Article Type

Original study

Title

Fracture risk in men with metastatic prostate cancer treated with radium-223

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Disclosures

CCP reports receiving honoraria from Bayer, Janssen and Clarity; and speaker fees from Janssen. HT reports grants received to institution to support salary from Pfizer, Janssen-Cilag Ltd, Merck, Astra Zeneca and Clovis. JS reports travel expenses received from Bayer. AT reports receiving honoraria and travel expenses from Bayer, Elekta, Ferring, Genesis Healthcare, Janssen and Astellas; and research funding from Accuray, Varian and Elekta. PC reports grants received to institution to support salary from Bayer and Astra Zeneca. EH reports grants from Cancer Research UK, Janssen-Cilag, Kyowa Hakko UK, Alliance Pharma (previously Cambridge Laboratories), Aventis Pharma Limited (Sanofi), and Accuray Inc; and grants and non-financial support from Astra Zeneca, Merck Sharp & Dohme, Bayer. All remaining authors have declared no conflicts of interest.

MicroAbstract

Radium-223 increases the risk of fracture in combination with abiraterone and prednisolone. Fracture risk of radium-223 monotherapy is unclear. This prospective study assessed fracture incidence in men treated with radium-223, matched with a cohort who did not have radium-223. 74 new fractures were identified in 20/36 patients receiving radium-223. Most fractures occurred in bones without apparent metastases. Bone health agents should be mandatory before starting radium-223.

Abstract

Background: Radium-223 is a bone-seeking, alpha-emitting radionuclide used in metastatic castration resistant prostate cancer (mCRPC). Radium-223 increases the risk of fracture when used in combination with abiraterone and prednisolone. The risk of fracture in men receiving radium-223 monotherapy is unclear.

Patients and Methods: Prospective, multicentre phase II study of radium-223 in 36 men with mCRPC, and a reference cohort (n=36), matched for fracture risk, not treated with radium-223. Bone fractures were assessed using whole body MRI (WB MR). The primary outcome was risk of new fractures.

Results: 36 patients were treated with up to six 4-weekly cycles of radium-223. With a median follow-up 16.3 months, 74 new fractures were identified in 20 patients. Freedom from fracture was 56% (95% CI: 35.3-71.6) at 12 months. On multivariate analysis, prior corticosteroid use was associated with risk of fracture. In the reference cohort (n=36), 16

new fractures were identified in 12 patients over median 24 months follow-up. 67% of all fractures across both cohorts occurred at uninvolved bone.

Conclusions: Men with mCRPC, and particularly those treated with radium-223, are at risk of fracture. They should receive a bone health agent to reduce risk of fragility fractures.

Keywords: fractures, prostate cancer, radium-223, skeletal-related events

Introduction

Radium-223 is a bone-seeking, alpha-emitting radionuclide that is approved for use in men with metastatic castration resistant prostate cancer (mCRPC). The ALSYMPCA trial showed that radium-223 improves both overall survival and time to skeletal-related events[1]. Subsequently, the ERA-223 trial, which compared abiraterone and prednisolone plus radium-223 versus abiraterone and prednisolone plus placebo, found a substantially increased risk of fracture in patients randomised to abiraterone and prednisolone plus radium-223[2]. In ALSYMPCA, the proportion of patients reporting a pathologic fracture was 4% for radium-223, and 5% for placebo. In ERA-223, the risk of fracture within 12 months was 23% for abiraterone and prednisolone plus radium-223, compared with 7% for abiraterone and prednisolone plus placebo. The explanation for the contrasting results of these two trials remains uncertain.

One hypothesis is that radium-223 increases the risk of fracture only if used in combination with other agents that have an adverse effect on bone health, such as abiraterone and prednisolone[3]. An alternative explanation relates to the frequency of imaging in the two trials: In ALSYMPCA, imaging was done according to clinical need, and not mandated at regular intervals. In ERA-223, CT and bone scans were done 3-monthly. It is possible that radium-223 increases the risk of fracture, even when used as a single agent, but that this was not observed in ALSYMPCA because of the lack of routine imaging.

We have conducted a prospective phase II study (REASURE) of radium-223 used as a single agent, incorporating routine whole body (WB) MRI, in men with mCRPC. The primary objective of the study was to evaluate treatment response by WB diffusion-weighted MRI[4]. Here, we present an exploratory analysis of the risk of fracture during and after treatment.

The objective of this exploratory analysis was to describe the risk of fracture in men receiving radium-223 as a single agent. We also assessed, as a benchmark, the fracture risk in a similar cohort of men with mCRPC, imaged in the same way, but who did not receive radium-223.

Methods

Patients with chemotherapy-naïve, bone-only, progressive mCRPC were enrolled in a prospective study of radium-223. They received treatment with radium-223 every 4 weeks for up to 6 cycles. Patients were randomised to one of two dose-levels, 55 or 88 kBq/kg. Whole body MRI scans were done at baseline, at cycle 2 and 4, and 1 month post-treatment. During the follow-up period, patients were evaluated every 4 months for 1 year, following which imaging was done according to routine clinical practice and scans were collected and reviewed centrally. Whole body MRI protocol included standard T1 weighted (T1W) and T2W sagittal spine supplemented by axial T1W Dixon, T2W HASTE and diffusion weighted imaging (DWI) sequences. The presence of a fracture was determined on T1W and T2W sequences; the differentiation between the malignant cause / non-malignant cause (presumed osteoporotic) was done using all available sequences including DWI and T1 Dixon derived fat fraction [5-9].

The REASURE trial was registered (ISRCTN17805587), approved by the NRES Committee London – Surrey Borders Research Ethics Committee (14/LO/1385), co-sponsored by The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, and conducted in accordance with the principles of good clinical practice. All the participants provided written informed consent prior to study entry. The Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU; London, UK) coordinated the study.

We also identified a separate reference cohort of men with mCRPC treated at the Royal Marsden Hospital, not treated with radium-223, to act as a benchmark for the fracture rate. This cohort was used in order to provide an estimate of the fracture rates among patients with similar disease pattern, utilization of bone-health agents, and corticosteroid usage compared to the REASURE population. Moreover, the extracted cohort also had regular use of WB MRI during follow-up. Scans were done as part of routine clinical practice, with a median time between scans of approximately 5 months. The use of this reference cohort was approved by the Committee for Clinical Research (CCR) of The Institute of Cancer Research and Royal Marsden Hospital.

The scans were reviewed by a radiologist experienced in mCRPC. Fractures were identified on whole body MRI in correlation with all other imaging available and the underlying bone was assessed as malignant or uninvolved depending on MRI appearances.

Statistical methods

Fractures identified prior to starting treatment were not included in analyses. All subsequent imaging tests were used for fracture assessment. Time to new fracture was calculated from the date of randomisation in REASURE to the first scan showing a new fracture. Time to fracture was presented using Kaplan Meier curves and association with other variables assessed via log-rank tests and Cox-Proportional Hazards models. The reference cohort was used as a benchmark only; no formal comparisons were made between the REASURE trial population and the reference cohort.

Results

Between July 2015 and June 2017, thirty-nine patients were randomised in a 1:1 ratio between the radium-223 dose levels. Three patients were excluded from analysis of fractures: two due to unmet eligibility criteria and one due to poor MRI tolerance, leaving 36 evaluable patients. In the evaluable population, median age was 75 years (IQR: 72-80). Baseline patient characteristics are demonstrated in table 1. Of note, bone health agents were used in only four (11%) patients. Eight patients (22%) were previously treated with abiraterone or enzalutamide. Patients have been followed up for a median of 16.3 months (IQR: 5.8 – 26.1).

Out of 36 evaluable patients, 20 (56%) completed 6 cycles of radium-223, while the remaining 16 had early discontinuation due to disease progression. Median number of treatment cycles among patients who discontinued early was 4 (table 2).

In total, 205 imaging scans after starting radium 223 were evaluated. Overall, 74 new fractures were identified in 20 (56%) patients. Freedom from fracture was 79% (95% CI: 61.1-89.6) at 6 months and 56% (95% CI: 35.3-71.6) at 12 months (figure 1). Median time to first new fracture was 13.6 months (95% CI: 9.8-18.6). Most new fractures developed within the axial skeleton (table 3). Out of all fractures, 50 (68%) occurred at a site of uninvolved bone (table 3) (see example case in figure 2). Of the 20 patients who had new fractures, 10 (50%) had symptomatic fractures, 4 had asymptomatic fractures, and 6 had uncertain symptomatic status.

On univariate analysis, high disease burden and baseline alkaline phosphatase (ALP) were associated with risk of fracture. There was no significant association between radium-223

dose and risk of fracture (table 4). On multivariate analysis, prior corticosteroid use was the only variable to be significantly associated with risk of fracture.

Median age for the reference cohort (*n*=36) was 70 years (IQR: 63-74). Thirty-one (87%) were starting treatment with abiraterone or enzalutamide, 18 (50%) had prior corticosteroids, and 2 (6%) received bone health agents. The median follow up time for the benchmarking group was 24.0 months (IQR: 17.1 to 26.6). In total, 150 imaging scans were evaluated. Overall, 16 new fractures were identified in 12 (33%) patients. Out of all fractures, 10 (62%) occurred at a site of uninvolved bone.

Discussion

We observed a fracture risk at 1 year of 44% in men with mCRPC treated with radium-223 as a single agent. Most fractures were of uninvolved bone, not at the site of metastases. These data suggest that men with mCRPC receiving radium-223, are at high risk of fracture, and highlight the role of bone health agents for prevention of fragility fractures in these patients.

It was already known that radium-223, in common with other treatments for mCRPC[3,10], increases the risk of fracture when used in combination with abiraterone and prednisolone[2]. However, there has been a lack of evidence until now concerning the effect of radium-223 monotherapy on fracture risk. Our data suggests that radium-223 may also increase the risk of fracture when used as a single agent.

The majority of fractures (68%) were at sites of uninvolved bone, and not at the site of metastases. This is consistent with results from the ERA-223 trial in which 78% of fractures were at uninvolved sites[2]. This suggests that most fractures in these patients are related to

poor bone health (fragility fractures), rather than a direct consequence of bone metastases (pathologic fractures). This is supported by the observation that fracture risk was associated with prior use of corticosteroids, which are known to impair bone health.

The fracture rates reported in men with mCRPC receiving radium-223 vary widely from one study to another. In ALSYMPCA, fractures were seen in 4% versus 5% of patients receiving radium-223 or placebo, respectively[1]. In ERA-223, fractures were seen in 29% versus 11% of patients receiving radium-223 or placebo, respectively[2]. The more frequently imaging is performed, the greater the probability that fractures will be detected. It is not surprising that the fracture rates in ALSYMPCA were relatively low, given that imaging was only done if clinically indicated. We observed fractures in 56% of patients receiving radium-223 in REASURE, even higher than the rate seen in ERA-223. This may reflect the high frequency of previous use of corticosteroids, and the low use of bone heath agents in REASURE.

We observed fractures in 33% of our reference cohort of men with bony mCRPC, not treated with radium-223. This rate appears relatively high in comparison with previous studies, which may also reflect differences in the use of prior corticosteroids and bone health agents. In the PREVAIL trial, among patients receiving enzalutamide, fractures were seen in 12% (versus 8% for control arm)[11]. In the COU-AA-301 study, among patients receiving abiraterone and prednisolone, fractures were seen in 21% (versus 8% for control arm)[12]. In both of these trials, the use of bone health agents (25% in PREVAIL, and 45% in COU-AA-301) was higher than in REASURE. Given that the patient characteristics, and particularly the use of bone health agents, vary between studies, we believe that our reference cohort provides the most useful benchmark against which to interpret the risk of fracture in REASURE.

The main strength of REASURE is that it is the first prospective study of men treated with radium-223 monotherapy with the use of imaging at pre-specified intervals to enable assessment of fracture risk during and after treatment. However, it has several limitations. First, the observed fracture risk may be regarded as a worst-case scenario, given that only a small proportion of patients were receiving a bone health agent, and as many as half had received prior corticosteroids. Second, half of the patients received an escalated dose of radium-223 (88KBq/kg). However, their fracture risk did not differ from those receiving the standard radium dose (55Kbq/kg). Third, some of the fractures seen on imaging may not be clinically relevant. However, even if, as we found, only half of patients with fractures are symptomatic, the risk of new fracture in mCRPC patients treated with radium-223 remains clinically important. Fourth, regular imaging will result in earlier detection of asymptomatic fractures. This would be true regardless of the imaging modality (MRI (bone oedema), bone scan (osteoblastic reaction), CT (sclerosis)). Using bone scan or CT scan, care must be taken to avoid misinterpreting these fractures as new sites of disease. The advantage of DWMRI is that it both distinguishes fractures from disease progression, and that it allows timely differentiation between a malignant and non-malignant fracture

The magnitude of the difference in fracture risk between men receiving radium-223 in REASURE and those in the reference cohort should be interpreted with caution. Although the reference cohort was selected to be similar to the REASURE population with regards to major risk factors for fracture (prior corticosteroids, bone health agents), it was not a randomised comparison. The two groups may have differed with respect to other risk factors for fracture, such as age, duration of prior hormone therapy, smoking and alcohol intake. The frequency of scans in the reference cohort was less than in REASURE, so

fractures may also have been detected later in the reference cohort. However, this would not affect the overall number of fractures detected over the whole observation period.

The study was not designed to assess the impact of bone health agents on fracture risk. However, bone health agents are known to reduce the risk of fracture in men with mCRPC, and it seems clear from the ERA-223 trial, and the early results from the PEACE 3 trial, that the use of bone health agents substantially reduces the risk of fracture in men treated with radium-223[13]. For example, in the radium-223 arm of ERA-223, fractures were seen in 15% versus 37% of those who were, or were not, on a bone health agent, respectively[2]. Taken together with our findings, we believe that it should now be mandatory to use a bone health agent in men treated with mCRPC, and particularly those receiving radium-223.

There remains uncertainty as to when bone health agents should be started, and what dose schedule should be used. Given that the aim of such treatment is to prevent fragility fractures, we believe that the use of bone heath agents should be similar to that in other populations at risk of fragility fracture, such as post-menopausal women. The ESMO Clinical Practice Guidelines recommend that men starting long-term androgen deprivation should be offered an oral bisphosphonate or be monitored with DEXA scanning, and treated according to the bone density results[14]. Our policy is to recommend the use of an oral bisphosphonate, such as alendronic acid, in men starting long-term androgen deprivation.

In summary, regular imaging with WB MRI shows that men with mCRPC, and particularly those treated with radium-223, have a high risk of developing new, predominantly non-malignant (osteoporotic) fractures. Men with mCRPC should receive a bone health agent to reduce their risk of fragility fractures.

Clinical Practice Points

- Radium-223, used in mCRPC, has been shown to increase the risk of fracture when used in combination with abiraterone and prednisolone, however the risk of fracture in men receiving radium-223 monotherapy is unclear.
- In this prospective study of radium-223, utilising regular imaging assessments, 36 men were assessed for fracture incidence. This was matched with 36 men not treated with radium-223, with a similar fracture risk, also having regular imaging assessments. 74 new fractures were identified in 20 (56%) patients receiving radium-223, and 16 new fractures were identified in 12 (33%) patients not receiving radium-223. 67% of all fractures across both cohorts occurred at uninvolved bone (i.e. non-pathological fractures).
- Men with mCRPC, particularly those receiving radium-223, are at risk of fracture and should receive a bone health agent to reduce the risk of fragility fractures

Acknowledgements

Grateful thanks to all the patients who participated in this study; all involved Investigators and staff at the participating centres; and trials unit staff at ICR-CTSU. We would also like to thank the REASURE Trial Management Group members past and present and the Independent Data Monitoring Committee and Trial Steering Committee for overseeing the trial.

Funding

This work was supported by Bayer via an investigator-initiated study grant. ICR-CTSU also receives programme grant funding from Cancer Research UK (Grant number: C1491/A15955, C1491/A25351). Trial recruitment was facilitated at participating sites by the National Institute for Health Research (NIHR)-funded National Cancer Research Network. This paper represents independent research supported by the National Institute for Health Research (NIHR) Biomedical Research Centre and the Clinical Research Facilities at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Table 1: Baseline patient characteristics

		REASURE Cohort						Reference Cohort	
		55 kBq/kg (*N*= 19)		88 kBq/kg (*N*= 17)		Total (*N*=36)		Total (*N*=36)	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Age	**Median (IQR)**	75.6 (73.0 – 80.1)		74.5 (72.6 – 78.1)		75.1 (72.8 – 79.5)		70.6 (63.1 – 73.9)	
Weight (kg)[a]	**Median (IQR)**	80.0 (70.0 – 91.0)		79.3 (70.6 – 101.6)		79.7 (70.2 – 91.3)		82.0 (73.0 – 92.0)	
	<80kg	9	47.4	9	52.9	18	50.0	17	47.2
	≥80kg	10	52.6	8	47.1	18	50.0	19	52.8
ALP (U/L)[a]	**Median (IQR)**	99.0 (73.0 – 235.0)		106.0 (94.0 – 128.0)		105.0 (83.5 – 174.5)		86.5 (65.0 – 152.5)	
	<220	13	68.4	16	94.1	29	80.6	31	86.1
	≥220	6	31.6	1	5.9	7	19.4	5	13.9
Bisphosphonate use[a]	**Yes[b]**	3	15.8	1	5.9	4	11.1	2	5.6
	No	16	84.2	16	94.1	32	88.9	34	94.4
Extent of bone disease	**<6 metastasis**	9	47.4	8	47.1	17	47.2	17	47.2
	6-20 metastasis	10	52.6	9	52.9	19	52.8	19	52.8
Prior corticosteroids	**No**	8	42.1	10	58.8	18	50.0	18	50.0
	Yes	11	57.9	7	41.2	18	50.0	18	50.0
Had fractures at baseline	**No**	17	89.5	15	88.2	32	88.9	32	88.9
	Yes	2	10.5	2	11.8	4	11.1	4	11.1

[a]Stratification factors at randomisation (REASURE cohort)

Table 2: Treatment compliance (REASURE cohort)

	55 kBq/kg (*N*= 19)		**88 kBq/kg (*N*= 17)**		**Total (*N*=36)**	
	n	**%**	***n***	**%**	***n***	**%**
Completed 6 cycles	**10**	**52.6**	**10**	**58.8**	**20**	**55.6**
Discontinued early	**9**	**47.4**	**7**	**41.2**	**16**	**44.4**
Number of cycles completed if discontinued early						
3	4	21.1	3	17.6	7	19.4
4	4	21.1	3	17.6	7	19.4
5	1	5.3	1	5.9	2	5.6

Table 3: Fracture location and distribution based on bone status [REASURE cohort] (involved vs. uninvolved by metastasis)

Location	**Patients** ***n* (%)**	**New fractures** ***n***	**New fractures at site of metastasis** ***n***
Spine	14 (38.9%)	49	15
Thorax	7 (19.4%)	19	4
Pelvis	4 (11.1%)	5	4
Extremities	1 (2.8%)	1	1
Total	20 (55.6%)	74	24

Table 4: Fracture risk in REASURE trial population: Cox regression analysis

	Univariate model			Multivariable model		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	***P*-value**
Treatment						
55kBq/kg	1	-	0.949	1	-	0.728
88kBq/kg	0.97	0.40 – 2.35		0.81	0.25 – 2.66	
Extent of bone disease						
< 6 metastasis	1	-	0.027	1	-	0.194
6 metastasis or more	3.00	1.12 – 8.04		2.21	0.66 – 7.37	
Weight						
<80kg	1	-	0.063	1	-	0.249
≥80kg	0.42	0.17 – 1.05		0.53	0.18 – 1.56	
ALP						
<220U/l	1	-	0.040	1	-	0.343
≥220U/l	5.92	1.22 – 28.74		2.58	0.37 – 18.09	
Bisphosphonates						
Yes	1	-	0.710	1	-	0.981
No	0.78	0.23 – 2.72		1.02	0.20 – 5.08	
Prior corticosteroids						
No	1	-	0.069	1	-	0.042
Yes	2.3	0.93-5.7		3.06	1.03-9.11	

*Estimates from the multivariable model were adjusted for treatment dose, extent of disease, weight, ALP levels, bisphosphonates use, time since diagnosis, time since bone metastases, cycles of radium and prior corticosteroid use.

Figure 1: Kaplan Meier curve for REASURE trial population

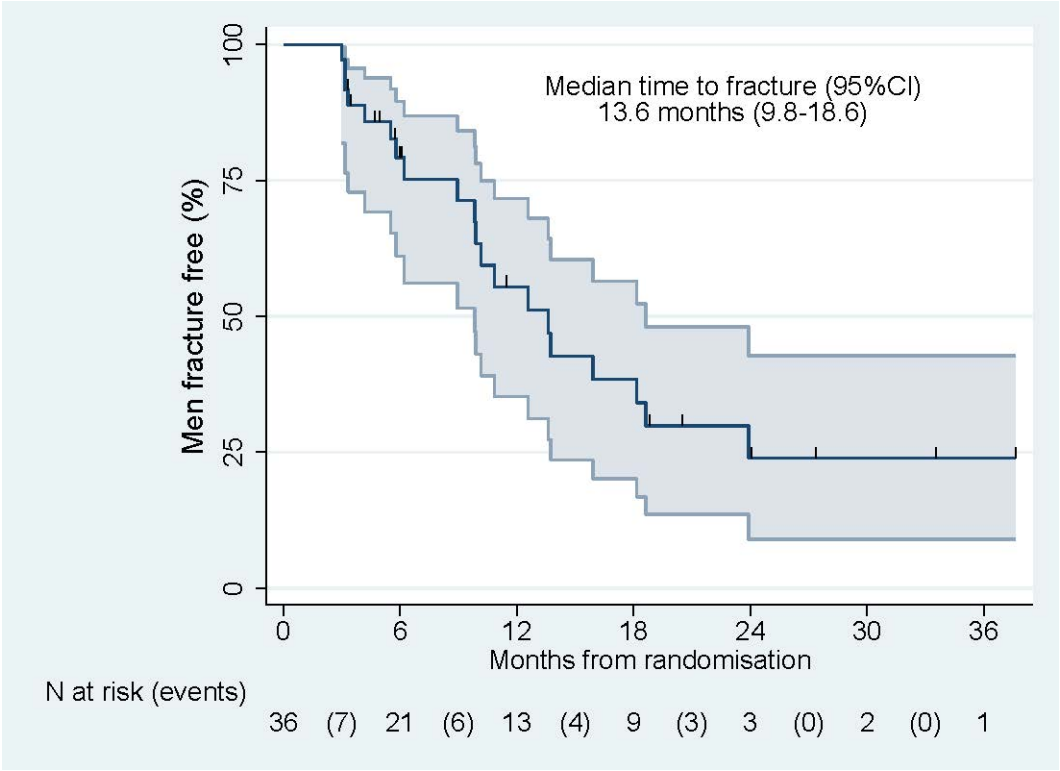

Figure 2: MRI images showing new fractures in a REASURE patient. Sagittal T2w composed spine images, in a 71 year old man with mCRPC, at baseline (a), and 2 years after 6 cycles of radium-223 (b). Follow-up images show multiple non-malignant endplate vertebral fractures at T7, T8, T9, T10, T12 and L4 (white arrows) with significant vertebral collapse at T10 and T12.