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Original Article

Single-center developing country analysis of radium-223 therapy in prostate cancer-preliminary results

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Abstract: We reviewed the records of mCRPC patients treated with off-label use of Ra-223. Ra-223 efficiency in this non-study population was correlated to outcome measures overall survival (OS), progression-free survival (PFS), bone event-free survival, bone marrow failure (BMF), and disease-related biomarkers. There were no limits regarding the number of prior hormonal agents or chemotherapy received before or during Ra-223. Exclusion criteria consisted of baseline platelet counts below 50,000/mm^3 and/or absolute neutrophil counts below 1,500/mm^3. Twenty-eight patients received 130 cycles of Ra-223 between 2017 and 2018. The overall median OS was 15.6 months. However, in patients submitted to 4 or fewer cycles, the median OS was 9.1 months; in contrast, the median OS was 18.5 months in patients submitted to 5 or 6 cycles. There was a significant inverse correlation between the number of cycles and the occurrence of bone events (76.2% of the patients that completed 6 cycles did not present bone events, while 71.4% of the patients that had skeletal-related events were submitted to less than 6 cycles). 82.1% of the patients were submitted to concomitant therapies with no significant side effects. There was also a decrease in ALP and LDH levels throughout treatment. Radium-223 increased OS and decreased bone events, especially when patients were able to complete 5-6 cycles. The proper selection of patients is crucial to improve outcomes.

Keywords: Radium-223, prostate cancer, bone metastasis

Introduction

The addition of chemotherapy, novel secondary hormonal therapies, and Radium-223 has delayed the progression of metastatic castration-resistant prostate cancer and improved overall survival [1].

Currently, Radium-223 (Ra-223) therapy is recommended as a category 1 treatment option in the National Comprehensive Cancer Network guidelines for patients with metastatic castration-resistant prostate cancer and symptomatic bone metastases but no visceral metastases [3, 4]. Ra-223 improves overall survival with low myelosuppression rates and few adverse events [5, 6].

Ra-223 is a targeted alpha therapy that is delivered during 6 months, with monthly injections, operating similarly to calcium and triggering double-strand DNA breaks in bone lesions with high osteoblastic activity, leading to a localized cytotoxic effect, targeting both cancer cells and the bone microenvironment [3, 7].

Although the ALSYMPCA trials included patients previously treated with docetaxel, newer generation drugs investigated after Ra-223 and docetaxel, such as abiraterone, enzalutamide and cabazitaxel have also demonstrated improved overall survival [8]. There is no clear algorithm for choosing between further hormonal treatment or radium-223, or both [1].

The lack of a clear algorithm to refer patients for Ra-223 therapy may delay treatment, especially in developing countries where the health care system suffers from an interruption in treatment due to a wide variety of issues. The

Table 1. Classification of ECOG *status*, pain score, and hematologic toxicity, according to the WHO criteria

ECOG (Eastern Cooperative Oncology Group) *status*			
0	Asymptomatic. Fully active, able to carry on all activities without restriction.		
1	Symptomatic. Restricted in physically strenuous activity; able to carry out work of a light or sedentary nature.		
2	Symptomatic. <50% in bed during the day. Ambulatory and capable of all self-care; unable to carry out any work activities.		
3	Symptomatic. >50% in bed. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.		
4	Bedbound		
Pain score (According to WHO criteria)			
0	No pain. Analgesia not required.		
1	Mild pain, no opioid use		
2	Moderate pain with occasional opioid use		
3	Severe pain with daily opioid use		
Hematologic toxicity (According to WHO criteria)			
	Hemoglobin (g/dL)	ANC (/mm^3)	Platelets (/mm^3)
1	>10.0	>1,500	>75,000
2	8.0 to <10.0	1,000 to <1,500	50,000 to <75,000
3	<8.0 (transfusion required)	500 to <1,000	25,000 to <50,000
4	Life-threatening; urgent intervention indicated	<500	<25,000

appropriate window of opportunity for delivering Ra-223 in a non-study population in developing countries may be missed.

The purpose of this study was to evaluate the characteristics of referrals for Ra-223 therapy in a single-center setting in a developing country.

Materials and methods

Study design

This study was approved by the local Ethics Committee (CAEE# 28788220.0.1001.5404). The waivers of Informed Consent and Authorization were granted for this retrospective analysis.

We reviewed the records of patients with metastatic castrate-resistant prostate cancer (mCRPC) treated with Ra-223 between September 2017 and August 2018.

Inclusion criteria to receive Ra-223 consisted of the age of at least 18 years and mCRPC with bone metastases. There were no limits regarding the number of hormonal agents or chemotherapy received before Ra-223 therapy.

Exclusion criteria to receive Ra-223 consisted of baseline platelet counts below 50,000/mm^3 and/or absolute neutrophil counts below 1,500/mm^3 or with life expectancy below 6 months.

Radium-223 treatment

The patients were treated with Ra-223 on off-label circumstances by a multidisciplinary team in a private sector, such as the conditions below: 1) Baseline hemoglobin levels below 10 g/dl before Ra-223; 2) Presence of visceral metastases on baseline imaging before Ra-223; 3) Use of concomitant chemotherapy during Ra-223; 4) Use secondary hormonal therapy during Ra-223.

Intravenous infusions of 50 kBq/kg (1.4 μCi/kg) of $Ra^{223}Cl_2$ doses were injected every 4 weeks. All patients completed between 1 and 6 cycles of Ra-223. Criteria to receive subsequent Ra-223 cycles were ANC above 1,000/mm^3 and PLT above 50,000/mm^3. After each Ra-223 cycle, the patients were counseled regarding radiation and expected side effects. Hb levels below 10 g/dL were not an exclusion criterion and patients with lower Hb levels were transfused before Ra-223.

Clinical, Laboratory and Imaging evaluation before Ra-223

The clinical evaluation consisted of determining the patient's ECOG (Eastern Cooperative Oncology Group) performance *status* and pain scores (WHO criteria) (**Table 1**) and evaluating all treatments (current, previous, and combined). The patient's hematologic *status* and the dynamics of the disease were evaluated by:

hemoglobin (Hb), absolute neutrophil counts (ANC), platelets (PLT), alkaline phosphatase (ALP), prostate-specific antigen (PSA), and *lactate dehydrogenase* (LDH) levels. Imaging studies were performed before Ra-223. These studies consisted of one or more of the following: whole-body skeletal ^{18}F-Fluoride PET/CT scan; whole-body metabolic ^{18}F-FDG PET/CT scan; whole-body ^{68}Ga-PSMA PET/CT scan; whole-body conventional bone scintigraphy; CT scans and MRI scans.

Outcome measures

Overall survival (OS) was determined from the initial Ra-223 dose until the date of death or last follow-up.

Progression-free survival (PFS) was determined from the first Ra-223 cycle to the last follow-up. Progression was defined by either a progression of bone lesions, a new nodal lesion, visceral involvement, or by a sudden deterioration of ECOG *status* (by at least 2 points).

Bone events were determined from the first Ra-223 cycle to the first bone event. The bone events were as follows: surgical intervention; spinal cord compression; pathologic fracture; bone pain; and lesion progression.

Statistical analysis

Categorical variables were calculated and displayed as absolute and percentage frequency values. Quantitative variables were obtained and displayed as descriptive measures (mean, standard deviation, minimum, median, and maximum). The differences in ALP and LDH levels (quantitative variable) were obtained between the last and first Ra-223 cycles. Both results were also displayed as descriptive measures [18-20].

To assess the relationship between the type of therapy with progression, survival, and bone event, Fisher's exact test was applied. The relationship between PFS, bone event, and OS with clinical and laboratory data was evaluated with Chi-square and Fisher's exact tests for categorical variables and Mann-Whitney test for numerical variables [18-20].

Kaplan-Meier curves were generated for OS. Boxplot graphs were constructed to present the trend of PSA, ALP, and LDH throughout the Ra-223 cycles [18-20].

The level of significance adopted for the study was 5%.

For the statistical analyses, the computer programs Statistical Analysis System (SAS) for Windows (version 9.4; SAS Institute Inc, 2002-2012, Cary, NC, USA) and the R (version 3.4.2; Copyright (C) 2017 The R Foundation for Statistical Computing) were used [18-20].

Results

Clinical, laboratory and imaging evaluation before Ra-223

A total of 28 patients (age 73.8±9.5 years) were submitted to 130 Ra-223 cycles between 2017 and 2018. The majority of patients (71.5%) initially presented a good ECOG performance *status* (ECOG 0-1) while the other 28.5% were symptomatic (ECOG 2-4). All patients were subjected to multiple other treatment options before Ra-223 therapy; Ra-223 was used as a 3rd line therapy. The majority of the patients (71.4%) presented no bone pain or only mild pain, treated with non-narcotic analgesia. Most patients (96.4%) had baseline hemoglobin (Hb) levels above 10 g/dl, absolute neutrophil counts (ANC) above 1,500/mm^3 and platelet counts above 75,000/mm^3 (**Table 2**).

All patients underwent baseline bone scintigraphy, abdominopelvic CT scans and, MRI scans before Ra-223. Some patients also underwent additional baseline imaging with ^{18}F-Fluoride PET/CT (3 patients), ^{68}Ga-PSMA PET/CT (7 patients) and ^{18}F-PSMA PET/CT (1 patient). All patients had bone metastases, 5 patients had lymph node metastases and 5 patients had visceral metastases (3 lungs, 2 liver, and 1 brain) (**Figures 1**-**3**).

Tolerability of Ra-223

Among all patients submitted to Ra-223, 50% (n=14) did not progress during treatment while 25% (n=7) presented at least one bone event. Among the subset of patients that presented bone events, 57% (n=4) were unable to complete 5 or 6 cycles of Ra-223.

However, 64.3% of the patients completed all 6 Ra-223 cycles, and among these, 53.6% developed some one or more forms of progression: visceral (n=6), bone (n=3), nodal progression (n=2), and/or deterioration of performance *status* (n=4).

Table 2. Patient clinical characteristics and outcomes

Variables	Types	Frequency	Percentage
ECOG status (WHO criteria)	0	8	28.6
	1	12	42.9
	2	2	7.1
	3	4	14.3
	4	2	7.1
Baseline Pain Scores (WHO criteria)	0	9	32.1
	1	11	39.3
	2	3	10.7
	3	5	17.9
Baseline Hematologic Profile (WHO criteria)	Hb >10 g/dL and ANC >1500/mm^3 and PLT >50000/mm^3	27	96.4
	Hb <10 g/dL or ANC <1500 mm^3 or PTL <50000/mm^3	1	3.6
Number of Ra-223 cycles	1	2	7.1
	2	6	21.4
	3	1	3.6
	4	0	0
	5	1	3.6
	6	18	64.3
Ra-223 exclusive or with concomitant therapies*	Ra-223 + concomitant therapies	23	82.1
	Ra-223 exclusive	5	17.9
Progression-related events	No	13	46.4
	Yes	15	53.6
Bone event	No	21	75
	Yes	7	25
Deaths	No	15	53.6
	Yes	13	46.4

ECOG = European Eastern Oncology Group; WHO = World Health Organization; Hb = hemoglobin; ANC = absolute neutrophyl counts; PLT = platelet counts. *Concomitant therapies: radiotherapy, any chemotherapy and/or hormonal agents.

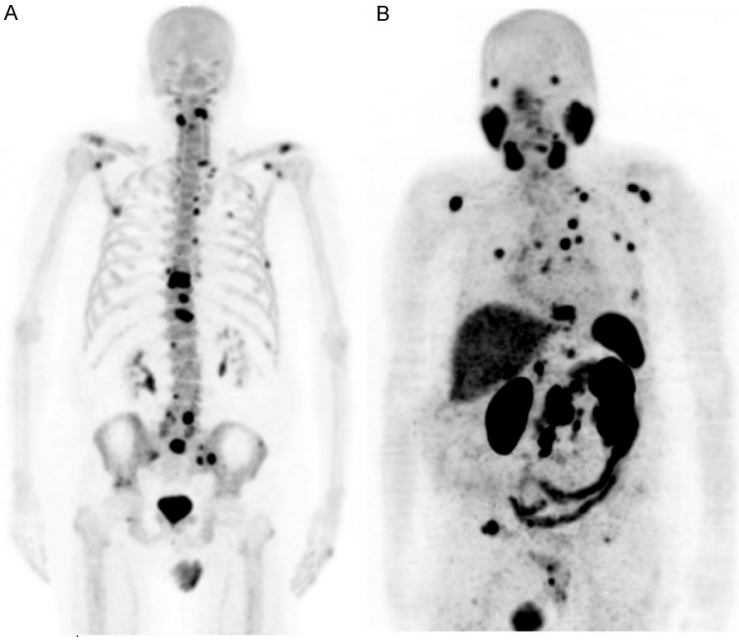

Figure 1. A. Baseline ^{18}F-Fluoride PET/CT scan demonstrates bone metastases in the spine, scapulae, sternum, ribs bilaterally, and pelvic bones. During treatment, the patient developed signs of progression. B. A ^{68}Ga-PSMA PET/CT scan demonstrated overexpression of PSMA receptors in similar sites as the ^{18}F-Fluoride PET/CT and the left supraclavicular, mediastinal, and hepatic hilar lymph nodes. Because of soft tissue lesions, the patient was treated with Ra-223 concomitant with secondary hormonal therapy and responded well to treatment.

Ten patients (35.7%) were unable to complete 5 or 6 cycles of Ra-223. The reasons for not completing cycles were: 1. Progression (n=3 patients) characterized by marked elevation of PSA, LDH, and ALP levels, increase ECOG score by 2 points and ^{68}Ga-PSMA PET/CT showing visceral metastases after the 2nd to 4th cycle (1 liver; 1 brain; and 1 bone). 2. Thrombocytopenia (n=1); 3. Vertebral body fracture and medullary compression (n=1); 4. Death after the 3rd cycle (n=2); 5. Patient request (n=3): intractable pain flare after 1st cycle (n=2); financial difficulties after the 2nd cycle (n=1).

Laboratory characteristics during Radium-223 cycles

The median baseline PSA value prior to Ra-223 was 42.9 ng/mL (mean =83.8 ng/mL ± 121.02 ng/mL) (**Figure 4**). The

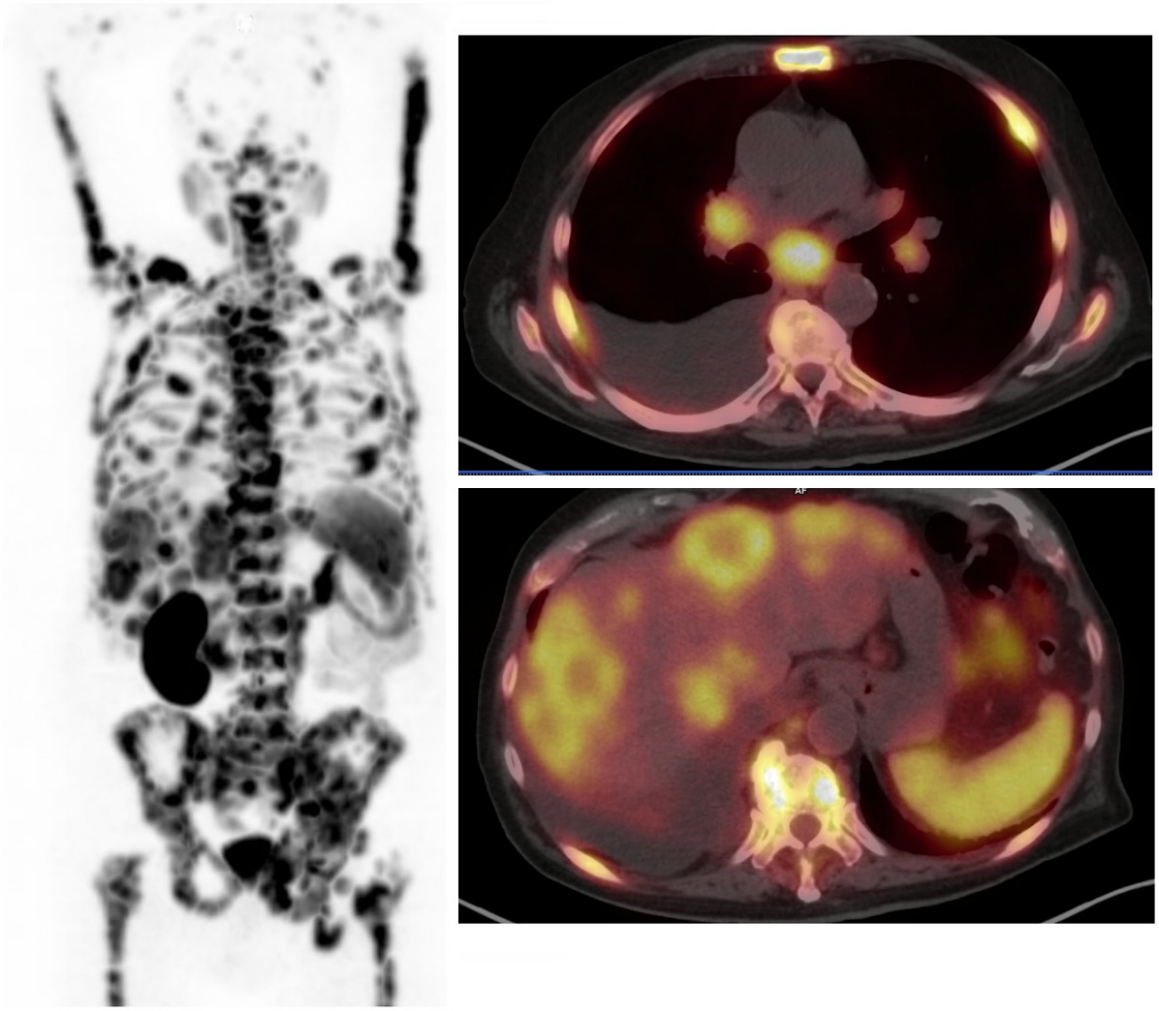

Figure 2. An example of the importance of pre-staging with radiolabeled PSMA PET/CT before radium-223. The patient was referred for Ra-223 as a 3rd line option with bone metastases and no known visceral or lymph node metastases on conventional bone scan and abdominopelvic CT imaging. After two cycles of Radium-223, the patient progressed. The interim ^{68}Ga-PSMA PET/CT scan performed after the 2nd cycle demonstrated disseminated bone metastases and also liver and lymph node metastases.

PSA levels tended to increase during Ra-223 until the 5th cycle and drastically dropped at the 6th cycle (median PSA levels: 1st cycle =42.9 ng/mL; 5th cycle =93 ng/mL; and 6th cycle =12.1 ng/mL). The median baseline ALP levels before Ra-223 was 92I U/L; these levels decreased during Ra-223 therapy (**Figure 5**). The LDH values also presented a decrease throughout the Ra-223 cycles albeit mainly noted in the sixth cycle (**Figure 6**; **Table 3**).

Radium-223 cycles and overall survival

The median follow-up time was 11.9 months. The median OS was 15.6 months and 53.6% (n=15) of the patients died. There was a significant difference in OS according to the number of cycles. Patients submitted to ≤4 cycles had a significantly lower median OS compared to patients submitted to ≥5 cycles (9.1 months versus 18.5 months; P=0.0217) (**Figure 7**).

Clinical and laboratory parameters and outcome measures

OS had a strong and significant correlation with the serum baseline Hb (P=0.0002), PSA (P=0.0002) and LDH (P=0.0092) levels but not with baseline serum ALP levels (P=0.0832), ANC (P=0.8538) and platelets counts (P= 0.2893).

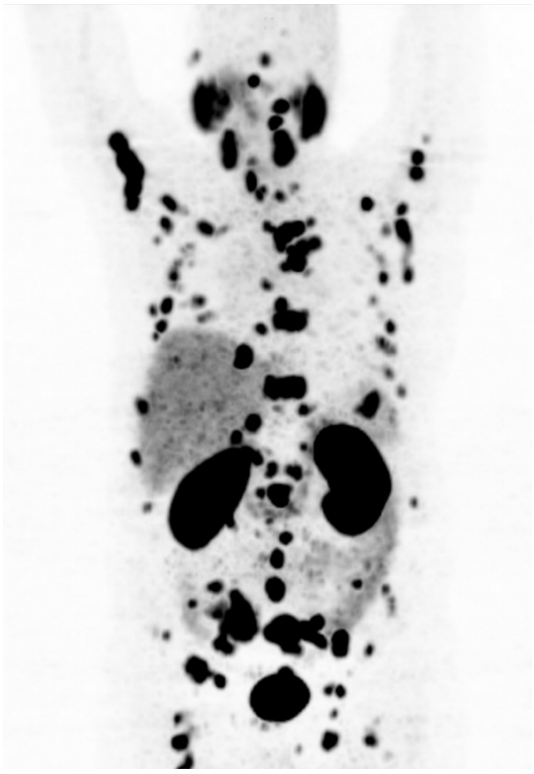

Figure 3. Baseline ^{68}Ga-PSMA PET/CT scan with multiple bone metastases and lymph node metastases (cervical and abdominal). The patient underwent Ra-223 concomitant with chemotherapy and secondary hormonal therapy. He completed all 6 cycles without signs of progression.

The patients that ultimately died had significantly lower median baseline Hb values compared to those that survived (11.1 g/dL vs. 12.6 g/dL, respectively), as well as higher baseline PSA levels (86 ng/mL vs. 11.8 ng/mL, respectively) and higher baseline LDH levels (375 UI/L vs. 272.5 UI/L, respectively). However, no significant correlation was noted with baseline ECOG status (P=0.0957), pain scores (P=0.667) nor total number of Ra-223 cycles (P=0.4328) (**Table 4**).

There was no significant correlation between PFS and the baseline serum Hb (P=0.0805), ANC (P=0.3012), PLT (P=0.4763), PSA (P=0.3664), ALP (P=0.7341) and LDH (P=0.1688). Furthermore, PFS did not have a significant correlation with patients exclusively treated with Ra-223 (P=0.3259), the number of Ra-223 cycles (P=0.43), baseline pain scores (P=0.4921) and ECOG scores (P=0.6776) (**Table 4**).

Interestingly, there was a significant inverse correlation between the number of Ra-223 cycles and the frequency of bone events. The frequency of bone events was lower among patients that completed all 6 Ra-223 cycles compared to patients that completed less than 6 cycles (23.8% versus 71.4%).

Similar to PFS, no significant correlation was noted between bone events and the baseline serum parameters Hb (P=0.0526), ANC (P=1.0), PLT (P=1.0), PSA (P=0.3958), ALP (P=0.0853) and LDH (P=0.2863). In the same manner, bone events did not have any significant correlation with patients exclusively treated with Ra-223 (P=1.0), baseline pain scores (P=0.6182) and ECOG scores (P=0.1423) (**Table 3**).

Treatments performed during Ra-223 cycles

Bone protecting agents were used concomitant to Ra-223 in 23 patients (82%). Other concomitant treatments were undertaken in 17 patients (60.7%) and were: radiotherapy (n=2), abiraterone (n=6), enzalutamide (n=12), chemotherapy with docetaxel (n=2) and leuprorreline (n=6) (**Table 5**).

Among the 12 patients treated with enzalutamide concomitant to Ra-223, 7 patients (58.3%) progressed. Three of these patients progressed to the bone and also to another site: lung (n=1), lymph nodes (n=2), and liver (n=1).

Six patients were treated with abiraterone plus Ra-223 and 3 progressed to the following sites: lymph node (n=1), bone and rectum (n=1), and brain (n=1). Bone progression was characterized as spinal cord compression after the 2nd Ra-223 cycle despite the use of bone-protective agents. All patients underwent therapy with abiraterone concomitant with Radium-223 before the ERA-223 trial [15] publication.

Two patients underwent radiotherapy during Ra-223. In one patient, radiotherapy was performed after the 1st Ra-223 cycle due to spinal cord compression, but he continued and completed all 6 Ra-223 cycles while using docetaxel and subsequently, enzalutamide concomitantly. The second patient was submitted to stereotactic radiotherapy due to a liver metastasis from the 3rd to the 6th Ra-223 cycle; additionally, enzalutamide was used concomitant to Ra-223 throughout all 6 cycles in this patient.

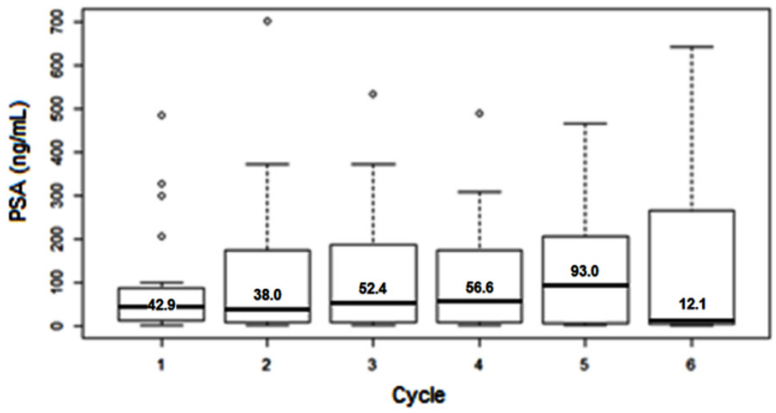

Figure 4. Blox plot graph of PSA levels per cycle.

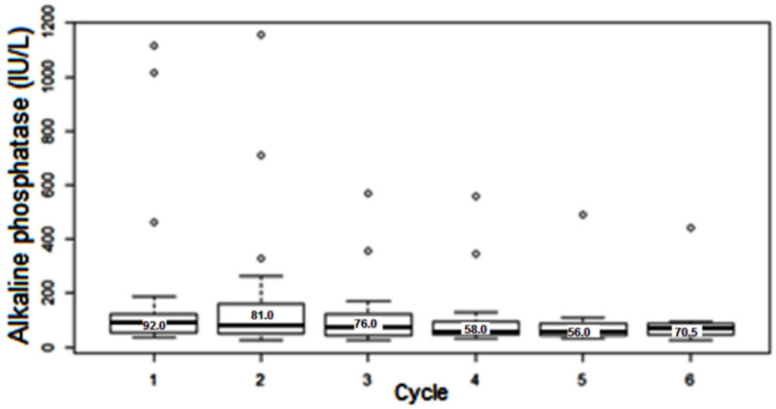

Figure 5. Blox plot graph of ALP levels per cycle.

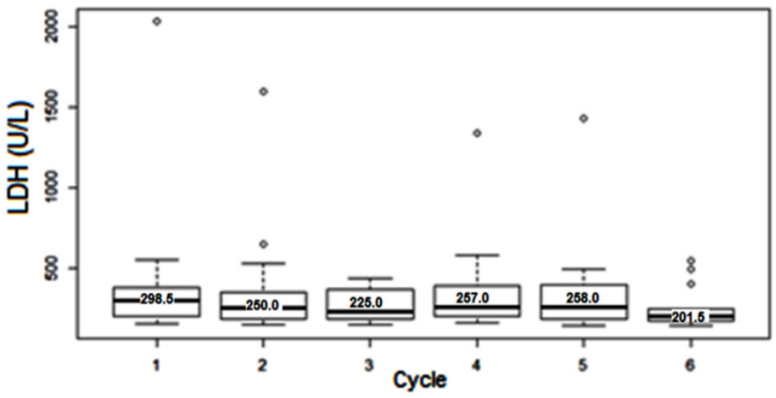

Figure 6. Blox plot graph of LDH levels per cycle.

Discussion

This retrospective analysis of a single-center real-world setting in a developing country has shown that performing Ra-223 with bone-protective agents and concomitant therapies, it was possible to achieve a median overall survival above 15 months, especially in patients submitted to ≥5 cycles, in which the median OS was 18.5 months. This high median OS (18.5 months) could be due to adequate referral within the proper window of opportunity for Ra-223; use of concomitant therapies; blood transfusion prior to Ra-223; good performance status of patients and not a widespread disease. Significant hematologic toxicity requiring interruption of Ra-223 treatment was observed in only one patient, after the first cycle. Furthermore, completing 6 cycles of Ra-223 was associated with a lower frequency of bone-related events.

The prolonged survival benefit was possible and easily achieved because of the close connection with the patient's referring physician, allowing for the necessary adjustments and additions in the treatment strategy. Although the current study was undertaken with a limited number of patients and does not permit further statistical evaluation with the ALSYMPCA trial results, the median OS in our study was not unlike ALSYMPCA results (15.6 months vs. 14.9 months, respectively) [5]. Similar to other studies the median OS was significantly higher in patients submitted to ≥5 Ra-223 cycles ≤4 cycles (18.5 vs. 9.1 months, respectively). Doelen *et al*. [9] retrospectively studied 45 patients and observed an overall median OS of 13 months; however, the median OS was higher in patients completing 6 cycles compared to ≤5 cycles (19.7 versus 5.9 months). Likewise, in a prospective study composed of 40 adequately

Table 3. Descriptive measures of quantitative variables (per cycle)

	N° of patients	Mean	Standard deviation	Minimum	Median	Maximum
Age	28	73.75	9.45	47	74	89
Baseline Hb (g/dl)	28	12.04	1.33	10	12	15.6
Baseline WBC (/mm^3)	28	5701.04	1969.29	2500	5205	10300
Baseline ANC (/mm^3)	28	3545.17	1482.19	1608	3260	8446
Baseline PLT (/mm^3)	28	244357	120303	63000	221500	602000
Baseline PSA (ng/mL)	25	83.8	121.02	0.65	42.9	485.1
Baseline ALP (IU/L)	27	171.49	270.85	38	92	1116
Delta ALP	26	-19.85	161.72	-574	-8.5	486
Baseline LDH (IU/L)	24	367.75	368.71	152	298.5	2031
Delta LDH	26	5	229.75	-436	-10	877
Follow-up (months)	28	13.19	8.51	1.67	11.87	29.07

Hb: hemoglobin; WBC: white blood cells; ANC: absolute neutrophil counts; PLT: platelets; PSA: prostate-specific antigen; ALP: alkaline phosphatase; LDH: lactate dehydrogenase.

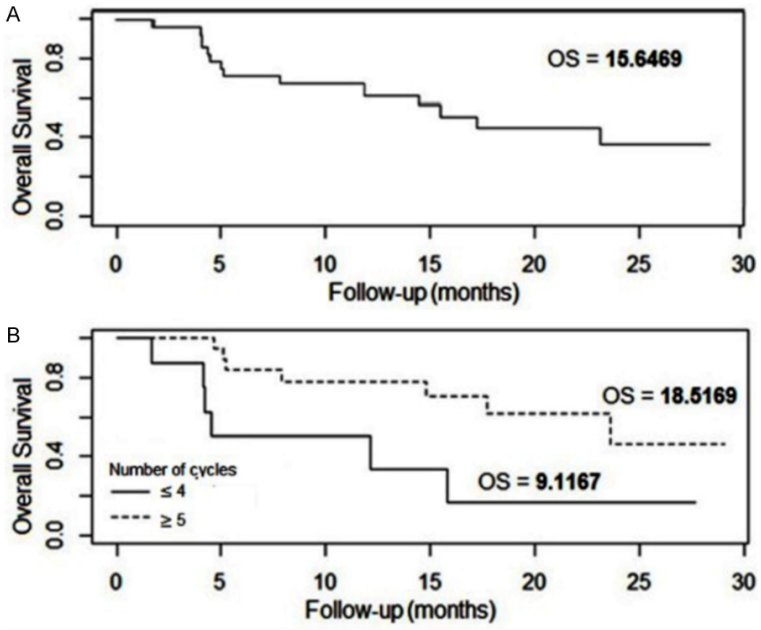

Figure 7. Kaplan-Meier estimates of the (A) global median OS and the (B) median OS according to the number of Ra-223 cycles.

selected patients, Vidal *et al*. [10] demonstrated that to gain a survival benefit, completing all Ra-223 cycles was required (median OS =17.1 months) compared to the patients that received incomplete treatment (median OS =13.6 months); and also, a greater OS was noted in patients submitted to Ra-223 as a first-line treatment strategy.

Similar to other studies [10, 11], a significant relationship was noted between the low baseline hemoglobin levels and poor outcome, which most likely represented extensive bone marrow metastatic infiltration.

Also as noted in the literature [11, 12], we did not use serum PSA levels to tailor treatment except when there was a marked PSA increase associated with a reduction of the patient's performance status. Unlike the ALSYMPCA trial [5] that observed a reduction in serum PSA levels after the 3rd cycle, we mostly found a considerable increase in PSA levels after the 2nd cycle; PSA maintained elevated throughout all cycles and decreased mainly after the 5th cycle.

Although our study did not demonstrate a significant correlation between baseline ALP levels and OS or PFS, numerous studies [9-13] have shown that ALP is a useful marker to monitor Ra-223 therapy. Our data is consistent with the retrospective study by Prelaj *et al*. [14] that showed that among the 32 patients treated with Ra-223, although ALP response was not significantly associated with survival benefit, ALP played a role in treatment management. Similarly, the ALSYMPCA trial [5] found a higher proportion of Ra-223 patients with an ALP response than the placebo group.

The strength of this investigation was the aggressive use of concomitant therapies and the survival gain [13, 16]. Although the ERA-223 trial [15] found that the addition of abiraterone and prednisone and radium-223 ther-

Table 4. Relationship between progression, bone events, death, and the variables

Variable	Types	Progression			Bone event			Death		
		No (N=14)	Yes (N=14)	*P*-value	No (N=21)	Yes (N=7)	*P*-value	No (N=15)	Yes (N=13)	*P*-value
Ra-223	Exclusive	13 (92.9%)	10 (71.4%)	0.3259	4 (19.0%)	1 (14.3%)	1.0000	2 (13.3%)	3 (23.1%)	0.6389
	Non-exclusive	1 (7.1%)	4 (28.6%)		17 (81.0%)	6 (85.7%)		13 (86.7%)	10 (76.9%)	
Number of cycles	<6	4 (28.6%)	6 (42.9%)	0.4302	5 (23.8%)	5 (71.4%)	0.0228	4 (26.7%)	6 (46.2%)	0.4328
	6 cycles	10 (71.4%)	8 (57.1%)		16 (76.2%)	2 (28.6%)		11 (73.3%)	7 (53.8%)	
Baseline pain (WHO score)	0	4 (28.6%)	5 (35.7%)	0.4921	8 (38.1%)	1 (14.3%)	0.6182	6 (40.0%)	3 (23.1%)	0.0667
	1	7 (50.0%)	4 (28.6%)		8 (38.1%)	3 (42.9%)		7 (46.7%)	4 (30.8%)	
	2	2 (14.3%)	1 (7.1%)		2 (9.5%)	1 (14.3%)		2 (13.3%)	1 (7.7%)	
	3	1 (7.1%)	4 (28.6%)		3 (14.3%)	2 (28.6%)		0 (0.0%)	5 (38.5%)	
Baseline ECOG score	0/1	11 (78.6%)	9 (64.3%)	0.6776	17 (81.0%)	3 (42.9%)	0.1423	13 (86.7%)	7 (53.8%)	0.0957
	2/3/4	3 (21.4%)	5 (35.7%)		4 (19.0%)	4 (57.1%)		2 (13.3%)	6 (46.2%)	
Baseline Hb g/dL	Mean (± SD)	12.4 (±1.0)	11.7 (±1.5)	0.0805	12.3 (±1.3)	11.2 (±1.0)	0.0526	12.9 (±1.1)	11.1 (±0.9)	0.0002
	Median	12.6	11.7		12.3	11.6		12.6	11.1	
Baseline WBC (/mm^3)	Mean (± SD)	6185.7 (±2356.1)	5216.4 (±1413.2)	0.4906	5730.5 (±20812)	5612.7 (±1732.4)	0.6712	6076.0 (±2320.4)	5268.4 (±1437.1)	0.5962
	Median	5405.0	5205.0		5100.0	5800.0		5130.0	5280.0	
Baseline ANC (/mm^3)	Mean (± SD)	3843.2 (±1658.0)	3247.1 (±1273.8)	0.3012	3535.9 (±1449.3)	3573.0 (±1698.0)	1.0000	3602.6 (±1678.0)	3478.9 (±1284.2)	0.8538
	Median	3570.0	3030.5		3120.0	3735.0		3120.0	3425.0	
Baseline PLT (/mm^3)	Mean (± SD)	263428.6 (±133091.5)	225285.7 (±107528.5)	0.4763	245761.9 (±116908.5)	240142.9 (±139792.0)	1.0000	230933.3 (±122926.5)	259846.2 (±120206.0)	0.2893
	Median	224500.0	221500.0		205000.0	244000.0		205000.0	272000.0	
Baseline PSA (ng/mL)	Mean (± SD)	54.7 (±85.8)	120.9 (±151.3)	0.3664	79.2 (±125.1)	102.2 (±114.0)	0.3958	20.4 (±27.6)	164.4 (±146.2)	0.0002
	Median	20.6	60.0		30.0	75.7		11.8	86.0	
Baseline ALP	Mean (± SD)	112.2 (±107.8)	235.3 (±371.3)	0.7341	140.4 (±220.0)	280.2 (±412.0)	0.0853	99.2 (±105.0)	261.8 (±378.6)	0.0832
	Median	93.0	73.0		71.0	123.0		69.0	114.5	
Baseline LDH (UI/L)	Mean (± SD)	271.7 (±92.5)	502.2 (±548.3)	0.1688	290.9 (±112.3)	659.6 (±768.4)	0.2863	253.3 (±83.3)	528.0 (±537.1)	0.0092
	Median	273.5	359.5		296.0	363.0		272.5	375.0	
Delta ALP	Mean (± SD)	-21.0 (±36.1)	-18.7 (±230.6)	0.5383	-46.5 (±131.8)	52.4 (±220.2)	0.0829	20.4 (±138.1)	-66.8 (±180.0)	0.9385
	Median	-8.0	-9.0		-11.0	37.0		-10.0	-4.5	
Delta LDH (UI/L)	Mean (± SD)	-36.5 (±101.8)	46.5 (±309.7)	0.5050	26.7 (±229.8)	-53.9 (±236.5)	0.6857	12.3 (±99.3)	-3.5 (±328.9)	0.2472
	Median	-11.0	65.0		-9.0	-36.0		7.0	-43.5	

Hb: hemoglobin; WBC: white blood cells; ANC: absolute neutrophil counts; PLT: platelets; PSA: prostate-specific antigen; ALP: alkaline phosphatase; LDH: lactate dehydrogenase.

Table 5. Descriptive measures of concomitant therapies according to cycles

Patient	RT	ABI	ENZA	Docetaxel	LEUPRO	B	N	V	Observations
#1	2nd-5th	---	6th	1st-5th	---	X	---	X	RT due to spinal cord compression; lung metastasis
#2	3rd-6th	---	1st-6th	---	---	---	---	X	Stereotaxic RT to liver metastasis
#3	---	1st	2nd-6th	---	---	---	X	---	Nodal progression after 6th cycle
#4	---	1st-6th	---	---	1st-6th	---	---	---	---
#5	---	1st-3rd	4th-5th	---	---	---	---	X	Interrupted at 5th cycle (cerebral metastasis)
#6	---	1st-6th	---	---	1st-6th	---	---	---	---
#7	---	1st-2nd	---	---	---	X	---	---	Interrupted at 2nd cycle (spinal cord compression)
#8	---	1st-6th	---	---	---	---	---	---	---
#9	---	---	1st-6th	---	1st	---	---	---	---
#10	---	---	1st	---	---	---	---	---	Interrupted at 1st cycle (irreversible thrombocytopenia)
#11	---	---	1st-6th	---	---	---	---	---	---
#12	---	---	5th-6th	1st- 6th	---	---	X	---	Nodal progression after 6th cycle
#13	---	---	2nd	---	---	X	X	X	Interrupted at 2nd cycle (bone, liver & nodal progression)
#14	---	---	1st-6th	---	1st	---	---	---	---
#15	---	---	1st-6th	---	1st-6th	---	---	---	---
#16	---	---	1st-3rd	---	---	X	X	---	Interrupted at 3rd cycle (bone & nodal progression)
#17	---	---	---	---	1st-6th	---	---	---	---

RT= radiotherapy; ABI= abriaterone; ENZ= enzalutamide; LEUPRO= leuprorreline; B= bone; N= nodal; V= visceral.

apy increased the frequency of bone fractures, we showed that patients responded well with the use of bone protective agents with abiraterone and prednisone and Ra-223. Shore et al. [17] retrospectively demonstrated in 625 patients that the combination of abiraterone + prednisone (or enzalutamide) with Ra-223 presented a median OS of 28.1 months and lower pathologic fracture reports.

The limitations of our study were the small number of patients and the heterogeneous cohort, as patients have visceral, nodal, liver, and bone metastases, making all of the comparisons difficult. Radium-223 is a high-cost treatment, not available throughout the country's healthcare system and only men with health insurance coverage (the wealthier population) have this treatment available.

This preliminary investigation in a real-world setting has demonstrated that even in patients referred for Ra-223 as the third-line treatment, the proper use of bone-protective agents and concomitant therapies with Ra-223 may improve overall survival, especially in patients submitted to ≥5 cycles. Large prospective real-world multicenter population studies involving patients using Ra-223 and concomitant therapies are necessary to confirm our findings.

Disclosure of conflict of interest

None.

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