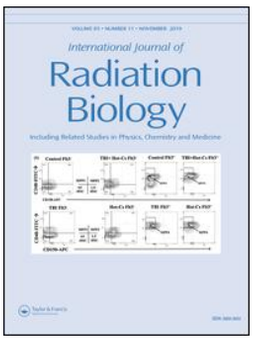

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ORIGINAL ARTICLE

Overall survival in mCPRC patients treated with Radium-223 in association with bone health agents: a national multicenter study

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ABSTRACT

Purpose: Radium-223 has demonstrated efficacy in improving overall survival (OS) and in delaying symptomatic skeletal-related events (SREs). Bone Health Agents (BHA), i.e. RANK ligand inhibitor (Denosumab) and bisphosphonate such as zoledronic acid, are indicated to prevent SREs without a clear survival benefit. SREs on patient health have a high impact and it is, therefore, important to consider the role of new therapies with BHA to better understand the involvement of combination therapy. The primary aim of this multicentric study is to assess OS in mCRPC patients treated with Radium-223 in combination with BHA.

Materials and methods: 430 consecutive patients treated with Radium-223 alone or in combination with BHA, affected by mCRPC, from January 2015 to July 2019 in six Italian Nuclear Medicine Units, were included. Furthermore, data were collected at baseline, after every Radium-223 administration, and during follow-up, at 3 and 6 months and 1 year after the 6th cycle. Clinical data have been evaluated before starting treatment with Radium-223 and at the end of treatment and/or at progression. Patients who received target bone therapy with BHA before Radium-223 treatment together with patients who did not receive this therapy at all (NO BHA GROUP), were compared to patients treated with concomitant Radium-223 and BHA (BHA GROUP).

Results: In univariate models ($p < .05$) several clinical aspects have an impact on OS: concomitant BHA ($p = .018$), BMI (p .001), ECOG PS ($p = .000$), Baseline Hb ($p = .000$), Baseline PSA ($p = .000$), Baseline tALP ($p = .000$), Baseline LDH ($p = .000$), and Baseline neutrophils ($p = .009$). Baseline Hb, Baseline tALP, and Baseline LDH have been confirmed as statistically significant parameters in multivariate models. Indeed, concomitant BHA has not a significant impact on OS ($p = .244$) in multivariate models.

Conclusions: At univariate analysis, our data showed that NO BHA GROUP and BHA GROUP differ in OS by 7 months (95%CI: (1–16.4), $p = .02$). This is not confirmed at multivariate analysis where after adjusting for other baseline factors, BHA is not significant anymore. This is clearly explained as bias by indication: patients with the same levels of tALP, Hb, and LDH receiving or not receiving BHA are expected to have a similar survival. Our results support and confirm the role of Radium-223 therapy on OS and, furthermore, appear to confirm that BHA treatment has not a survival benefit.

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Radium-223 dichloride; prostate cancer; overall survival; bone health agents; mCRPC

Introduction

During the past years, significant progress has been achieved in patients with metastatic castration-resistant prostate cancer (mCRPC) using several treatment approaches(Basch et al. 2014). The relatively recent approval of new treatments, including the radiopharmaceutical Radium-223 dichloride (Radium-223, with a half-life of 11.4 days). The specific activity of Radium-223 is 1.9 MBq/ng), have provided clinicians with a greater choice of treatments(Logothetis et al. 2018; Saad et al. 2019). This compound has benefits in terms of overall survival (OS) based on the results of ALSYMPCA phase 3 studies (Parker et al. 2013). Radium-223 has also proven efficacy in delaying symptomatic skeletal-related events (SREs), as

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Table 1. Baseline patients' characteristics.

Baseline variable	Patients ($n = 430$)	Percentage
Age Mean (SD)	74.1 (1.9) years	
Height Mean (SD)	170.6 (10.4) cm	
Weight Mean (SD)	78.1 (13.4) kg	
Gleason score Mean (SD)	6.5 (5–10)	
5	3	0.7
6	22	5.1
7	108	25.1
8	99	23
9	110	25.6
10	9	2.1
Unknown	79	18.4
Skeletal burden		
0–6 mets	66	15.3
6–20 mets	266	61.9
$\geq$ 20 mets	98	22.8
ECOG Performance Status Mean (SD)	0.82 (0.82)	
0	181	42.1
1	151	35.1
2	89	20.7
3	7	1.6
Unknown	2	0.5
Brief Pain Inventory Pain Score Mean (SD)	4.8 (2.6)	
Low (0–3)	139	32.3
Intermediate (4–7)	214	49.8
Severe (8–10)	75	17.4
Unknown	2	0.5
Number of previous systemic treatments		
0	65	15.1
1	117	27.2
2	74	17.2
$\geq$3	78	18.1
Unknown	96	22.3
Baseline PSA Mean (SD)	198 (655) ng/ml	
Baseline tALP Mean (SD)	267 (308) U/l	
Baseline Hb Mean (SD)	12.2 (2.5) g/dl	
Baseline LDH Mean (SD)	359 (221) U/l	
Baseline PLT Mean (SD)	240.4 (94.5) 10^3/mmc	
Baseline neu Mean (SD)	4.6 (1.8) $10^3/\mu$l	

well as improving OS with its effects on bone metastases (Miller et al. 2018). On the other hand, Bone Health Agents (BHA), i.e., bisphosphonate (BPs) such as zoledronic acid (ZA) and the RANK ligand (RANKL) inhibitor (Denosumab), are indicated for the prevention of SREs but studies of these compounds have not demonstrated a survival benefit (Saad et al. 2018). Nevertheless, in a prospective phase IIIb study, OS appeared to be better in those patients treated with Radium-223 that concomitantly received Denosumab or Abiraterone (Sartor et al. 2018). Therefore, the effects of concomitant medication on benefit, safety, and survival advantage in mCRCP treated with Radium-223 are still matter of debate. SREs have a high impact on patient health and hence it is important to consider the role of new therapies with BHA to better understand the role of combination therapy. The primary aim of this multicentric study is to assess OS in patients treated with Radium-223 in combination with BHA. Moreover, the secondary objective was to confirm the role validated biomarkers to predict treatment effectiveness and safety, such as prostate-specific antigen (PSA), total alkaline phosphatase (tALP), lactate dehydrogenase (LDH), and bone marrow function parameters.

Materials and methods

This is a multicenter study conducted in six Italian Nuclear Medicine Units. All consecutive patients treated with Radium-223 affected by mCRPC, from January 2015 to July 2019, were included. This retrospective study was approved by the local Ethical Committee and conducted in accordance with Helsinki Declaration of 1975 and later amendments. Informed consent was obtained from all individual participants included in the study. Inclusion criteria: all patients had an histological confirmation of prostatic adenocarcinoma, at least two symptomatic bone secondary lesions detected by 99m-Tc HDP bone scintigraphy and no known visceral metastases at contrast-enhanced CT scan, except for malignant lymphadenopathy with less than 3 cm in the short-axis diameter, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2 and adequate hematological, hepatic and renal function (Baldari et al. 2017). 430 consecutive mCRPC patients with symptomatic bone metastases, receiving Radium-223 treatment alone or in combination with BHA, were included. The use of BHA depended on the choice of the reference clinician, as this was a study on real life data. All patients were treated following the current Radium-223 treatment schedule consisting of 6 intravenous injections (55 kBq per kg of body weight) administered every 28 days (Du et al. 2017). Available baseline clinical data relevant to the survival analysis were retrospectively collected including patients characteristics (age, height, weight, complete blood count, ECOG PS, tALP, PSA, LDH, and pain score by Numeric Rating Scale), mCRPC characteristics (Gleason Score (GS), skeletal burden) as well as additional clinical data about previous and current treatments (cycles of Radium-223 received, prior systemic treatment and concomitant use of BHA). A general overview of the examined population at baseline is reported in Table 1. Furthermore, data were collected at baseline, after every Radium-223 administration and during follow-up, at 3 and 6 months and 1 year after the 6th cycle. Clinical data have been evaluated before starting the treatment with Radium-223 at the end of the treatment and/or at progression. The primary endpoint of the study was OS, which was established from the first Radium-223 administration until the date of death from any cause. For the statistical analysis, in terms of OS, it has been considered a timeframe starting from the date of the I cycle of Radium-223 treatment to the time of analysis. Patients who received targeted bone therapy with BHA before Radium-223 treatment together with patients who did not receive this therapy at all (NO BHA GROUP, $n = 298$), were compared to patients treated with

Table 2. BPs and NO groups baseline characteristics.

	BHA group ($n = 132$)	NO BHA group ($n = 298$)	p Value
Age (years) Mean (SD)	72.97 (7.93)	74.65 (7.75)	.043
Gleason Score Mean (SD)	8.0 (0.9)	7.8 (1.0)	.12
5	0	3 (1%)	.53
6	5 (3.8%)	17 (5.7%)	
7	31 (23.5%)	77 (25.8%)	
8	35 (26.5%)	64 (21.5%)	
9	38 (28.8%)	72 (24.2%)	
10	3 (2.3%)	6 (2%)	
Unknown	20 (15.1%)	59 (19.8%)	
Skeletal burden Mean (SD)	1.81 (0.65)	1.97(0.59)	.016
0-6 mets	18 (13.64%)	48 (16.1%)	.012
6-20 mets	72 (54.54%)	194 (65.1%)	
≥20 mets	42 (31.82%)	56 (18.8%)	
N of previous systemic treatments Mean (SD)	1.68 (1.22)	1.53 (1.2)	.24
0	16 (12.2%)	49 (16.4%)	.08
1	44 (33.3%)	73 (24.5%)	
2	23 (17.4%)	51 (17.1%)	
≥3	28 (21.2%)	50 (16.8%)	
Unknown	21 (15.9%)	75 (25.2%)	
Baseline PSA Mean (SD)	214.08 (1039.94) ng/ml	190.97 (363.99) ng/ml	.07*
Baseline Hb Mean (SD)	12,29 (1.47) g/dl	12.15 (1.56) g/dl	.38
Baseline tALP Mean (SD)	207.54 (228.69) U/l	287.63 (335.7) U/l	.016*
Baseline LDH Mean (SD)	343.9 (202.07) U/l	362.97 (227.86) U/l	.68*

* Mann–Whitney non-parametric test.

concomitant Radium-223 and BHA (BHA GROUP, $n = 132$).

Statistical analysis

Data are expressed as mean ± standard deviation or median ± IqR as appropriate. Means were compared by Student's two-sample T-test with Welch correction or Mann–Whitney test, accordingly. Association among categorical variables is evaluated by means of Chi-squared test. Survival distributions were estimated using the Kaplan–Meyer product-limit estimator and compared using the log-rank test. The association of predictors with OS was evaluated by means of univariate Cox regression models. A multivariable Cox regression model was then selected using a stepwise forward procedure based on Akaike Information Criterion. Variance Inflation Factors were checked for collinearity and residual analysis was used to assess the proportionality of hazards assumption. All analyses were conducted using the R software, version 3.5.1 (SPSS Inc., Chicago, IL). The significance level was set at 5%.

Results

Four hundred and thirty patients were enrolled in this multicenter study and their data were analyzed. A general overview of patients based on the status of BHA treatment at baseline is reported in Table 2. Patients have been divided into two groups according to the status of bone-targeted chemical treatment concomitant to Radium-223: the NO BHA GROUP (mean(SD): 74.65 (7.75) years) and the BHA GROUP (mean(SD): 72.97 (7.93) years). An overview of statistical analysis is reported in Table 3. Considering clinical covariates in univariate models ($p < .05$) several clinical aspects showed an impact on OS: higher body mass index (BMI) ($p = .001$), lower ECOG PS (p .000), concomitant BHA ($p = .018$, higher Baseline hemoglobin (Hb) ($p = .000$), lower Baseline PSA ($p = .000$), lower Baseline tALP ($p = .000$), lower Baseline LDH ($p = .000$), and higher Baseline neutrophils ($p = .009$). On the contrary, GS and Baseline platelet (PLT) values did not show a significant impact on survival ($p > .05$). At univariate analysis, our data showed that NO BHA GROUP and BHA GROUP differ in OS by 7 months (95%CI: (1–16.4), $p = .02$). In multivariate models Baseline Hb, Baseline tALP and Baseline LDH have been confirmed to be statistically significant parameters. On the contrary, concomitant BHA therapy did not exhibit a significant impact on OS ($p = .244$). In the global population ($N = 430$ patients enrolled), only eight cases of SREs have been reported during the fourth-years study (five patients in NO BHA GROUP and three patients in the BHA GROUP). The effect of BHA therapy on SREs is not statistically significant ($p = .7056$). An additional classification of patients based on specific chemical compounds (86 patients treated with BPs and 46 patients treated with Denosumab) resulted to be not statistically significant.

Discussion

The therapeutic landscape for men with CRPC has evolved rapidly in recent years (Ricci et al. 2019). Novel compounds such as abiraterone acetate and enzalutamide, second-line chemotherapy cabazitaxel and the radiopharmaceutical Radium-223, have provided new treatment possibilities (Saad et al. 2018). Nevertheless, patients with CRPC mainly develop bone metastases, which have a substantial impact on quality of life (De Vincentis, Frantellizzi, et al. 2019; De Vincentis, Follacchio, et al. 2018; De Vincentis, Monari et al. 2018; De Vincentis, Gerritsen et al. 2019; Sciarra et al. 2018; Frantellizzi et al. 2018). Treatment targeting both cancer cells and bone microenvironment have led to a two-pronged approach for the management of patients with mCRPC thanks to the use of BP (Sciarra et al. 2019). This research field has now expanded including receptor activator of nuclear factor-kappa B RANK ligand inhibition. The use of radiopharmaceuticals for palliation of bone pain due to metastatic disease has evolved with the approval of Radium-223, which was found to prolong OS in addition to SREs reduction (Wong et al. 2017; Dorff and Agarwal 2018). Further studies are needed to optimize timing and combination strategies for BHA (Zeng et al. 2012). Future studies are required to identify response biomarkers to improve cost-effectiveness and efficacy of these agents. In our paper, patients treated with concomitant Radium-223 and BHA have been compared to patients receiving Radium-223 therapy alone (including

Table 3. Univariate and multivariable analysis of OS in relation to baseline variables.

Clinical covariates	Univariate models HR (95% CI)	*p* value	Multivariable model HR (95% CI)	*p* Value
BMI	0.948 (0.918–0.979)	.001		
Gleason score	0.928 (0.818–1.053)	.246		
ECOG performance status	1.534 (1.325–1.775)	.000		
Bone-targeted therapy (BHA)	0.728 (0.560–0.947)	.018	0.589 (0.242–1.435)	.244
Baseline Hb	0.722 (0.663–0.787)	.000	0.675 (0.542–0.841)	.000
Baseline PSA	0.001 (1.001–1.001)	.000		
Baseline tALP	1.001 (1.001–1.002)	.000	1.002 (1.001–1.003)	.001
Baseline LDH	0.003 (1.002–1.004)	.000	1.003 (1.002–1.004)	.000
Baseline PLT	1.001 (1.000–1.003)	.148		
Baseline neu	1.098 (1.024–1.178)	.009		

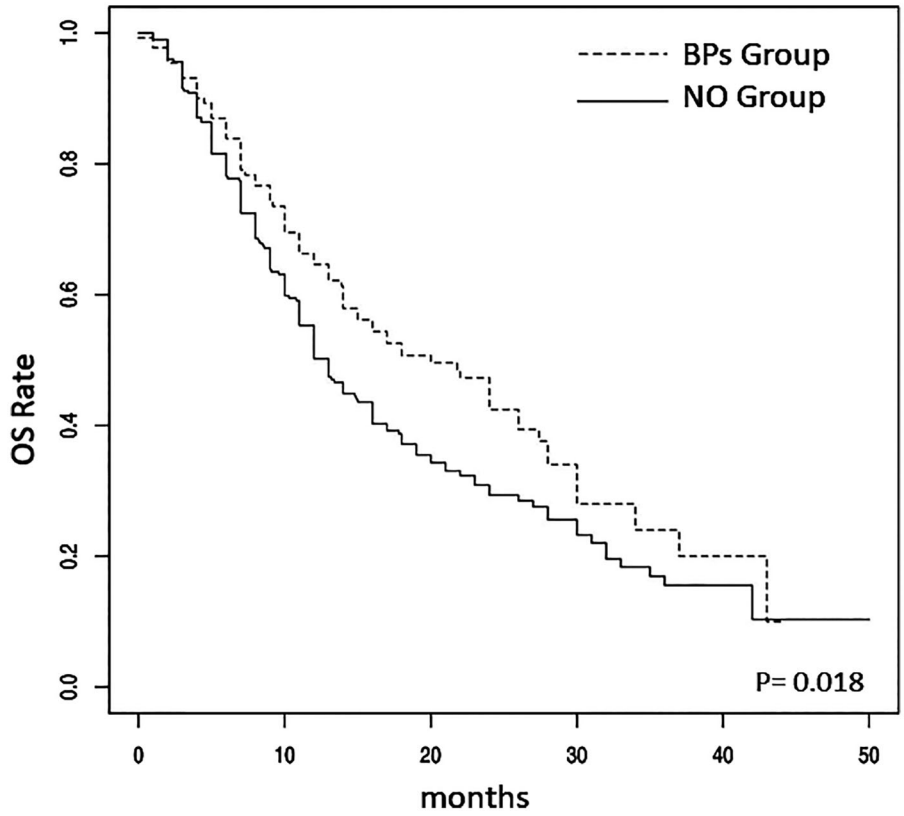

Figure 1. Kaplan–Meyer analysis shown the BHA and the NO BHA groups. The curve underlines the advantage in the overall survival of the BHA group against the NO BHA group.

both naïve BHA therapy patients and patients who received BHA therapy before Radium-223 treatment). In fact, the aim of the paper is to assess OS in patients treated with Radium-223 in combination with BHA. According to our results BMI, ECOG PS, BHA, Baseline Hb, Baseline PSA, Baseline tALP, Baseline LDH, and Baseline neutrophils are significant predictors of OS in univariate models (Figure 1). Nevertheless, only Baseline Hb, Baseline tALP, and Baseline LDH confirmed to have an impact on OS in multivariate models. These results are in line with previous papers concerning reliable prognostic and predictive biomarkers (De Vincentis et al. 2017; Frantellizzi et al. 2018; Heinrich et al. 2018). Several baseline prognostic markers associated with survival have been proposed in mCRPC patients treated with Radium-223, such as ECOG PS, tALP, Hb value and the number of prior systemic treatments, while PSA does not provide accurate information on the effectiveness of Radium-223 treatment (Sabbatini et al. 1999; van der Doelen et al. 2019). Particularly tALP decline at 4 weeks may be used as an early pharmacodynamic marker to monitor treatment efficacy (Sartor et al. 2017) and a significantly longer OS has been reported in case of tALP decline at 12 weeks (Parker et al. 2013). Moreover, in a previous work of this group, we proposed a multidimensional clinical evaluation (the best score was obtained by combining baseline ECOG PS with Hb < 12 g/dl and PSA ≥ 20 ng/ml) to maximize clinical benefit and minimize toxicities of Radium-223 treatment (Frantellizzi et al. 2018). Nevertheless, the effects of concomitant medication in mCRCP treated with Radium-223 are still unclear, particularly the role on benefit, safety, and survival advantage. Previous evidence reported that the ZA administration in combination with chemotherapy is beneficial in patients with mCRPC, even though there was no benefit in terms of

OS (James et al. 2016). Radium-223 is able to prolong survival when administered in those patients with better baseline clinical parameters (Prelaj et al. 2019), while bone-targeted therapy with BHA are not associated to a survival benefits, even if these compounds are indicated for the prevention of SREs (Saad et al. 2018). According to our results, at univariate analysis our data showed that NO BHA GROUP and BHA GROUP have different OS (Figure 1 and Table 3). This is not confirmed at multivariate analysis, where BHA is not significant anymore after adjusting for other baseline factors ($p = .244$). This is clearly explained as a bias by indication: patients with the same levels of tALP, Hb, and LDH receiving or not receiving BHA can be expected to have a similar survival. On the other hand, BHA is apparently typically prescribed to patients with better prognosis as predicted by tALP, Hb, and LDH. Our results support and confirm the role of Radium-223 therapy on OS and, demonstrated that BHA treatment does not prolong OS. In the case of bone metastases, skeletal complications may occur and can require radiotherapy and/or surgery. Thus, effective bone-targeted therapies are essential to improve disease-free and quality of life in cancer patients with bone metastases (De Vincentis, Gerritsen, et al. 2019). According to a recent phase 3 trial mainly focused on SREs, the addition of Radium-223 to abiraterone acetate plus prednisone or prednisolone did not improve SREs-free survival and was associated with an increased frequency of bone fractures compared with placebo (Smith et al. 2019). In our paper, we reported only 8 cases of SREs (<2%) in the entire population and, thus, not statistically significant for a group comparison analysis. Therefore, future papers with larger samples may include the assessment of SREs on combination treatment. Furthermore, a future perspective analysis should include further stratifications of previous BHA treatment including dose and timing to focus on survival aspects of previous bone-targeted therapy on Radium-223 treatment. In fact, a limit of this study is that, even with this relatively large sample size, it was not possible to stratify patients according to drugs used for bone therapy (BPs or Denosumab). Future papers may explore differences between BPs and Denosumab. Furthermore, we underline how the lack of advantages of the combination of BHA with Radium-223 affects only OS. It is not the purpose of this paper to examine the effects of the pharmacological association on pain palliative effect.

Ethical approval

For this type of study, formal consent is not required.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals

This article does not contain any studies with animals performed by any of the authors.

Disclosure statement

The authors declare that they have no conflict of interest.

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