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Radium-223 treatment in castration resistant bone metastatic prostate cancer. Should be the primary tumor always treated?

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Abstract

Introduction: Radium-223 (223Ra) improves symptoms and survival in patients with bone metastatic castration-resistant prostate cancer (mCRPC).

Study aim: To evaluate the impact of a previous radical prostatectomy (RP) on the outcome of 223Ra therapy in mCRPC patients. The primary prostate tumor left untreated could progress during 223Ra treatment.

Materials and methods: mCRPC symptomatic patients treated with 223Ra were enrolled. Luteinizing Hormone-Releasing Hormone analogue was maintained. No other anticancer therapy was given. 223Ra was administered i.v. at the dose of 55 kBq/kg every 4 weeks for 6 cycles. Patients were stratified according to previous RP or not. Hematological toxicity was monitored. Statistical analysis of 223Ra discontinuations, progressions, and deaths were performed.

Results: Forty-four patients were enrolled, 16 (36.4%) previously received RP, 5 (11.3%) prostate radiotherapy and 23 (52.3%) maintained the primary prostate tumor after local treatment. All patients presented only bone metastases, 24 patients (54.5%) had more than 20. Twenty-six (59.1%) patients were treated after first or second line systemic chemotherapy. Treatment interruptions occurred in 14 patients (50%) with prostate and in 4 (25%) without ($P = 0.04$). After a median follow-up of 18 months (6–30 months), 15 (53.6%), and 7 (43.7%) progressions ($P = 0.34$) and 13 and 1 (6.2%) deaths ($P = 0.04$) occurred in patients with and without prostate respectively.

Conclusion: The presence of the primary prostate tumor seems to play a detrimental role in mCRPC patients undergoing 223Ra treatment in absence of other concomitant anticancer therapy. On the other hand a previous RP might play a protective role.

Keywords: Radium-222; Castration resistant prostate cancer; Radical prostatectomy; Radiotherapy; Primary tumor

1. Introduction

Prostate cancer remains the fifth leading cause of cancer death in Europe, with a mortality of almost 19 cases per 100,000 men despite increasing health awareness and early diagnosis [1]. In patients with metastatic disease, the 5-year survival is lower than 30% and the great majority of men dying of prostate cancer have a castration resistant tumor and skeletal metastases [2]. In metastatic hormone-sensitive disease, the androgen-deprivation therapy (ADT) is the first

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line but progression to metastatic castration-resistant prostate cancer (mCRPC) finally occurs [2,3]. The recent introduction of 223Ra has significantly changed the therapeutic approach to bone metastatic prostate cancer [4–6].

In the past, the principal aim of the radionuclide metabolic therapy was bone pain reduction and delay of severe complications [7]. Similar results with lower toxicity can be obtained also with bisphosphonates or denosumab [8].

Pivotal placebo-controlled phase-II studies conducted with 223Ra in mCRPC patients, detected not merely a bone pain control but also a significant reduction in bone alkaline phosphatases (ALP), longer prostate specific antigen (PSA) progression-free period and a longer trend in overall survival [9–11].

More than 27,000 patients worldwide and 12,000 in Europe received 223Ra so far, and in Italy more than 500 patients were treated in 2016 [11].

Although hormonal therapy with LHRH agonists or antagonists is maintained, further treatments for CRPC are not administered in patients undergoing 223Ra. In addition, a relevant part of patients could have not received any local treatment, therefore the primary prostate tumor could progress during 223Ra treatment or later. This situation may be frequent in case of hematological toxicity or factors limiting the immediate start of the subsequent therapies. The value of radical prostatectomy or radiotherapy in patients with naive metastatic prostate cancer to improve symptoms and reduce progression is still object of debate and is not recommended by international guidelines as standard option [12]. Nevertheless, a speculation is that the treatment of the primary tumor may change the tumor biology in metastatic prostate cancer [13–15]. Similarly, the presence of an untreated primary prostate cancer in the castration resistance phase could deteriorate the outcome of subjects submitted to the only aimed bone metastases target agents 223Ra.

The aim of our study was to evaluate the clinical impact of the presence of the primary prostate tumor in patients with mCRPC receiving 223Ra in absence of other concomitant therapy except for LHRH analogues; furthermore disease progression, death, and treatment discontinuation were assessed.

2. Patients and methods

Patients with mCRPC were treated with 223Ra between January 2016 and December 2017. All patients obtained informed consent. Main inclusion criteria were: 2 or more symptomatic skeletal metastases on imaging in absence of visceral metastasis, absence of lymph nodal metastases except for lesions less than 3 cm in maximum diameter as recommended by European label. Patients progressing after cytotoxic chemotherapy or unfit for docetaxel chemotherapy were included. Main exclusion criteria were: detection of visceral lesions, impaired renal function (creatinine >2 times than normal), impaired bone marrow function (hemoglobin less than 9 g/dl, white count less than 3,000/mmc, platelets less than 75,000/mmc), prostate and/or pelvic radiotherapy received after metastatic progression, previous administration of investigational drugs or a cytotoxic chemotherapy regimen within 4 weeks before starting 223Ra.

All patients received antiandrogen therapy with LHRH analogues to achieve castration levels of plasma testosterone (<0.5 ng/ml). No anticancer therapy different from LHRH analogues was given during 223Ra therapy. Bisphosphonates or denosumab were allowed although these therapies could not be administered at the same day of 223Ra injection.

Complete blood count was measured before each cycle of 223Ra. PSA and ALP, were obtained within 15 days before the treatment start, 1 and 3 months after the last dose and at physicians' decision. Technetium-99m bone scan and total-body CT scan were performed within 1 month of the day of first treatment. PET was performed if clinically indicated. Other laboratory or imaging exams were carried out at the discretion of the treating physician.

The 223Ra was administered according to the schedule reported in label: 55 kBq/kg e.v. every 4 weeks and 6 injections were planned.

Revised RECIST criteria (version 1.1) were adopted to evaluate response to 223Ra therapy. PSA was monitored but not considered as a marker of response due to the relatively modest effect of 223Ra on PSA levels. Thus, a rising of PSA level did not indicate treatment withdrawal [10].

ALP response was defined as a decline of more than 30% from baseline after a complete treatment. PSA level was monitored but it was not evaluated as a response criteria. A skeletal event after 223Ra treatment was defined as use of palliative external beam radiation therapy, new symptomatic pathologic fracture, spinal cord compression.

Toxicity was graded according to Common Terminology Criteria for Adverse Events version 3.0.

Radium-223 was discontinued in case of neutropenia, anemia, or thrombocytopenia classified as grade 3 or 4 (according the Common Terminology Criteria for Adverse Events version 4.03) lasting longer than 14 days, visceral progression or dose delay of more than 4 weeks. Patients were stratified according to the presence or absence of the primary prostate tumor. Patients previously treated by prostate radiotherapy and showing local progression with upstaging from cT2 to cT3-4 before or at the same time of metastatic progression and castration resistance were included.

Clinical outcomes in terms of progression, death, and treatment withdrawal due to toxicity were analyzed in relation to the presence or absence of the primary prostate tumor.

Statistical analysis: Patient and clinical characteristics were summarized using descriptive statistics. Continuous variables were summarized as median and interquartile range; counts and percentages were used to summarize categorical variables. The Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables were used.

The Wilcoxon signed rank test (paired, 2-tailed) was applied for the comparison of the different response parameters for continuous variables. The association of the

categorical variables summarized in the contingency tables was evaluated using the Fisher's exact test. All statistical tests used a significance level of 5%. A P value <0.05 was considered statistically significant. The statistical analyses were performed with the Software R version 3.4.2.

3. Results

Forty-four patients were treated. Median age was 76 years. Almost 60% of the patients had Gleason grade ≥8. Twenty-three (52.3%) patients maintained the primary prostate tumor free from any local treatment till the appearance of bone metastasis, 16 (36.4%) had been previously submitted to radical prostatectomy and 5 (11.3%) patients had received prostate radiotherapy for a cT2-3 N0M0 tumor and showed local progression and upstaging to cT3-4 before or at the same time of metastatic progression and subsequent castration resistance. The median time from the treatment of the localized tumor to the appearance of bone metastases was 24 months (range: 12 −96 months).

The patients' characteristics are reassumed in Table 1.

No significant statistical differences emerged at baseline between the 2 groups except for the higher Gleason grade in patients previously submitted to radical prostatectomy in consideration of final pathology report. However, no difference in Gleason grade distribution was observed after biopsy examination.

Table 1
Patients' characteristics

	With prostate	Without prostate	All	P value
Number Pz.	28	16	44	
Median age	74	77	76	0.79
Median BMI	27.6	26.5	27.4	0.17
Performance status (WHO)				
0−1	11	2	19	1
2−3	10	2	12	
Number of bone metastases				0.715
<6	5	2	7	
6<x<20	6	5	11	
>20	16	8	24	
Gleason Grade				0.04
6	1	0	1	
7	8	2	10	
8	10	4	14	
9	3	9	12	
10	1	0	1	
unkown	5	1	6	
PSA(median)[a]	33.75	17.36	35.6	0.38
ALP(median)[a]	182	135	165	0.16
Hb (median)[a]	13	12.8	12.9	0.95
WBC (median)[a]	5,850	5,010	5,850	0.43
Plateletes (median)[a]	211,000	202,000	207,000	0.84

[a] IQ ranges are given in Table 3.

Table 2
Compliance to 223Ra treatment

223Ra treatment	Prostate	No prostate	Total
	28	16	44
Completed	14 (50%)	12 (75%)	26 (59.1%)
Interrupted[a]	14 (50%)	4 (25%)	18 (40.9%)

[a] P value = 0.044.

All patients had exclusively bone metastases and the number of bone metastatic sites resulted more than 20 in 24 patients (54.5%). 223Ra was administered at castration resistant progression in 4 patients (9.1%) unfit for chemotherapy, after fist-line chemotherapy in 14 (31.8) and after second-line therapy in 26 (59.1%). No difference in the intensity of previous treatments emerged between the 2 groups. Fourty-six patients (59.1%) received all the 6-cycles scheduled in label while 18 patients (40.9%) interrupted the radiopharmaceutical, in these subjects 14 (50%) presented prostate at baseline while 4 (25%) were previously submitted to radical prostatectomy ($P = 0.044$). Drug interruption was toxicity in 10 patients (55.6%) and progression in 8 (44.4%) (Table 2, Fig. 1).

Toxicity is reported in Table 3.

The hematological, PSA, and ALP measurements at entry and 1 week after the sixth cycle of 223Ra are given in Table 4. A statistically significant reduction of platelets and hemoglobin levels, although no clinically relevant, was evident in both groups. PSA increased in both groups, ALP slightly increased in the group of patients with prostate and remained almost stable in the others.

The clinical response is reported in Table 5. After a median follow-up of 18 months (range 6−30 months)

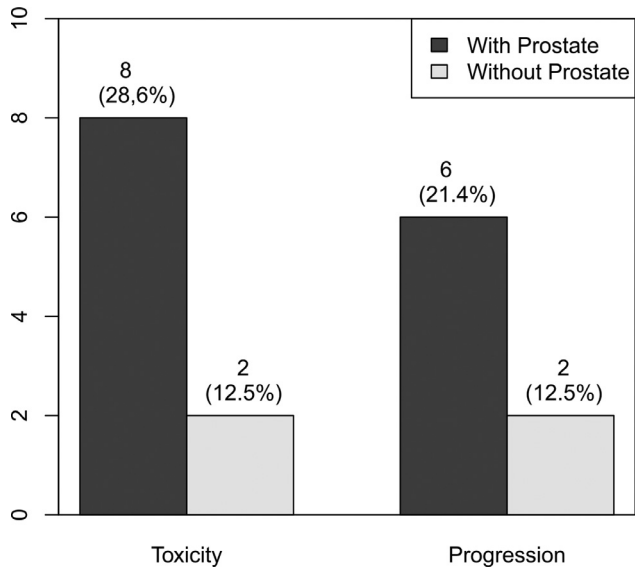

Fig. 1 Treatment interruptions due to toxicity or progression during 223Ra treatment according to the presence of the primary prostate tumor.

Table 3
Hematological, PSA, and ALP values at entry and 1 week after the sixth cycle of 223Ra

	Pre-223Ra		Post-223Ra		
	Median	IQR range	Median	IQR range	*P* value
PSA					
With prostate	27.03	8.02–41.75	56.63	31.56–100	0.065
Without prostate	16.60	5.37–113.11	250,00	86.57–347.85	0.036
ALP					
With prostate	139	84–188	146	109–211	0.6115
Without prostate	79	69.9–129	72	65–113	1
Hb					
With prostate	13.55	13.03–14.1	11.95	10.3–12.98	0.0423
Without prostate	12.9	12–13.25	11.1	10.5–12.5	0.015
Gb					
With prostate	4,420	4,022.5–4,640	4,750	4,090–6,000	0.195
Without prostate	4,465	4,227.5–4,520	5,815	4,272.5–6,352.5	0.1226
Platelets					
With prostate	198,000	153,250–255,250	148,000	131,250–197,000	0.0039
Without prostate	207,500	179,250–255,500	209,000	173,750–228,750	0.0754

Table 4
Clinical response in patients undergoing 223Ra treatment

Response	Prostate	No prostate	Total
Patients	28	16	44
Partial response	5 (17.8%)	3 (18.7%)	8 (18.2%)
Partial response + stable disease	5 (17.8%)	4 (25%)	9 (20.4%)
Progression[a]	15 (53.6%)	7 (43.7%)	22 (50%)
Deaths[b]	12 (42.8%)	1 (6.2%)	13 (29.5%)

[a] *P* value = 0.34.
[b] *P* value = 0.04.

Table 5
Clinical response in patients undergoing 223Ra treatment

Response	Prostate	No prostate	Total
Patients	28	16	44
Partial response	5 (17.8%)	3 (18.7%)	8 (18.2%)
Partial response + stable disease	5 (17.8%)	4 (25%)	9 (20.4%)
Progression[a]	15 (53.6%)	7 (43.7%)	22 (50%)
Deaths[b]	12 (42.8%)	1 (6.2%)	13 (29.5%)

[a] *P* value = 0.34.
[b] *P* value = 0.04.

no statistically significant difference was detectable in terms of objective response and progression. Among the 22 progressions in the whole population, 15 (53.6%) were observed in patients with prostate and 7 (43.7%) in the other cohort ($P = 0.34$). Thirteen patients died (29.5%), 12 (42.8%) in the group of patients with primary prostate tumor and 1 (6.2%) in the other group ($P = 0.04$). All death, except 1 due to car accident and occurring in a patient previously submitted to RP, were disease related. No death due to toxicity was recorded.

4. Discussion

Radium 223 has been approved for the treatment of mCRPC since 2013, nevertheless published experiences in common clinical practice remain limited [16].

In the Alpharadin Symptomatic Prostate Cancer Patients (ALSYMPCA) approval study, patients were randomized to 223Ra or placebo and no other concomitant antineoplastic drug was allowed except for LHRH analogues therapy [10]. This limitation of combo strategies has been generally adopted also for 223Ra administration in clinical practice,

where more heterogeneous patients' population is likely to be treated. In this setting, patients can receive the radiopharmaceuticals lately and after heavy therapies of the castration resistance phase: in our experience, almost the 60% of patients had a bulky disease progressed after first or second line systemic chemotherapy.

Wong et al. [17] recently analyzed the factors that might influence in common clinical practice the outcome of 223Ra treatment in 64 patients. They found that prior chemotherapy use, more than 5 bone lesions, baseline ALP, and its response to treatment statistically impacted patients' survival. Up to date, the selection criteria for 223Ra treatment are not internationally identified and the results of prospective randomized trials combining 223Ra with other therapies should be awaited before adopting such combinations [18].

It must be taken into account that the patients submitted to 223Ra treatment do not receive any antineoplastic agent different from LHRH analogues in the phase of castration resistance for a period not inferior than 6 months. Thus, the patients may suffer of heavy complications due the progression of the primary tumor as hydronephrosis, renal function impairment, hematuria, and bladder outlet obstruction [19]. Moreover, the presence of the primary tumor could be responsible for seeding new metastatic growths to distant sites different than bone, in addition circulating cells can reinfiltrate the prostate promoting tumor progression [13,20].

The hypothesis of our study is that the presence of the primary tumor might play a detrimental role in patients receiving 223Ra therapy outcomes and the concomitant treatment of the primary tumor or its absence as due to previous radical prostatectomy, might play a protective role.

During the 6 months of 223Ra therapy, 40% of our patients interrupted the treatment due to progression or toxicity. The great majority of them harbored their untreated primary tumor. Although no difference in progression rate emerged between the 2 groups, almost all the deaths occurred among the patients with prostate, confirming a statistically significant difference in terms of cancer-specific mortality.

A limit of our study is that quality of life and pain score were not consistently documented in patients' records therefore these points were not included in our analysis.

The different natural history between patients who receive local therapy and progress thereafter and those with metastatic disease at first diagnosis and not receiving any local treatment, according to the current standard of care, must be considered a potential bias of our study. The higher number, albeit not statistically significant, of patients without previous local treatment and with more than 20 bone lesions could be responsible of the difference in cancer specific survival between the 2 groups. Clearly, some of the demonstrated benefits can be attributed to selection bias; men undergoing surgery are more likely to benefit, to have a lower burden of metastatic disease, or to have robust disease responses with systemic therapy that would have done well despite surgical or radiation intervention [21].

The preliminary promising data obtained in highly selected patients should be confirmed by the results of prospective randomized trials. Moreover, our paper is the first dealing with the potential benefit of RP in CRPC patients undergoing 223Ra.

Specifically, patients with a relatively low tumor risk and good general health status appear to benefit the most.

Considering the small number of patients, our results do not permit any meaningful conclusion and these should be considered as preliminary ones. Nevertheless, our pilot observation may have relevant clinical implications and it could be the first step of further investigational studies.

5. Conclusion

Our experience in patients with mCRPC treated with 223Ra without concomitant therapy except for LHRH analogues identify the presence of primary prostate tumor as negative prognostic factor in terms of 6-cycles completion and survival. Differently, the absence of the primary prostate tumor following to radical prostatectomy seems to play a protective role unless concomitant therapies are given.

Conflict of interest

None.

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