravenously every 4 weeks up to six cycles according to standard of care.⁹ Institutional criteria for initiation of ²²³Ra 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 × 10⁹/L and platelet count >100 × 10⁹/L. Laboratory evaluation was carried out within 60 days before ²²³Ra initiation. Within 3 months prior to start of ²²³Ra 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 ²²³Ra 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 ²²³Ra therapy.

Adverse Events

Adverse events during ²²³Ra 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 ²²³Ra 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 ²²³Ra 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 ²²³Ra 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 ²²³Ra 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 ²²³Ra therapy had a median OS of 19.7 months (95% CI 14.9–24.6), while patients who received one to five ²²³Ra 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 ²²³Ra injections (7.3 vs 19.7 months, *P* < 0.01).

Adverse Events

Persistent hematologic toxicity was the reason to discontinue ²²³Ra 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) | | P |
|--|--------------------------|---------------------------------------|---|---------------------------------------|---|---------------------------------------|---------------|
| | n | Median [range] or Mean ± SD or n (%)† | n | Median [range] or Mean ± SD or n (%)† | n | Median [range] or Mean ± SD or n (%)† | |
| 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.

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

²E.g. abiraterone plus prednisone or enzalutamide.

³66% docetaxel, 4% mitoxantrone.

⁴62% cabazitaxel, 38% docetaxel.

⁵At 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) | | P |
|--------------------------------------|--------------------------|--------------------------|---|--------------------------|---|--------------------------|---------------|
| | n | Median [range] or n (%)† | n | Median [range] or n (%)† | n | Median [range] or n (%)† | |
| Hemoglobin (g/dL) | 45 | 12.0 [9.3–15.4] | 24 | 11.8 [9.3–14.9] | 21 | 12.6 [9.3–15.4] | 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 (×10 ⁹ /L) | 45 | 240 [140–466] | 24 | 238 [140–461] | 21 | 254 [142–466] | 0.794 |
| WBC count (×10 ⁹ /L) | 45 | 7.5 [3.4–12.7] | 24 | | 21 | | |
| NLR (×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 ²²³Ra 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 ²²³Ra 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 ²²³Ra therapy. The two patients with lung metastases completed ²²³Ra therapy, while both patients with liver metastases discontinued therapy after the fourth injection.

After ²²³Ra 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 ²²³Ra Therapy

In patients who discontinued ²²³Ra therapy, best supportive care (67%) or a second-generation anti-hormonal agent (33%) was started. In patients who completed ²²³Ra 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 ²²³Ra 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

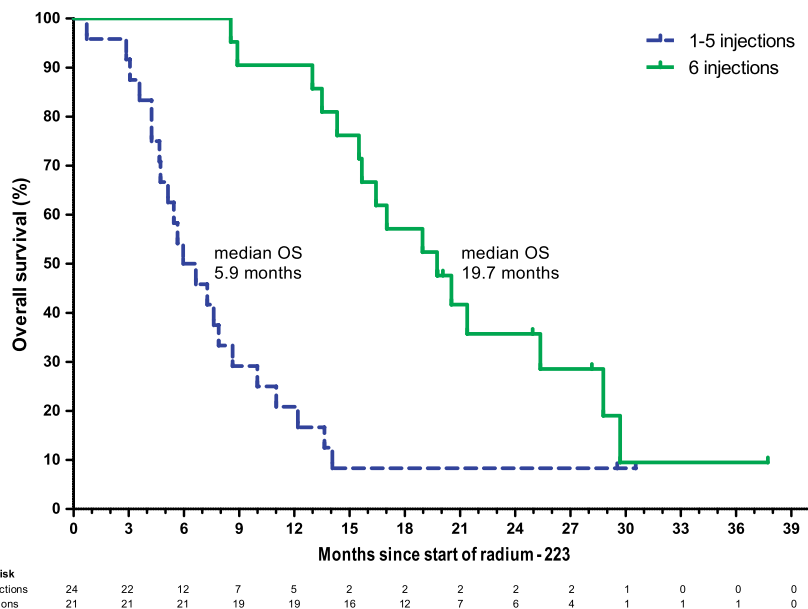


FIGURE 1. Kaplan–Meier curve of overall survival (OS), stratified by number of injections received (1–5 versus 6 injections). Log-rank P value < 0.001.

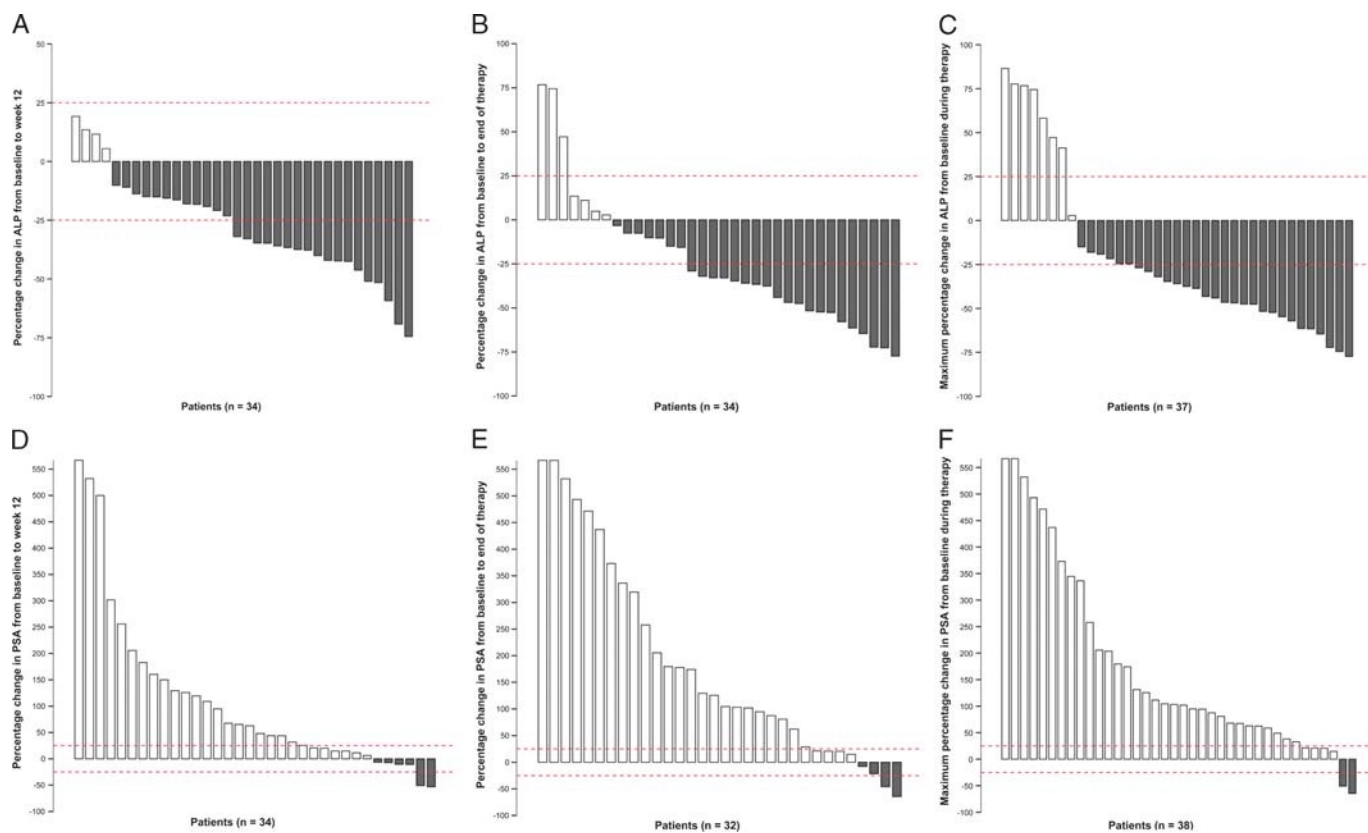


FIGURE 2. Waterfall plots showing percentages change in alkaline phosphatase (ALP) and prostate-specific antigen (PSA). Percentage change in ALP from baseline to week 12, from baseline to end of therapy and maximum percentage change in ALP from baseline during therapy (A–C). Percentage change in PSA 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 ²²³Ra in CRPC patients.¹⁶

Number of Injections

Remarkable difference in OS between patients who completed and discontinued ²²³Ra therapy was found. Recently, several retrospective studies described significant associations between the received number of ²²³Ra 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 ²²³Ra 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, $\geq 25\%$ 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 ²²³Ra treatment.¹¹ This indicates response evaluation of ²²³Ra should consist of more than biochemical evaluation alone. There is a clinical need for reliable biomarkers for optimal patient selection and effect monitoring during ²²³Ra therapy.

In this study, only 44% of patients underwent CT within 3 months after termination of ²²³Ra 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 extraskelatal disease progression in even 46% of patients.¹⁹ Advanced imaging techniques, such as ⁶⁸Ga-PSMA-11 PET/CT, may be helpful to rule out extraskelatal disease prior to ²²³Ra therapy initiation and was also described to be useful as a gatekeeper during ²²³Ra 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 ²²³Ra 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 ²²³Ra, 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.

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