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Clinical-prostate cancer

Radium-223 in patients with prostate specific antigen (PSA) progression and without clinical metastases following maximal local therapy: A pilot study

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Abstract

Background: Despite the curative intent of radical prostatectomy (RP) (+/- radiotherapy (RT)), 30% of the clinically localized prostate cancer (CaP) patients will develop rising PSA (prostate specific antigen). In absence of clinical recurrence, there is a lack of effective treatment strategies in order to control the disease at its earliest (micro)metastatic stage. The aim of this study was to assess safety, tolerability, and biochemical response of off-label Radium-223 (Xofigo) treatment in CaP patients with PSA relapse following maximal local therapy.

Methods: We conducted a prospective, single arm, single center open-label, pilot study with Radium-223 in CaP patients with rising PSA (>0.2 ng/ml) following RP + adjuvant/salvage RT. Negative staging with ^{68}Ga-PSMA-11 PET/CT and whole-body MRI was mandatory at time of inclusion. Patients were eligible if they exhibited adverse clinico-pathological features predictive of significant recurrence. Safety, tolerability, biochemical progression (defined as PSA increase >50% from PSA nadir) and clinical recurrence were assessed.

Results: In total, 23 patients were screened of whom 8 patients were included is the study. Radium-223 treatment was safe with no serious treatment related adverse events. One patient developed grade 3 lymphopenia. All patients rapidly developed PSA progression (median PSA progression-free survival: 5.5 months). Eventually all patients experienced clinical recurrence (median clinical recurrence-free survival 11.0 months) of whom only 2 patients developed skeletal recurrence.

Conclusions: Radium-223 in patients with PSA relapse following maximal local treatment without clinical metastases is safe. However, the clinical benefit of Ra-223 in this setting is doubtful as significant oncological benefit is lacking.

Keywords: Prostate cancer; Radium-223; Micro-metastases; PSMA PET/CT; Biochemical recurrence

1. Introduction

Despite primary local treatment with curative intent, 27% to 53% of clinically localized prostate cancer (CaP) patients will develop rising prostate-specific antigen (PSA), also known as biochemical recurrence (BCR). Although PSA represents a specific marker of tumor growth even when metastases are not yet detectable on imaging, BCR following local therapy does not necessarily indicate that a patient will develop clinically relevant metastases and will die of the disease. Patients with BCR following radical prostatectomy (RP) (+/- adjuvant/salvage radiotherapy (RT) and/or androgen deprivation therapy (ADT)) had an

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estimated 15-year cancer-specific survival of 83.6% [1]. However, some patients with poor tumor differentiation and rapidly rising PSA have an increased risk of developing metastases and cancer-related death. Pathological Gleason score 8 to 10 and PSA doubling time <10 months were demonstrated to be associated with the onset of metastatic disease [2]. A recent systematic review by the European Association of Urology (EAU) guidelines supported these risk factors demonstrating that short PSA doubling time (<12months) and high pathological Gleason score (≥8) are the strongest prognostic factors of distant metastases, cancer-related death and overall mortality [3]. Besides high pathological Gleason score and short PSA doubling time, high pathological T stage (pT3-4) and pN1 disease were also associated with cancer-specific mortality [4]. Even following maximal local therapy (RP + adjuvant/salvage RT), 50% of the patients with the aforementioned adverse prognostic factors will develop BCR within 5 years of follow-up [5,6]. This might be explained by the presence of micrometastases at time of diagnosis. It has been demonstrated by several studies that micrometastatic bone (marrow) disease is often already present at time of RP, especially in patients with high pathological Gleason score [7−10]. These patients had a sevenfold increased risk of (biochemical) recurrence compared to their counterparts at the time of RP without cancer cells in the bone marrow [11].

With the introduction of molecular-based imaging such as prostate specific membrane antigen (PSMA) PET/CT, we are now able to detect recurrences at lower PSA levels. The EAU guidelines recommend to perform a PSMA PET/CT in post-prostatectomy patients when PSA rises above 0.2 ng/ml provided that this would change the therapeutic management of the patient [12]. However, approximately 50% of the PSMA PET/CT scans will not show any lesions when the PSA is between 0.2 and1 ng/ml [13].

The high proportion of CaP patients with adverse pathological characteristics who experience PSA relapse without visible lesions on imaging, represent a contemporary challenge. Developing effective treatment strategies in order to control the disease at its earliest metastatic stage (microscopic metastatic disease) is an unexplored field. The possibility to efficiently treat the disease at this stage may be curative or at least delay further progression. Hormonal therapy is often prescribed to patients with rapidly rising PSA after maximal local treatment, but it has important negative implications on the patient's quality of life without having a curative effect [14]. The possibility of an efficient therapy with minimal side effects, avoiding the deleterious effects of ADT is an unmet need.

Radium-223 dichloride (Ra-223; Xofigo) is an alpha-emitter which has similar molecular characteristics as calcium and binds to hydroxyapatite in newly formed bone [15]. Following intravenous injection, it selectively accumulates into areas of increased bone remodeling such as osteoblastic bone metastases, emitting high-energy, short-range (<100 μm) alpha particles. These alpha particles induce double-stranded DNA breaks in CaP cells and the tissue microenvironment (osteoblasts, osteoclasts,...) resulting in a localized cytotoxic effect [16]. Ra-223 was the first bone-targeted therapy to improve overall survival in metastatic castration resistant CaP (mCRPC) patients and is associated with low toxicity [17]

Assuming that rapidly rising PSA following maximal local therapy with negative imaging is caused by micrometastasic disease confined to the bone, Ra-223 provides interesting therapeutic opportunities. Theoretically, Ra-223 might delay the time to clinical progression or even lead to cure in these patients. In this pilot study, we aimed to assess feasibility, safety, and biochemical response of off-label Ra-223 therapy in CaP patients with rapidly rising PSA and adverse pathological factors following maximal local treatment and without metastases on advanced imaging.

2. Materials and methods

2.1. Patient population

We conducted a prospective, single arm, single center (University Hospitals Leuven) open-label, pilot study with Ra-223 in CaP patients with rising PSA (>0.2 ng/ml) following maximal local treatment (supplementary fig. 1). Table 1 provides an overview of the in- and exclusion criteria. To decrease the chance of developing local or lymph node recurrence, eligible patients had to have received RP + pelvic lymphadenectomy (PLND) and adjuvant/salvage RT. Patients with rising PSA were also eligible for inclusion in case of prior salvage lymph node dissection (sLND) for pelvic lymph node recurrence following maximal local therapy (RP + adjuvant/salvage RT). Moreover, patients had to comply with at least one negative prognostic factor for developing significant recurrence (table 1). Negative staging with ^{68}Ga-PSMA-11 PET/CT and diffusion weighted whole-body MRI (wbMRI) was mandatory at time of inclusion. The study was approved by the Belgian federal agency for medicines and health products (FAMHP), registered as EudraCt 2014-002833-70 and approved by the local ethical committee (S56892).

2.2. Treatment

Ra-223 was administered at a dose of 50 to 55 kBq/kg as IV injection every 4 weeks for 6 cycles.

2.3. Objectives

2.3.1. Safety and tolerability

Safety data (Adverse Events (AE) and Serious AE (SAE)) were collected in order to confirm tolerability for the present study population (Common Terminology Criteria for Adverse Events version (CTCAE) 4.03).

Table 1
Inclusion and exclusion criteria

Inclusion criteria		Exclusion criteria
Male ≥18 y with histological confirmation of prostatic adenocarcinoma		Radiotherapy to >25% of bone marrow
Informed consent		Bone systemic therapy
Biochemical progression		Malignancies treated within the last 3 y
- PSA >0.2 ng/ml following RP, PLND, and adjuvant or salvage EBRT (group A)		
- PSA >0.2 ng/ml following to salvage LND in patients treated formerly by RP and adjuvant or salvage EBRT (group B)		
No metastases on ^{68}Ga-PSMA-11 PET/CT and whole body MRI		CaP metastases (visceral, bone or nodular)
Adequate liver, hematological, and renal function:		Contraindications to ^{68}GA PSMA PET/CT and whole body MRI
Variable	*n*	Serious illnesses or medical conditions (e.g. any major infection, cardiac failure NYHA III or IV, ulcerative colitis, Crohn's disease, Bone marrow dysplasia, fecal incontinence and others)
Absolute neutrophil count	≥ 1.5 × 10^9/l	
Platelet count	≥ 100 × 10^9/L	
Hemoglobin	≥ 10.0 g/dl (100g/l; 6,2 mmol/l)	
Total Bilirubin level[1]	≤ 1.5 x ULN[1]	Life expectancy < 6 mo
Aspartate Aminotransferase	≤ 2.5 x ULN	ECOG performance status ≥2
Alanine Aminotransferase	≤ 2.5 x ULN	
Creatinine	≤ 1.5 x ULN	Ongoing Androgen deprivation therapy within a period of 6 mo before screening
Albumin	>25 g/l	Testosterone level <20 ng/dl
At least 1 negative prognostic factor for clinical progression in case of:		
Salvage EBRT following RP		- PSADT <12 mo (postoperative PSA) AND/OR - ≥pT3 AND/OR - pGS ≥8
Adjuvant EBRT following RP		- ≥pT3 and pGS ≥ 8 AND/OR - PSADT <12 mo (PSA post adjuvant EBRT)
pN1 at time of RP		- pGS ≥8 AND/OR - ≥pT3 AND/OR - ≥3 positive nodes AND/OR - Positive surgical margins
sLND		- Retroperitoneal lymph node positivity at sLND AND/OR - PSA ≥0.2 ng/ml relapse within 40 dafter SLND

CaP = prostate cancer; ECOG= Eastern Cooperative Oncology Group; EBRT = External Beam Radiation Therapy; NYHA = New York Heart Association; pGS = pathological Gleason score; PLND = Pelvic lymph node dissection; pN = pathological N-stage; PSA = prostate specific antigen; PSADT = PSA doubling time; PSMA = prostate specific membrane antigen; pT = pathological T stage; sLND = salvage lymph node dissection; ULN = upper limit of normal.
[1] or Gilbert Syndrome without any other liver dysfunction.

2.3.2. Assessment of PSA and bone alkaline phosphatase (bALP) response

PSA was used as a primary indicator of disease progression. PSA progression was defined as every confirmed PSA relapse (3 confirmatory PSA measurements at least 1 week apart) with an increase >50% from PSA nadir. Time to PSA progression was defined as the median time to PSA progression from the moment of the first Ra-223 injection. PSA doubling time during Ra-223 was compared to PSA doubling time following last Ra-223 injection. bALP progression was defined as 2 bALP increases from the nadir level, at least 1 week apart. Time to bALP progression was defined as the median time to bALP progression from the moment of the first drug administration.

2.3.3. Assessment of clinical recurrence

Imaging (^{68}Ga-PSMA-11 PET/CT + whole body MRI) was performed at the beginning of the study and repeated at time of PSA progression. If no PSA progression was detected during follow-up, imaging (^{68}Ga-PSMA-11 PET/CT +/- whole body MRI) was performed at the end of the study (24 months since first Ra-223 injection). Imaging was not allowed prior to the last Ra-223 injection even in case of PSA increase. All scans (^{68}Ga-PSMA-11 PET/CT and wbMRI) were performed at the University Hospitals Leuven.

2.4. Statistical analysis

A sample size calculation is generally not required for pilot studies which, per definition, have an explorative aim (feasibility, safety, and tolerability) [18]. The planned sample size was 15. Enrolment period was 24 months. Results regarding safety and feasibility were presented by descriptive statistics. Kaplan-Meier estimates were used to visualize median time to PSA and clinical recurrence. Comparison of PSA doubling during Ra-223 treatment and following last Ra-223 injection was compared using a paired samples *t* test. Statistics were performed using the

statistical software Medcalc, version 18.9 (*MedCalc Software bvba, Ostend, Belgium*;http://www.medcalc.org;2018)

3. Results

3.1. Patient characteristics

In total, 23 patients were screened from April 2016 to December 2017 (supplementary fig. 2). Eventually, 8 patients were included of whom 7 completed all trial visits. All patients provided written informed consent. Patient characteristics at the time of RP are described in table 2. Three patients received a sLND for pelvic lymph node recurrence following maximal local treatment. Table 2 provides the patient and treatment characteristics at the time of Ra-223 treatment. During the trial, 1 patient (patient 8) did not want to have further study visits due to PSA progression. Seven patients completed all 6 cycles of Ra-223. One patient (patient 5) voluntarily decided to only complete 3 cycles of Ra-223 due to rising PSA, but completed all follow-up study visits.

3.2. Safety and tolerability

Safety and tolerability was assessed in patients who received at least one dose of the study drug. An overview of related (S)AE is shown in table 3. Treatment related AEs were observed in 5 patients (mostly low grade). Fatigue and diarrhea (grade 1–2) were reported in 4 patients. One patient developed grade 3 lymphopenia. These AEs did not cause discontinuation of the Ra-223 therapy. No treatment related deaths were reported. Unrelated AEs are provided in supplementary table 1.

3.3. PSA and bALP kinetics

Baseline PSA level varied between 0.3 and 6.3 ng/ml (median PSA 1.3 ng/ml). All patients developed PSA progression during follow-up. Median time to PSA progression was 5.5 months (95% CI. 5.1–7.4 months) (supplementary fig. 3). No difference in PSA doubling time was observed during Ra-223 therapy and following Ra-223 therapy (mean PSA doubling time 9.0 and 9.7 months, respectively; $P = 0.84$). Baseline bALP level (reference value 6.9–20 μg/L) varied from 6.3 to 17.5 μg/L (median bALP value before treatment 11.1 μg/L). Median time to bALP progression was 3.4 months (95% CI. 1.3–14.5 months). Only 1 patient did not develop bALP progression (patient dropped out after visit F5). Fig. 1 and supplementary fig. 4 provide an overview of PSA and bALP measurements for each individual patient, respectively.

3.4. Clinical recurrence

Median follow-up since first Ra-223 injection until last follow-up or death was 46 months (IQR: 40.5–49 months). Three out of 8 patients showed disease progression on imaging during the study period and another 5 patients presented with disease progression on imaging after the study period (after visit F9) (table 3). Two patients developed bone metastases, 4 patients developed recurrence confined to the lymph nodes and 2 patient developed local recurrence. Median time to imaging recurrence was 11.0 months (95% CI: 2.8–47.0) (supplementary fig. 5). One patient died from CaP (patient 5). No severe adverse events related to Ra-223 were observed after the study period. One patient (patient 5) received another 2 cycli of Ra-223 at time of progression following previous therapy with degarelix, docetaxel (10 cycli), enzalutamide, and cabazitaxel (8 cycli).

4. Discussion

In this pilot study, we assessed the safety, and efficacy of administrating Ra-223 in patients with rising PSA following maximal local treatment without detectable lesions on ^{68}Ga-PSMA-11 PET/CT and whole body MRI. This is one of the first studies investigating the safety of Ra-223 in hormone-sensitive CaP patients without hormonal therapy. In these patients, Ra-223 might have a different safety profile compared to previous studies with subjects with higher tumor load in the mCRPC setting. Overall, treatment with Ra-223 was well tolerated with no treatment-related SAEs. One patient voluntarily discontinued treatment because of PSA progression. Fatigue and diarrhea were the most common AEs in our study population. Only 1 patient in our study developed grade 3 lymphopenia; however, due to the small sample size, the ability to exclude high rates of toxicity is low. Our findings are thus consistent with earlier described findings in literature as the common side effects of Ra-223 include anemia, transient myelosuppression, nausea, vomiting, and diarrhea [17,19]. Similar adverse events were also observed in a pilot study in which de novo hormone-sensitive metastatic CaP patients were treated with Ra-223 therapy [20,21].

Despite Ra-223 treatment, all patients in our pilot study experienced PSA progression (median 5.5 months following first Ra-223 injection). This might be explained by several factors. Firstly, at time of protocol design (*2015*), the recurrence pattern of CaP following primary treatment was not well understood. With the introduction of molecular imaging, various papers have been published looking at the recurrence patterns in patients with BCR following maximal local treatment. Nehra et al. (*2017*) mapped the recurrence pattern of 550 post-RP patients using ^{11}C-choline PET/CT and MRI of the prostate at time of BCR [22]. Of the patients who received maximal local therapy (RP + adjuvant/salvage RT; $n = 442$), 71% developed local, lymph node or visceral recurrence. Only 18% of the patients solely developed skeletal recurrence. In another series by our group, 191 post-RP patients with BCR were assessed by ^{68}Ga-PSMA-11 and ^{11}C-choline PET/CT [23]. Of these patients, 142 received maximal local treatment (adjuvant/salvage RT following RP), of whom 77%

Table 2
Baseline patient characteristics at time of maximal local therapy.

Patient	1	2	3	4	5	6	7	8
Age at RP (y)	66	60	56	60	58	57	56	62
Date of RP	Jan 2008	Mar 2012	Sep 2001	Mar 2015	Apr 2010	Jan 2000	Mar 2014	Jun 2014
Initial PSA (ng/ml)	4.4	2.8	3.6	12.7	8.0	73.0	8.0	18.0
Pathological T-stage	pT2	pT3b	pT2	pT2	pT3b	pT4a	pT3a	pT3b
Pathological N-stage	pN0	pN0	pN0	pN0	pN0	pN1	pN0	pN0
Pathological Gleason Score	7 (3 + 4)	7 (3 + 4)	7 (3 + 4)	7 (4 + 3)	9 (4 + 5)	8 (4 + 4)	8 (4 + 4)	7 (4 + 3)
Adjuvant/ salvage RT	Salvage RT	Adjuvant RT	Salvage RT	Adjuvant RT	Adjuvant RT	Salvage RT	Salvage RT	Salvage RT
-Date	27/04/09	19/06/12	30/06/14	22/06/15	25/01/11	4/5/06	19/05/16	30/09/14
-Dose + fractions	70 Gy	66 Gy	66 Gy	70 Gy	66 Gy	70 Gy	Unknown	66 Gy
-Concomitant ADT?	No	No	Yes	No	No	Yes	No	No
sLND	Yes	No	No	Yes	Yes	No	No	No
-Date	19/02/15			24/08/16	11/06/13			
-Location of metastatic LN	Obturator left			External iliac bilateral	Presacral			
-Imaging technique	PSMA PET/CT			CT-scan	Choline PET/CT			
-Number of LN removed	66			11	2			
-Number of + LN removed	10			0	2			
Risk factors for aggressive disease	Retroperitoneal positive nodes at sLND	≥pT3 and detectable PSA	PSADT <12 mo	PSA relapse ≥0.2ng/dl within 40 d after sLND	PSA relapse ≥0.2ng/dl within 40 d after sLND	≥pT3 and pGS ≥8	≥pT3 and pGS ≥8	≥pT3

ADT = androgen deprivation therapy; LN = Lymph nodes; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiotherapy; sLND = salvage lymph node dissection

Table 3
Patient characteristics at time of inclusion and Radium-223 treatment

Patient	1	2	3	4	5	6	7	8
Age at inclusion (y)	74	65	71	62	65	74	59	66
Inclusion date	25/04/16	7/07/16	21/12/16	12/01/17	17/02/17	17/03/17	16/11/17	14/12/17
Completed cycles of Ra-223	6/6	6/6	6/6	6/6	3/6	6/6	6/6	6/6
Early discontinuation (reason)	No	No	No	No	Yes (voluntary withdrawal because of PSA increase)	No	No	No
Study completed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No (progression: Stopped at F5)
Related adverse events (grade)	Diarrhea (1), Right malleolar joint effusion (1), Fatigue (1)	Fatigue (1), Loss of appetite (1), Metal taste (1), Diarrhea (1), Articular muscle pain (1)	No related AE	Lymphopenia (3), itch (1), Fatigue (1)	No related AE	No related AE.	Diarrhea (2), Fatigue (1) Arthralgia (2), Nausea (2)	Diarrhea (1).
PSA at first Ra-cycle (ng/ml)	1.3	0.3	1.8	1.2	1.7	1.3	1.1	6.3
PSA progression	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PSA progression date	6/01/17	26/01/17	27/07/17	22/09/17	24/08/17	26/10/17	30/05/18	26/07/18
bALP at first Ra-cycle (U/l)	15.2	6.3	7.5	9.5	12.6	8.4	17.5	16.0
bALP progression date	9/09/16	13/03/17	18/01/18	23/03/17	2/06/17	18/08/17	8/03/19	No
Clinical recurrence								
-Nodal/bone/ visceral/mixed	- cN1 (2 pelvic LN)	- Local recurrence	- cM1b (1 bone lesion)	- cN1 (1 pelvic LN)	- cM1b (M + bone lesions)	- Local recurrence	-cM1a (M+ retroperitoneal LNs	- cM1a (M+ Retroperitoneal LNs)
-Imaging (date)	- wbMRI + PSMA PET/CT (02/17)	- PSMA PET/CT (07/20)	-PSMA PET /CT (12/18)	-PSMA PET/CT (01/18)	- PSMA PET/CT (06/17)	- PSMA PET/CT (05/19)	-PSMA PET/CT (12/20)	-wbMRI (09/18)
-PSA at imaging (ng/ml)	-PSA: 2.2	-PSA: 1.4	-PSA: 10.6	-PSA: 1.9	-PSA: 4.7	-PSA: 4.1	-PSA: 5.4	-PSA: 21.2
Status last follow-up (date)	mCRPC (02/04/21)	WW for local recurrence (09/11/20)	Repeated MDT for oligorecurrence CaP, start palliative ADT (22/02/21)	Repeated MDT for oligorecurrence CaP (14/01/21)	Death due to CaP (27/08/20)	WW for local recurrence (26/02/21)	MDT for oligorecurrence (17/03/21)	MDT for oligorecurrence (17/03/21)

LN = lymph nodes; MDT = metastasis-directed therapy; M+ = multiple; CaP = prostate cancer; PSMA = prostate specific membrane Antigen; PSA = prostate-s antigen; Ra-223 = radium 223; wbMRI = whole body MRI; WW = watchful waiting

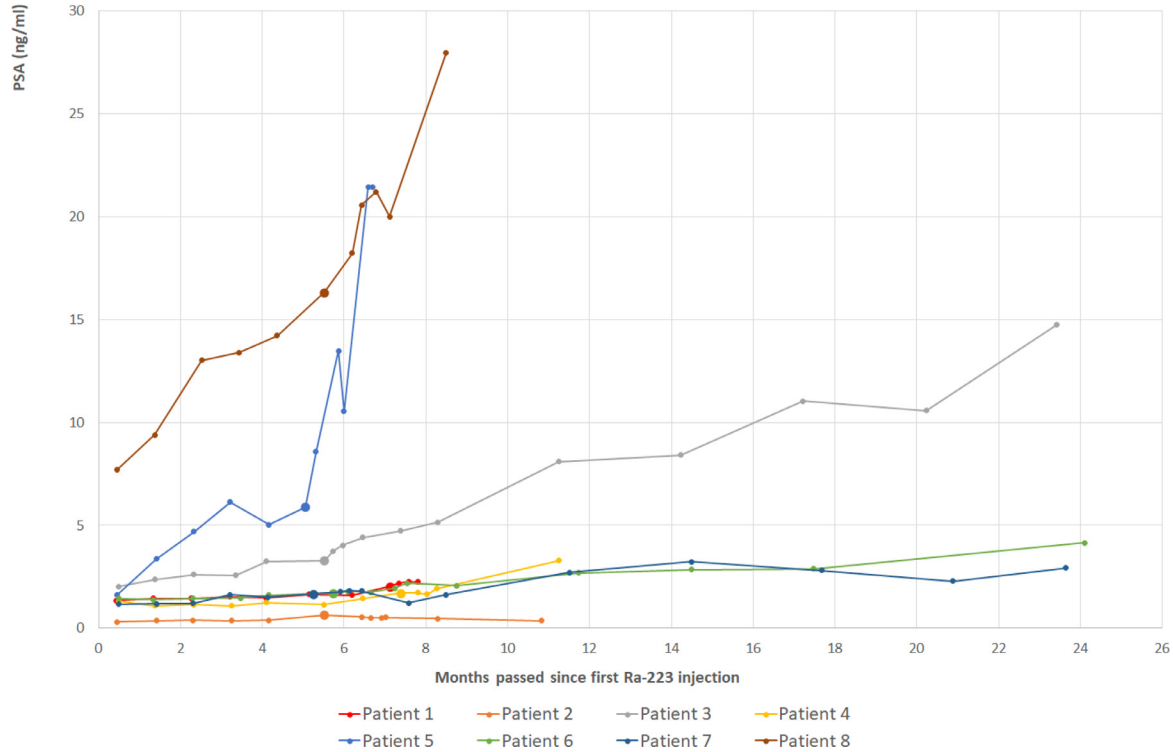

Fig. 1. Overview of PSA kinetics for each patient during the study since the first Ra-223 injection until study end (24 months). Values are provided until the patients received additional treatment or until drop-out. Patient 1 was initiated on ADT because of lymph node recurrence. Patient 2 received a short period (3 months) of ADT. Patient 4 received a sLND for lymph node recurrence. Patient 5 voluntarily stopped Ra-223 treatment because of rising PSA and was initiated on ADT. PSA stabilized for a while and subsequently increased (CRPC). Patient 8 stopped at F5 because of PSA progression and received retroperitoneal RT for retroperitoneal lymph node recurrence. Patient 3, 6, and 7 did not receive any other treatment during follow-up visits. Time of PSA progression is indicated with fat dot for each patient. ADT = androgen deprivation therapy; PSA = prostate specific antigen; CRPC = castration resistant prostate cancer; RT = Radiotherapy; sLND = salvage lymph node dissection.

eventually developed lymph node recurrence. In the current pilot study, also 75% of patients eventually developed local or lymph node recurrence. However, the benefit of Ra-223 treatment was hypothesized in patients with (isolated) micro-bone-metastases. At the time of the study, there were no validated instruments available to accurately predict development of bone metastatic disease in this setting. Although our patient selection was adequate to identify patients at high risk of developing clinical recurrence, it lacked precision to identify patients that would develop isolated skeletal recurrence. Secondly, despite Ra-223 therapy, 2 patients in our study eventually developed skeletal only recurrence. This might be explained by the fact that not all CaP cells in the bone marrow progress to develop metastases but some remain in a dormant state [24]. Bone metastases are established by a complex mechanism involving interactions with osteoblasts, osteoclasts, and CaP cells leading to increased local bone turnover [25]. However, evidence suggests that bone remodeling is important in the formation of bone metastases out of these dormant CaP cells [26]. An early event in the process of bone remodeling is the formation of new blood vessels at the remodeling site as angiogenesis is necessary for normal bone remodeling and bone growth [25]. Interestingly, preclinical evidence has demonstrated that Ra-223 accumulation is dependent on the local blood vessel density for its delivery [27]. As such dormant CaP cells might be less sensitive to drugs such as Ra-223 due to the low angiogenesis level [28]. Moreover, these dormant CaP cells will not give rise to mineralized matrix and hydroxyapatite, rendering the binding site of Ra-223 less accessible [24]. In addition, preclinical evidence suggests that castration-induced bone loss might trigger progression of these dormant cells into bone metastases. As none of the patients in our study received concomitant hormonal therapy during Ra-223 therapy, this might also help explain the lack of efficacy of Ra-223 therapy. It is unclear whether Ra-223 was effective in preventing some dormant CaP cells from developing into bone metastases in the included patients. An exploratory comparison of the mean PSA doubling time during Ra-223 therapy showed no difference with the PSA doubling time Post Ra-223 therapy. Therefore, it is difficult to make firm conclusions on the effectiveness of Ra-223 in this patient population.

This study suggests that Ra-223 is not beneficial in hormone-sensitive CaP patients with BCR following maximal local treatment without clinical metastases. In contrast, more encouraging results in terms of PSA response were observed with Ra-223 in hormone-sensitive CaP patients with bone metastases on conventional imaging [20,21]. It is unclear whether improvement of patient selection would also translate into better outcomes in hormone-sensitive CaP patients

with PSA relapse without metastases on conventional imaging. Currently, an ongoing trial (NCT04206319) is investigating the role of Ra-223 in this patient population. However, to optimize patient selection in the abovementioned study, eligible patients should have visible lesions in the bone on NaF PET/CT prior to Ra-223 therapy.

5. Conclusion

In patients with PSA progression following maximal local treatment without detectable lesions on PSMA PET/CT and whole body MRI, Ra-223 treatment is safe. However, the clinical benefit of Ra-223 in this setting is doubtful as significant oncological benefit is lacking. Improved patient selection by identifying patients who develop isolated skeletal recurrence might provide better oncological outcomes.

Disclosures

Availability of data and material: On request; Ethics approval: The study was approved by the local ethics committee (s56892) and the Federal Agency for Medicines and Health Products (FAMHP) and registered on the EudraCT archive (EudraCT 2014-002833-70); Consent to participate: All patients provided their informed consent.

Author's contribution

Protocol/project development: Steven Joniau, Hendrik Van Poppel, Lorenzo Tosco; Data collection or management: Gaëtan Devos, Lorenzo Tosco, Laura Schillebeeckx; Data analysis: Gaëtan Devos, Laura Schillebeeckx; Manuscript writing/editing: All authors.

Conflicts of interest

Wouter Everaerts: received travelling grants from Ferring, Ipsen, and honoraria from Janssen. Lorenzo Tosco: received travelling grants from Bayer, Ipsen, Ferring and Janssen. Consulting or advisory role for Ipsen. Accomodation expenses from Astellas, Bayer and Pierre-Fabre.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.04.034.

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