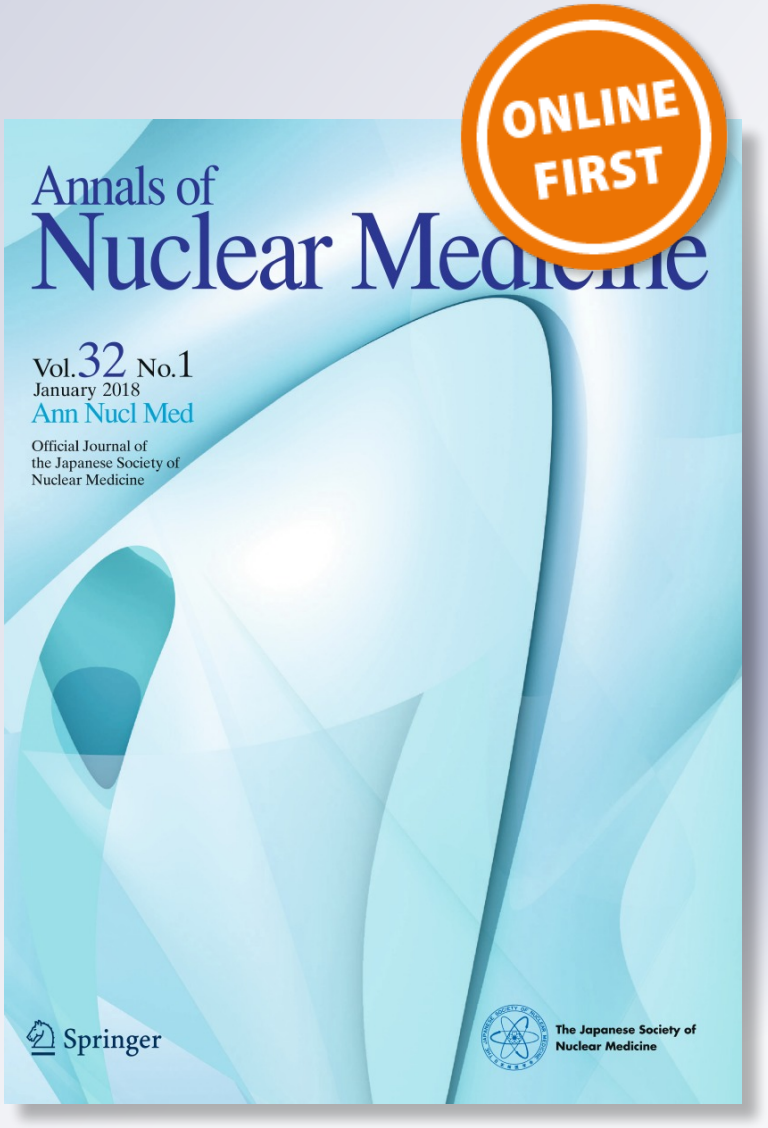
A 3-variable prognostic score (3-PS) for overall survival prediction in metastatic castration-resistant prostate cancer treated with ^{223}Radium-dichloride

Viviana Frantellizzi, Alessio Farcomeni, Giulia Anna Follacchio, Massimiliano Pacilio, Rosanna Pellegrini, Roberto Pani, et al.

Annals of Nuclear Medicine

ISSN 0914-7187

Ann Nucl Med
DOI 10.1007/s12149-017-1228-6



Springer

Annals of Nuclear Medicine
https://doi.org/10.1007/s12149-017-1228-6

ORIGINAL ARTICLE

A 3-variable prognostic score (3-PS) for overall survival prediction in metastatic castration-resistant prostate cancer treated with ^{223}Radium-dichloride

Viviana Frantellizzi[1,2] · Alessio Farcomeni[3] · Giulia Anna Follacchio[1] · Massimiliano Pacilio[4] · Rosanna Pellegrini[5] · Roberto Pani[6] · Giuseppe De Vincentis[1]

Received: 19 November 2017 / Accepted: 26 December 2017

Abstract

Objective In mCRPC patients treated with ^{223}Ra, a major issue is the validation of reliable prognostic and predictive biomarkers to maximize clinical benefit and minimize toxicities and costs. Bearing in mind how changes in tALP did not meet statistical requirements as surrogate marker for survival, aim of this single-center retrospective study was to characterize the prognostic and predictive role of baseline clinical variables associated with overall survival in patients receiving ^{223}Ra treatment.

Methods 92 consecutive CRPC patients with symptomatic bone metastases receiving ^{223}Ra treatment were included. Available baseline clinical data relevant to the survival analysis were retrospectively collected. The primary end-point of the study was overall survival, which was established from the first ^{223}Ra administration until date of death from any cause.

Results Median follow-up time from the first ^{223}Ra administration was 6 months (range 1–31 months). The univariate analysis evaluating the prognostic value of all baseline clinical variables showed that patients' weight, BMI, ECOG PS, Hb and tALP values were independently associated with OS. On multivariable analysis only baseline Hb value and ECOG PS remained significantly correlated with OS. To determine reliable baseline predictive factors for survival in patients receiving ^{223}Ra treatment, we produced a predictive score. We tried all possible variable combinations, and found that the best score was obtained by combining baseline ECOG PS with Hb < 12 g/dl and PSA ≥ 20 ng/ml. This resulted in a score ranging from 0 to 4, with AUC 78.4% ($p < 0.001$).

Conclusions We propose a multidimensional clinical evaluation to select those mCRPC subjects suitable to receive the maximum benefit from ^{223}Ra treatment.

Keywords ^{223}Ra-dichloride · mCRPC · Predictive score · PSA · Overall survival

✉ Viviana Frantellizzi
viviana.frantellizzi@uniroma1.it

[1] Department of Radiological Sciences, Oncology and Anatomo-Pathology, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy

[2] Angio-Cardio-Thoracic Pathophisiology and Imaging, "Sapienza" University of Rome, Rome, Italy

[3] Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Piazzale Aldo Moro, 5, 00161 Rome, Italy

[4] Department of Medical Physics, Azienda Ospedaliera Universitaria Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy

[5] Department of Molecular Medicine, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy

[6] Department of Sciences and Medico-Surgical Biotechnologies, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy

Published online: 28 December 2017

Introduction

During the past 10 years significant progress has been achieved in treatment of metastatic castration-resistant prostate cancer (mCRPC). In the course of ^{223}Ra treatment, a major challenge is represented by the assessment of treatment effectiveness due to lack of reliable, validated and easily available biomarkers for predicting outcomes and clinically relevant endpoints. Looking at the history of the mCRPC therapeutic scenario, several biomarkers have previously been described including prostate-specific antigen (PSA), circulating tumor cells (CTC), total alkaline phosphatase (tALP) [1, 2]. However, these markers are not always straightforward or interpretable beyond doubt. PSA can rise during the first phase of therapy before declining [3]. Baseline CTC enumeration and changes during therapy have been shown to be surrogate for survival endpoints [4], but lack broad availability and display limited accuracy with currently available kits [5, 6]. tALP has prognostic potential in mCRPC treated with Docetaxel and ^{223}Ra [7, 8] but changes during therapy have not yet been evaluated in depth. Baseline levels of tALP do not correlate with the efficacy of ^{223}Ra; therefore, baseline tALP have no predictive value in this field. However, there are indications of a correlation between pre-treatment tALP levels ($\geq$ 146 U/l) and increased risk of death, time to progression, skeletal-related events, and bone marrow failure, which suggests a prognostic value for baseline tALP [9, 10]. Survival benefit distinguishes ^{223}Ra from other bone-targeted therapies, such as local EBRT, radioisotopes ^{89}Sr and ^{153}Sm-EDTMP, Zoledronic acid and Denosumab, which have demonstrated to be effective on pain palliation without impact on Overall Survival (OS) [11]. Recently, several clinical trials conducted in expanded access setting have confirmed ^{223}Ra safety and efficacy [12–14]. Given the rapid change in CRPC therapeutic landscape and the complexity in clinical decision-making, a major priority in both, clinical practice and research, is now represented by the validation of reliable prognostic and predictive biomarkers, able to guide an appropriate treatment sequencing to maximize clinical benefit and minimize toxicities and costs [15]. Despite the increasing clinical experience involving ^{223}Ra-dichloride use in mCRPC patients, clinical variables that may predict response to ^{223}Ra treatment are still hard to identify. Aim of this single-center retrospective study was to characterize the prognostic and predictive role of baseline clinical variables associated with overall survival, with the aim of maximizing the treatment efficacy in patients receiving ^{223}Ra.

Materials and methods

This retrospective study was approved by the local Ethical Committee and conducted in accordance with Helsinki Declaration of 1975. Informed consent was obtained from all individual participants included in the study. 92 consecutive CRPC patients with symptomatic bone metastases receiving ^{223}Ra treatment in our institution were included. Currently, ^{223}Ra treatment schedule consists of 6 intravenous injections (55 kBq per kg of body weight) administered every 28 days [16] in patients without visceral metastasis. Available baseline clinical data relevant to the survival analysis were retrospectively collected including age, height and weight, Gleason Score, Eastern Cooperative Oncology Group (ECOG) performance status (PS), number of systemic treatments prior to ^{223}Ra therapy and hemoglobin (Hb) value. Baseline body mass index (BMI) was calculated for every patient. Serum levels of PSA and tALP were collected at baseline, after every ^{223}Ra administration and during follow-up 3 and 6 months after 6th cycle. A ^{99m}Tc-diphosphonate bone scan was performed 1 month before starting ^{223}Ra treatment to assess the baseline burden of skeletal disease, expressed according to Soloway classification [17]. The primary end-point of the study was OS, which was established from the first ^{223}Ra administration until date of death from any cause.

Statistical methods

Data are expressed as mean $\pm$ standard deviation or median $\pm$ IQR as appropriate. OS was estimated through Kaplan–Meier estimates, and effects of predictors were assessed through log-rank tests and univariate Cox regression. A multivariable Cox regression model was estimated, where the final set of predictors was selected based on minimization of the Akaike Information Criterion in forward selection stages. To evaluate the relationship between time-dependent biomarkers repeatedly measured at different follow-up occasions and OS (and the relationship between trends and OS) we used Joint Models for survival and longitudinal data, where a single shared parameter captures the association of interest. Predictive scores were built based on dividing numerical variables into two classes for simplicity of scoring, with the exception of Gleason and ECOG scores, and then rounding coefficients estimated at Cox regression analysis. The prognostic significance of the new scores was evaluated via time-dependent receiver operating characteristic (ROC) curves. Area under the curve (AUC) was also estimated and their significance was assessed via the bootstrap. The final score was selected by maximizing the AUC. All tests are two

tailed, a $p < 0.05$ was deemed as statistically significant. All analyses were carried out using R (R development core team, Vienna, Austria) version 3.4.0.

Table 1 Baseline patients' characteristics

Baseline variable	Patients ($n = 92$)	%
Age (years)		
Mean (range)	73 (50–90)	
Height (m)		
Mean (range)	1.71 (1.58–1.95)	
Weight (kg)		
Mean (range)	77.7 (56–120)	
BMI		
Mean (range)	25 (19–39)	
Gleason score		
Mean (range)	8 (6–9)	
6	2	2
7	22	24
8	22	24
9	23	25
Unknown	23	25
ECOG performance status		
Mean (range)	1.1 (0–3)	
0	17	19
1	51	55
2–3	24	26
No. of previous systemic treatments		
0	20	22
1	30	32
2	24	26
≥ 3	18	20
Skeletal burden		
0–6 mets	9	10
6–20 mets	73	79
≥ 20 mets	10	11
Baseline Hb		
Median (range)	12 (10–15.3)	
< 12 g/dl	46	50
≥ 12 g/dl	46	50
Baseline tALP		
Median (range)	226 (36–1750)	
< 226 U/l	46	50
≥ 226 U/l	46	50
Baseline PSA		
< 20 ng/ml	36	39
≥ 20 ng/ml	56	61

Results

390 ^{223}Ra cycles were delivered to 92 pts (mean ^{223}Ra administrations 4, range 1–6) in a period between September 2013 and December 2016. Baseline patients' characteristics are summarized in Table 1. Among 92 patients, 40 (43%) completed the 6 scheduled administrations, 27 patients (29%) discontinued ^{223}Ra treatment due to disease progression (10%), bone marrow failure (3%) or death (15%), while 25 (27%) were still receiving ^{223}Ra therapy at the time of analysis, when 44 patients were deceased and 22 patients were in follow-up. Median follow-up time from the first ^{223}Ra administration was 6 months (range 1–31 months). Median overall survival time was 10 months (95% CI 7–16 months), as shown in Fig. 1. The univariate analysis evaluating the prognostic value of all baseline clinical variables showed that patients' weight, BMI, ECOG PS, Hb and tALP values were independently associated with OS. Higher weight (i.e., higher administered activity), BMI and higher baseline Hb levels resulted as favorable prognostic factors, whereas a deteriorated performance status and higher initial tALP values were associated with an increased risk of death. When adjusting for other measures on multivariate analysis, only baseline Hb value and ECOG PS remained significantly correlated with OS. Results of regression analysis are shown in Table 2. The median value of baseline tALP in our cohort was 226 U/l. To determine the ability to predict OS of baseline tALP, the median baseline value was used as cut-point to stratify the entire cohort into two groups. Notably, the subgroup of patients with baseline tALP levels < 226

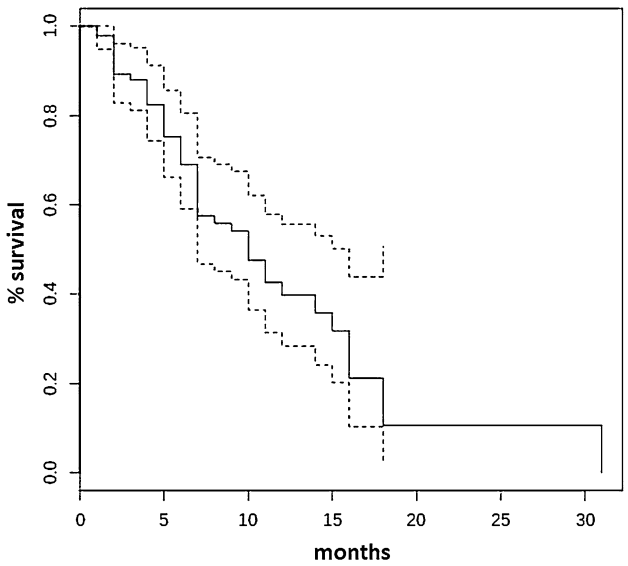


Fig. 1 Kaplan–Meier estimate showing overall survival in our cohort, with 95% confidence interval in dashed lines

Table 2 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
Age (years)	1.03 (0.99–1.07)	0.19		
BMI	0.90 (0.82–0.99)	0.03		
Gleason score	0.97 (0.90–1.06)	0.52		
ECOG performance status	1.88 (1.28–2.76)	< 0.01	1.89 (1.27–2.83)	< 0.01
No. of previous systemic treatments	1.31 (0.99–1.75)	0.06		
Baseline Hb	0.71 (0.58–0.86)	< 0.01	0.71 (0.58–0.86)	< 0.01
Baseline PSA	1.00 (1.00–1.00)	0.15		
Baseline tALP	1.001 (1.000–1.001)	0.03		

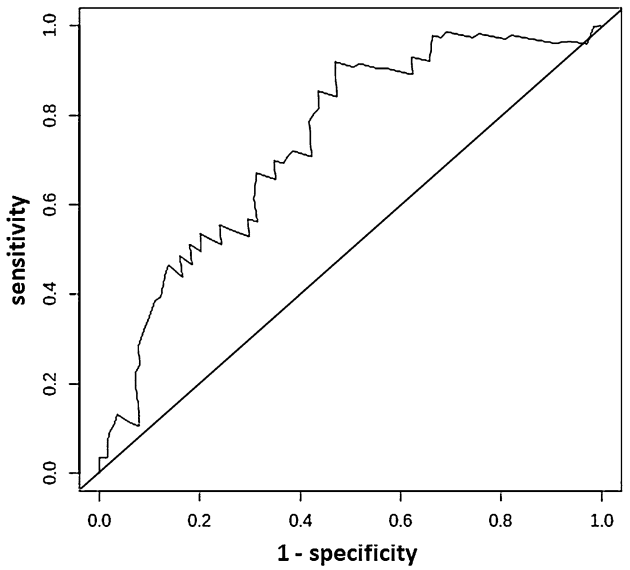


Fig. 2 ROC curve for baseline tALP value

U/l ($n = 46$, 50%) showed a median OS of 14 months (95% CI 11 months-NE) while for patients with baseline tALP levels ≥ 226 U/l ($n = 46$, 50%) the median survival was 7 months (95% CI 6–11 months). This subgroup stratification showed a hazard ratio of 2.291 (95% CI 1.237–4.241) with a $p = 0.008$. Given the significant predictive value found for baseline tALP, a time-dependent ROC curve was built to evaluate the strength of this biomarker as a baseline predictor for survival (Fig. 2). For this value, an AUC of 74% was found. To determine reliable baseline predictive factors for survival in patients receiving ^{223}Ra treatment, we produced a predictive score. We tried all possible variable combinations after dividing into opportune classes, and found that the best score (maximizing the AUC) was obtained by combining baseline ECOG PS (0: 0 points, 1: 1 point, 2–3: 2 points) with Hb < 12 g/dl (1 point) and PSA ≥ 20 ng/ml (1 point). This resulted in a score ranging from 0 to 4 (Table 3), with AUC 78.4% ($p < 0.001$). Notably, inclusion of tALP did not lead to increase in AUC; on the contrary, it was obtained with the PSA value more or less 20 ng/ml which did not show significant results in the univariate analysis. The choice of the parameters and their combination was exclusively based on statistical criteria, with the aim of determining the parameters' configuration capable of providing the highest value of AUC. The entire cohort was stratified into five subgroups on the basis of this 3-variable predictive score (3-PS) so obtained; the estimated overall survival for each subgroup is reported in Table 4. An evaluation of the

Table 3 3-variable predictive score scoring system

	3-variable predictive score
Baseline ECOG PS	
0	0
1	1
≥2	2
Baseline PSA	
<20 ng/ml	0
≥20 ng/ml	1
Baseline Hb	
≥ 12 g/dl	0
< 12 g/dl	1

Table 4 Subgroup analysis of survival with 3-variable predictive score cohort stratification

3-variable predictive score	Patients ($n = 92$)	Overall survival	95% CI
0	6	> 31 months	(> 31 to > 31)
1	18	> 31 months	(7 to > 31)
2	23	11 months	(7 to > 31)
3	32	9 months	(7 to > 31)
4	13	4 months	(2 to > 31)

association between serum biomarkers' trend during treatment and survival was then performed. A linear association between PSA trend and OS was found although this could not reach the significance threshold ($p = 0.0528$). Notably, tALP trend during ^{223}Ra treatment was found to be significantly associated with OS ($p = 0.0004$), with an increased risk of death in patients characterized by a rising trend of tALP values. Due to the heavily skewed distribution of PSA values in our cohort, a logarithmic transformation was applied to this variable for the regression analysis. The baseline value of logPSA resulted significantly associated with OS at univariate analysis (HR = 1.20, 95% CI 1.02–1.43) with a $p = 0.033$, whereas the lack of correlation between logPSA trend during treatment and survival was confirmed ($p = 0.0528$).

Discussion

In mCRPC patients treated with ^{223}Ra, several baseline prognostic markers associated with survival have been proposed such as Eastern Cooperative Oncology Group (ECOG) Performance Status, tALP, Hb value and the number of prior systemic treatments. Nonetheless, no predictive clinical variable assessing ^{223}Ra therapeutic benefit has been currently identified [18].

Furthermore, it is known that the effectiveness of the treatment on survival is obtained after at least five administrations of ^{223}Ra [12], as a consequence, the ability to stratify the expected survival for the subjects during the treatment period is of primary importance.

Whilst tALP is currently under evaluation as a potential predictive biomarker in patients receiving ^{223}Ra therapy, both ALSYMPCA trial and reports from the Expanded Access Programs assessed that PSA does not provide accurate information on the effectiveness of ^{223}Ra treatment. In fact, on the one hand, the minor decline in PSA level recorded during ^{223}Ra therapy could be related to the fact that ^{223}Ra mechanism of action is predominantly directed at bone metastasis microenvironment, rather than at prostate cancer cells [19]. On the other hand, an increase in PSA value during treatment may result from the onset of visceral metastases, not influenced by ^{223}Ra dynamics. Furthermore, a recent report exposed that ^{223}Ra treatment can be associated with a PSA "flare phenomenon", similar to other anticancer drugs [20]. It is now clear that, due to its complex trend, PSA should not be considered as a reliable biomarker to guide therapeutic decisions in patients receiving ^{223}Ra treatment. A recent exploratory analysis on LDH, PSA and tALP dynamics during ^{223}Ra treatment concluded that tALP decline at 12 weeks may be used as an early pharmacodynamic marker to monitor treatment, but changes in tALP did not meet statistical requirements as surrogate marker for survival [21]. A recent analysis from the ALSYMPCA study [22] showed significant differences between the ^{223}Ra-treated group and placebo for tALP reduction, normalization and median time to tALP increase. Baseline levels of tALP do not correlate with the efficacy of ^{223}Ra; therefore, baseline tALP values have no predictive value. ^{223}Ra has been shown to increase OS both in patients with baseline tAL $p < 220$ U/l and in those with values > 220 U/l. In our series, we substantially confirmed these data by assuming a reference value of 226 U/l.

However, there are indications of a correlation between pre-treatment tALP levels (≥ 146 U/l) and increased risk of death, time to progression, skeletal-related events, and bone marrow failure, which suggests a prognostic value for baseline tALP [23]. Indeed, a retrospective analysis of data from the registrational ALYMPCA trial [22] showed that patients treated with ^{223}Ra and with confirmed decline in tALP at week12 had significantly longer OS (median 17.8 vs 10.4 months for patients with vs without tALP decline). A decrease in total and bone ALP (post-treatment vs pre-treatment) was also observed by Nome et al., which is thought to be related to the killing and/or stunning effect of ^{223}Ra deposition in sites of increased osteoblastic activity [24]. In patients treated with ^{223}Ra, a twofold increase in the risk of progression has been reported for patients with initial PSA levels > 10 ng/mL; these, however, did not significantly correlate with other outcome variables [25]. The overall number of delivered ^{223}Ra therapy cycles was also related to decreased tALP levels, as well as significantly better pain scores. The 3-PS baseline evaluation we propose in this paper is strongly associated with the overall survival of the patients. It takes into account, at the same time, the majority of parameters commonly used in clinical practice for mCRPC evaluation, such as ECOG PS, PSA and Hb, all at baseline. Multidimensional clinical evaluation is certainly the most conceptually appropriate approach, allowing to evaluate the best pharmacological approach, individualized in each patient by maximizing clinical outcomes and optimizing healthcare costs. In fact, it should be underlined that the estimated survival with the 3-PS in patients with a baseline score of 3 or 4 would be rarely associated with a completion of the six scheduled administrations of ^{223}Ra treatment, thus not allowing the survival advantage offered by ^{223}Ra, when properly used. Our experience confirms literature data that state that tALP is the most reliable marker currently available in evaluation during treatment.

However, one aspect to be taken into consideration is the role played by the PSA, which although ineffective as a single disease predictor results in more powerful multiparametric assessment than tALP, which confirms its statistical significance as a single predictor, but resulted less effective than the 3PS we propose.

To our knowledge this is the first study examining the possibility of predicting survival in patients treated with ^{223}Ra through a multidimensional approach that takes into account multiple clinical and laboratory parameters.

The limited number of our sample does not allow us to draw definitive conclusions; in fact, our data need to be confirmed on a larger number of cases.

Another limitation of this study may derive from patients' therapeutic history, considering that previous systemic therapy, especially chemotherapy, might impact on overall survival and it, almost partially, might reflect general health condition of the patients rather than the effect of ^{223}Ra treatment, but just considering the different therapeutic pathways and the different compliances to various therapies, appear necessary to have a simple and reliable method of punctual prognostic stratification for every subject candidate to ^{223}Ra treatment, regardless of its history.

Our follow-up period ends at 31 months after starting therapy, so the data presented should be considered in terms of the hope of completing the treatment with ^{223}Ra, while longer time frames and larger sample sizes are needed to be able to draw conclusions in terms of overall survival.

However the 3-PS evaluation model seems to be a promising tool, helpful in the identification of mCRPC patients that are most likely to benefit from a ^{223}Ra treatment planning in clinical routine.

Conclusion

Literature data show that ^{223}Ra therapy demonstrates maximum effectiveness only in those who are able to receive almost all of the six doses provided by the current treatment scheme. It, therefore, appears evident that there is a need to stratify the patients at the time of enrollment for ^{223}Ra treatment to select patients suitable to fully benefit from this therapeutic approach. We propose a multidimensional clinical evaluation to select those mCRPC subjects suitable to receive the maximum benefit from ^{223}Ra treatment. This approach promises to enhance the treatment effectiveness along with cost optimization.

Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

Human and animal rights statement This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all patients.

References

1. Berthold DR, Pond GR, Roessner M, et al. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. Clin Cancer Res. 2008;14:2763–7. https://doi.org/10.1158/1078-0432.CCR-07-0944.
2. Stein WD, Gulley JL, Schlom J, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. Clin Cancer Res. 2011;17:907–17.
3. Fossa SD, Vaage S, Letocha H, et al. Liposomal doxorubicin (Caelyx) in symptomatic androgen-independent prostate cancer (AIPC)—delayed response and flare phenomenon should be considered. Scand J Urol Nephrol. 2002;36:34–9.
4. Scher HI, Heller G, Molina A. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COA-AA-301, a randomized double-blind, placebo controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. J Clin Oncol (Meet Abstr). 2011;29:LBA4517.
5. De Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res. 2008;14:6302–9.
6. Scher HI, Morris MJ, Basch E, et al. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol. 2011;29:3695–704.
7. Nilsson S, Franzen L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007;8:587–94.
8. Sonpavde G, Pond GR, Berry WR, et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. Urol Oncol. 2012;30:607–13.
9. Fizazi K, Massard C, Smith M, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration resistant prostate cancer. Eur Urol. 2015;68(1):42–50. https://doi.org/10.1016/j.eururo.2014.10.001.
10. Baldari S, Boni G, Bortolus R, et al. Management of metastatic castration-resistant prostate cancer: a focus on radium-223. Opinions and suggestions from an expert multidisciplinary panel. Crit Rev Oncol Hematol. 2017;113:43–51. https://doi.org/10.1016/j.critrevonc.2017.03.001.
11. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 2005;6:392–400.
12. Sartor O, Coleman RE, Morris MJ, et al. Baseline characteristics, number of radium-223 dichloride (radium-223) injections, and overall survival (OS) in US Expanded Access Program (EAP) and ALSYMPCA. In: 26th International prostate cancer update meeting; 2016. https://doi.org/10.1016/S0959-8049(16)31349-1.
13. Vogelzang NJ, Fernandez DC, Morris MJ, et al. Radium-223 dichloride (Ra-223) in US expanded access program (EAP). 2015 Genitourinary Cancers Symposium. J Clin Oncol. 2015;33(suppl 7; abstr 247).
14. Morris MJ, Sartor AO, Vogelzang NJ, et al. Effect of radium-223 dichloride (Ra-223) on pain from US EAP. 2015 Genitourinary Cancers Symposium., J Clin Oncol. 2015;33(suppl 7; abstr 160).
15. Yin L, Hu Q, Hartmann RW. Recent progress in pharmaceutical therapies for castration-resistant prostate cancer. Int J Mol Sci. 2013;14(7):13958–78.

16. Xofigo (radium Ra 223 dichloride) injection, for intravenous use [package insert]. Wayne; Bayer HealthCare Pharmaceuticals Inc; 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf.
17. Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer. 1988;61(1):195–202.
18. Du Y, Carrio I, De Vincentis G, et al. Practical recommendations for radium-223 treatment of metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2017;44(10):1671–8.
19. Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. Clin Cancer Res. 2017. https://doi.org/10.1158/1078-0432.CCR-16-2955.
20. De Vincentis G, Follacchio GA, Frantellizzi V, et al. Prostate-specific antigen flare phenomenon during 223Ra-dichloride treatment for bone metastatic castration-resistant prostate cancer: a case report. Clin Genitourin Cancer. 2016;14(5):e529–e533. https://doi.org/10.1016/j.clgc.2016.04.014.
21. Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. Ann Oncol. 2017;28(5):1090–7. https://doi.org/10.1093/annonc/mdx044.
22. Parker C, Nilsson S, Heinrich D, et al. ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213–23. https://doi.org/10.1056/NEJMoa1213755.
23. Gravis G, Boher JM, Fizazi K, et al. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. Eur Urol. 2015;68(2):196–204.
24. Nome R, Hernes E, Bogsrud TV, et al. Changes in prostate-specific antigen, markers of bone metabolism and bone scans after treatment with radium-223. Scand J Urol. 2015;49(3):211–7.
25. Etchebehere EC, Araujo JC, Milton DR, et al. Skeletal tumor burden on baseline 18F-fluoride PET/CT predicts bone marrow failure after 223Ra therapy. Clin Nucl Med. 2016;41(4):268–73.