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ORIGINAL ARTICLE

Prostate Cancer

The safety of radium-223 combined with new-generation hormonal agents in bone metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis

Ming-Hao Wang*, Jin-Dong Dai*, Xing-Ming Zhang, Jin-Ge Zhao, Guang-Xi Sun, Yu-Hao Zeng, Hong Zeng, Nan-Wei Xu, Hao Zeng, Peng-Fei Shen

Patients with bone metastatic castration-resistant prostate cancer (mCRPC) might benefit from radium-223 (^{223}Ra) combined with new-generation hormonal agents (NHAs) in terms of survival and quality of life (QoL). However, the safety of combination therapies remains unclear. Therefore, we aimed to perform a network meta-analysis by reviewing the literature about the combination of ^{223}Ra with abiraterone acetate plus prednisone (AAP) or enzalutamide and to evaluate the safety of combination therapy in bone mCRPC patients. Ultimately, ten studies (2835 patients) were selected, including four randomized controlled trials (RCTs), five retrospective cohort studies, and one single-arm study. Overall, there was no difference in the incidence of fracture between the ^{223}Ra+NHA combination group and the ^{223}Ra monotherapy group (odds ratio [OR]: 1.46, 95% confidence interval [CI]: 0.91–2.34, $P = 0.66$), but the incidences in both the ^{223}Ra+NHA combination group (OR: 3.22, 95% CI: 2.24–4.63, $P < 0.01$) and the ^{223}Ra monotherapy group (OR: 2.24, 95% CI: 1.23–4.08, $P < 0.01$) were higher than that in the NHA monotherapy group. However, in the meta-analysis involving only RCTs, there was no difference between the ^{223}Ra monotherapy group and the NHA monotherapy group (OR: 1.14, 95% CI: 0.22–5.95, $P = 0.88$), while the difference between the ^{223}Ra+NHA combination group and the NHA monotherapy group remained significant (OR: 3.22, 95% CI: 2.24–4.63, $P < 0.01$). Symptomatic skeletal events (SSEs), SSE-free survival (SSE-FS), all grades of common adverse events (AEs), and ≥grade 3 AEs among all groups did not show any significant difference. Our results indicate that the combination of ^{223}Ra with NHAs was well tolerated in bone mCRPC patients compared to ^{223}Ra monotherapy, even though the incidence of fracture was higher in patients who received ^{223}Ra than that among those who received NHA monotherapy. More evidence is needed to explore the safety and efficiency of ^{223}Ra combination therapies.

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INTRODUCTION

The most common metastatic site of prostate cancer (PCa) is bone, with an incidence of nearly 75%. Bone metastatic lesions manifest symptoms and even cause pathological fractures, which not only seriously affect the quality of life (QoL) but also sometimes threaten the patient's life.[1,2] As a bone-seeking calcium mimetic, radium-223 (^{223}Ra) concentrates in osteogenic active sites and emits high-energy alpha particles to induce double-stranded DNA breaks to exert a therapeutic effect on osteogenic bone metastatic tumors.[3] In the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA; NCT00699751) clinical trial, ^{223}Ra prolonged the overall survival (OS) of patients with symptomatic bone metastatic castration-resistant prostate cancer (mCRPC) and delayed the occurrence of the first skeletal symptom event (SSE).[3] Therefore, ^{223}Ra was approved as one of the first-line therapies for symptomatic bone mCRPC by the Food and Drug Administration (FDA) of America in 2013.

In a recent study, combination therapies of ^{223}Ra with new-generation hormonal agents (NHAs), docetaxel, immunotherapeutic drugs, and polyadenosine diphosphate-ribose polymerase inhibitors (PARPis) have been extensively explored.[4] Among them, ^{223}Ra combined with NHAs, especially abiraterone or enzalutamide, has been widely investigated. Several studies showed that patients who received ^{223}Ra combined with abiraterone acetate plus prednisone (AAP) or enzalutamide had a longer survival time, a better QoL, and better tolerance to the combination therapy than those treated with ^{223}Ra alone.[5–14]

In contrast, the results of the phase 3 clinical trial (evaluation of radium-223 dichloride in combination with abiraterone in castration-resistant prostate cancer [ERA223]; NCT02043678) showed that the addition of AAP to ^{223}Ra was associated with an increased frequency of bone fracture and did not improve SSE-free survival (SSE-FS) or

Department of Urology, West China Hospital of Sichuan University, Chengdu 610041, China.
*These authors contributed equally to this work.
Correspondence: Dr. PF Shen (pfshen1@scu.edu.cn) or Dr. H Zeng (kucaizeng@163.com)
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OS compared to AAP monotherapy.[15] Therefore, the combination of ^{223}Ra with AAP is not recommended in the National Comprehensive Cancer Network and European Association of Urology guidelines. ^{223}Ra is always used after the failure of treatment with docetaxel or at least one novel antiandrogen receptor agent in clinical practice.[16,17] Whether the combination of ^{223}Ra and NHAs could lead to a worse outcome is still controversial. Therefore, we aimed to perform a network meta-analysis by reviewing the literature about the combination of ^{223}Ra with AAP or enzalutamide and to evaluate the safety of combination therapy in bone mCRPC patients.

MATERIALS AND METHODS

Literature search and inclusion criteria

The inclusion criteria were as follows: (1) enrolled patients were aged 18 years or older with histologically or cytologically confirmed bone mCRPC (with no restriction as to whether they were symptomatic or asymptomatic; without any visceral diseases but lymph node metastases were allowed and no matter the size); (2) patients in the study were classified as ^{223}Ra combined with NHAs versus ^{223}Ra or NHA monotherapy; (3) primary or secondary endpoints of the study included safety indicators, such as fracture, SSEs, and adverse events (AEs); and (4) retrospective studies, randomized controlled trials (RCTs), and ongoing clinical trials.

The following databases were searched for studies that fulfilled the above inclusion criteria: Web of Science, PubMed, Embase, Scopus, and American Society of Clinical Oncology (ASCO) conference proceedings. Literature was searched by using titles and abstracts. The search terms were ("radium-223" OR "ra-223") AND ("new-generation hormonal agents" OR "abiraterone" OR "enzalutamide") AND ("combined" OR "combination" OR "concomitant" OR "concurrent") AND ("castration-resistant prostate cancer" OR "CRPC"). The publication language was limited to English language publications, and the publication period was from the earliest available date to May 1, 2022.

Data extraction and quality assessment

Basic information (authors and year of publication), study design (prospective or retrospective), patient characteristics (prior treatment, baseline prostate-specific antigen [PSA] and alkaline phosphatase [ALP], performance status, and histology), treatment regimen (^{223}Ra combined with NHAs, ^{223}Ra monotherapy, and NHA monotherapy), the incidence of fracture, SSEs, SSE-FS, and the incidence of other AEs were collected by two reviewers independently (MHW and JDD). The two reviewers independently evaluated the quality of the selected articles based on the Newcastle–Ottawa scale (NOS), Jadad scale, and methodological index for nonrandomized studies (MINORS). Disagreements between the two reviewers were resolved by discussion with the third reviewer (PFS).

Treatment groups

Patients were categorized into three groups based on their treatment regimens. Since there were no significant differences in the incidences of fracture, SSEs, or other AEs in the studies that examined AAP or enzalutamide from the preliminary analysis, the two NHAs were combined in the final analysis. Patients were eventually assigned to the ^{223}Ra+NHA combination group, ^{223}Ra monotherapy group, or NHA monotherapy group.

Outcome measures

The primary outcomes included the incidence of fracture and the incidence of SSEs; the secondary outcomes included SSE-FS, other common AEs based on available data (fatigue, diarrhea, nausea, vomiting, constipation, anorexia, and hypertension), and ≥grade 3 AEs.

Data syntheses and analyses

A network meta-analysis was performed to compare the outcomes of the incidence of fracture, SSEs, and common AEs among the ^{223}Ra+NHA combination group, ^{223}Ra monotherapy group, and NHA monotherapy group. A paired meta-analysis was performed to compare all primary and secondary outcomes between combination therapy and monotherapy. RevMan version 5.4 (The Cochrane Collaboration, Oxford, UK) and R software version 4.1.2 (Lucent Technologies, Inc., Murray Hill, NJ, USA) were used for the meta-analysis.[18–23] Statistical heterogeneity was tested using the I^2 test. The results were expressed as the odds ratio (OR) with 95% confidence interval (CI) for dichotomous variables and as the weighted standard mean difference (SMD) with 95% CI for continuous variables. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Literature search and study selection

A total of 364 potentially relevant articles were identified from our search, and 10 articles (consisting of 2835 patients) were subsequently enrolled in the meta-analysis.[5–7,9,15,24–28] The detailed steps of the literature search are shown in **Supplementary Figure 1**. These articles included four RCTs, five retrospective cohort studies (RCSs), and one single-arm trial. All ten studies were included in the final analysis after the quality assessment, and the characteristics and results of the quality assessment of these ten studies are shown in **Table 1**. The net plot for the network meta-analysis is shown in **Supplementary Figure 2**.

Fracture

Overall, there was no difference in the incidence of fracture between the ^{223}Ra+NHA combination group and the ^{223}Ra monotherapy group (OR: 1.46, 95% CI: 0.91–2.34, $P = 0.66$; **Supplementary Figure 3**), but the fracture incidence in the ^{223}Ra+NHA combination therapy group (OR: 3.22, 95% CI: 2.24–4.63, $P < 0.01$) and the ^{223}Ra monotherapy group (OR: 2.24, 95% CI: 1.23–4.08, $P < 0.01$) was higher than that in the NHA monotherapy group (**Figure 1a**, and **Supplementary Table 1** and **Table 2**).[6,10,15,25,28] However, in the network meta-analysis of RCTs, there was no difference between the ^{223}Ra monotherapy group and the NHA monotherapy group (OR: 1.14, 95% CI: 0.22–5.95, $P = 0.88$), while the difference between the ^{223}Ra+NHA combination group and the NHA monotherapy group remained significant (OR: 3.22, 95% CI: 2.24–4.63, $P < 0.01$; **Figure 1b**, and **Supplementary Table 3** and **Table 4**).[6,15,25] Although there is a discrepancy, the results suggested that the increased fracture frequency might have been mainly associated with the use of ^{223}Ra, and the ^{223}Ra+NHA combination group did not significantly increase the fracture incidence compared to the ^{223}Ra monotherapy group.

SSEs and SSE-FS

There was no significant difference in the incidence of SSEs among all groups (**Figure 2**, and **Supplementary Table 1** and **Table 2**).[5,6,10,21,27,28] The pairwise comparison of SSEs and SSE-FS between the ^{223}Ra+NHA combination group and the ^{223}Ra monotherapy group did not yield significant differences (SMD: 0.11, 95% CI: −0.13–1.01, $I^2 = 80\%$, $P = 0.13$; **Supplementary Figure 3** and **4**).[6,27,28] This result suggested that the use of ^{223}Ra combined with NHAs did not cause a higher incidence of SSEs or shorter SSE-FS.

Table 1: Baseline and quality assessment of included studies

Study	*Study type*	Contrast setting	*Patient (n)*	*Disease stage*	*Prior treatment (n)*	*Median age (year)*	*Median PSA (ng ml^{-1})*	*Median ALP (U l^{-1})*	*Concomitant BPA (%)*	*Histology*	*Performance status (n)*	*Primary endpoint*	*Secondary endpoint*	*Median follow-up (month)*	*Quality assessment*
Dan *et al.*[24] 2017	RCS	^{223}Ra ^{223}Ra + AAP/ ENZ	11 14	mCRPC	Docetaxel (46) Aurora kinase inhibitor, antiprolactin receptor antibody, androgen biosynthesis inhibitor (orteronel), or mTOR inhibitor (8)	78 69	45 106.9	NR	NR	NR	Karnofsky median (80)	Hematologic adverse events	NR	6	NOS=7
Saad *et al.*[5] 2016	Single-arm trial	^{223}Ra ^{223}Ra + AAP/ ENZ	507 189	Bone-predominant mCRPC	Radiotherapy (490) Prostatectomy (159) Orchiectomy (32) Docetaxel (418) Abiraterone (277) Enzalutamide (56)	73 70	164.2 98.9	161 142	19	Gleason score: 2–4 (16) 5–7 (268) 8–10 (350) Missing (62)	ECOG: 0 (261) 1 (348) ≥2 (87)	Safety and OS	QoL	7.5	MINORS=21
Rathbun and Franklin[26] 2019	RCS	^{223}Ra ^{223}Ra + AAP/ ENZ	16 19	mCRPC	Abiraterone/ enzalutamide (33)	75	71	163	NR	Gleason score: 5–7 (13) ≥8 (17) Missing (5)	ECOG: 0 (2) 1 (20) 2 (10) 3 (3)	Predictive biomarkers of improved OS in a clinically advanced cohort	NR	NR	NOS=8
Smith *et al.*[15] 2019	RCT	^{223}Ra + AAP AAP	401 405	Bone-predominant mCRPC	Docetaxel (15) Ketoconazole (12) Enzalutamide (53) Sipuleucel-T (22)	71 71	30 31	129 121	39 42	Gleason score: <8 (140) ≥8 (246) Missing (15) Gleason score: <8 (154) ≥8 (233) Missing (18)	ECOG: 0 (262) 1 (137) Missing (2) ECOG: 0 (281) 1 (121) Missing (3)	SSE-FS	OS, time to opiate use for cancer pain, time to cytotoxic chemotherapy, rPFS, safety	21.2	JADAD=7
Tombal *et al.*[25] 2019	RCT	^{223}Ra + ENZ ENZ	76 84	Bone-predominant mCRPC	NR	NR	NR	NR	NR	NR	NR	rPFS	OS, SSE-FS, SSE incidence, AEs, QoL	63 (ongoing)	JADAD=NA
Shore *et al.*[9] 2020	RCS	^{223}Ra ^{223}Ra + AAP ^{223}Ra + ENZ	322 136 167	mCRPC	Abiraterone (269) Enzalutamide (292) Docetaxel (95) Cabazitaxel (28) Sipuleucel-T (32) Enzalutamide (43) Docetaxel (36) Cabazitaxel (4) Sipuleucel-T (13) Abiraterone (75) Docetaxel (33) Cabazitaxel (4) Sipuleucel-T (17)	73	38	108	50 61 60	NR	NR	SSE incidence	OS from diagnosis of mCRPC and from initiation of radium-223	9	NOS=7
Zhao *et al.*[27] 2021	RCS	^{223}Ra ^{223}Ra + AAP/ ENZ	198 120	Bone-predominant mCRPC	Docetaxel (121) Docetaxel (72)	70 68	115.4 77.7	147 132	34 33	Gleason grade: 1 (11) 2–3 (49) 4–5 (87) Unknown (55) Gleason score:	NR	OS	SSE incidence	25.3	NOS=8

Contd...

Table 1: Contd...

Study	*Study type*	Contrast setting	*Patients (n)*	*Disease stage*	*Prior treatment (n)*	*Median age (year)*	*Median PSA (ng ml^{-1})*	*Median ALP (U l^{-1})*	*Concomitant BPA (%)*	*Histology*	*Performance status (n)*	*Primary endpoint*	*Secondary endpoint*	*Median follow-up (months)*	*Quality assessment*
										1 (5) 2–3 (29) 4–5 (49) Unknown (33)					
Kim *et al*.[28] 2021	RCS	^{223}Ra ^{223}Ra + AAP/ ENZ	41 19	Bone-predominant mCRPC	Abiraterone (32) Enzalutamide (21) Docetaxel (14) Sipuleucel-T (11) Ketoconazole (4) Apalutamide (1) Cabazitaxel (1) Abiraterone (13) Enzalutamide (11) Docetaxel (5) Sipuleucel-T (5)	71 72	101 29	170 128	49 58	Gleason score: <8 (19) ≥8 (22) Gleason score: <8 (6) ≥8 (13)	ECOG: 0–1 (21) ≥2 (5) Missing (15) ECOG: 0–1 (14) ≥2 (3) Missing (2)	OS	PFS, SSE incidence, SSE-FS, incidence of drug-related AEs	13.3	NOS=7
Petrylak *et al*.[6] 2021	RCT	^{223}Ra ^{223}Ra + AAP ^{223}Ra + ENZ	19 22 22	Bone-predominant mCRPC	Docetaxel (5) Sipuleucel-T (4) Docetaxel (6) Sipuleucel-T (3) Docetaxel (3) Sipuleucel-T (5)	72 68 73	31 17 17	96 101 101	49 32 36	NR	ECOG: 0 (10) 1 (9) ECOG: 0 (13) 1 (9) ECOG: 0 (11) 1 (11)	BSLA RR at week 24	rPFS, SSE-FS, OS, safety	19 7 7	JADAD=4
Maughan *et al*.[7] 2021	RCT	^{223}Ra + ENZ ENZ	35 12	mCRPC	NR NR	71 NR	72.4 NR	98 NR	97 NR	NR	ECOG: 0 (17) 1 (18) NR	Safety, bone metabolism markers	PSA-PFS, rPFS, OS	22	JADAD=4

FS: free survival; RCS: retrospective cohort study; RCT: randomized controlled trial; ^{223}Ra: radium-223; ENZ: enzalutamide; AAP: abiraterone and prednisone; mCRPC: metastasis castration-resistance prostate cancer; PSA: prostate specific antigen; ALP: alkaline phosphatase; NR: not report; BPA: bone protect agent; OS: overall survival; ECOG: Eastern Cooperative Oncology Group; SSE: systematic skeletal event; PFS: progression-FS; BSLA RR: bone scan lesion area response rate; QoL: quality of life; NOS: Newcastle–Ottawa scale; MINORS: methodological index for nonrandomized study; JADAD: Jadad scale; AEs: adverse events; rPFS: radiologic progression-free survival; mTOR: mammalian target of rapamycin

Other AEs

Due to the control setting of the included studies, AEs of the hematopoietic system and ≥grade 3 AEs were only compared between the ^{223}Ra+NHA combination group and the ^{223}Ra monotherapy group. No significant differences in neutropenia (OR: 1.03, 95% CI: 0.47–2.26, $P = 0.93$), thrombocytopenia (OR: 0.92, 95% CI: 0.53–1.61, $P = 0.78$), anemia (OR: 0.72, 95% CI: 0.39–1.35, $P = 0.31$), and ≥grade 3 AEs (OR: 1.18, 95% CI: 0.86–1.61, $P = 0.31$) were observed between the two groups (**Figure 3**).[5,24,26,28] There were no significant differences in other common AEs among all groups (**Figure 4**, and **Supplementary Table 1** and **Table 2**).[5,6,24,26,28] Except for fractures and SSEs, the safety of ^{223}Ra+NHA combination therapy related to other AEs was not a concern.

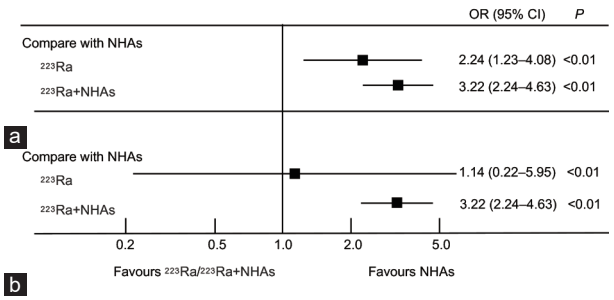

Figure 1: Forest plot of network meta-analysis in fracture. (**a**) Results from all included studies; (**b**) result from RCTs alone. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; RCTs: randomized controlled trials; OR: odds ratio; CI: confidence interval.

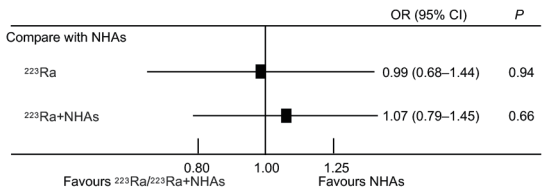

Figure 2: Forest plot of network meta-analysis in SSE. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; SSE: skeletal symptom events; OR: odds ratio; CI: confidence interval.

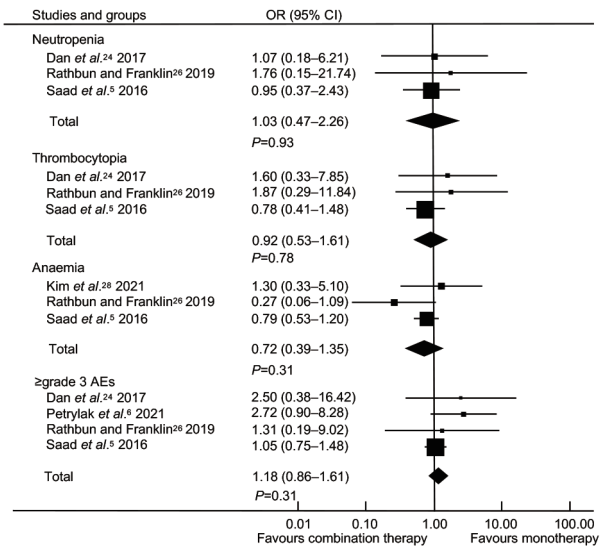

Figure 3: Forest plot of pairwise comparison between the ^{223}Ra+NHA combination therapy group and the ^{223}Ra monotherapy group in hematopoietic system AEs and ≥grade 3 AEs. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; OR: odds ratio; CI: confidence interval; AEs: adverse events.

Bone protection agents (BPAs)

Due to insufficient data, analysis of the protective effects of BPAs could not be performed, but several studies revealed the importance of BPAs. A retrospective study examined the effects of BPAs on fracture incidence. The incidence rates of fracture in all groups were 7% and 15% in patients with and without concomitant BPA use, respectively, and in the ^{223}Ra and AAP groups, the incidence rates were 11% and 31%, respectively.[9] In the ongoing randomized phase III EORTC-1333-GUCG/PEACE III trial (NCT02194842) of ^{223}Ra in combination with enzalutamide in mCRPC patients, the incidence of fracture in patients treated with ^{223}Ra plus enzalutamide after 1 year was 33% without BPA use, and it was as low as 3% in the patients with BPA. If BPA was used at least 6 weeks before the first dose of ^{223}Ra injection, the fracture incidence could be reduced to 0.[25] The protective effect of BPA on bone was particularly significant in mCRPC patients, especially when used with ^{223}Ra.

DISCUSSION

This meta-analysis evaluated the safety of the combination therapy of ^{223}Ra with NHAs based on published data. In general, ^{223}Ra combined with NHAs was well tolerated in bone mCRPC patients, and it did not increase the risk of fracture, SSEs, or other AEs, even though fracture incidence varied when different studies were included. In addition, the protective effect of BPA on fracture was particularly significant.

In our study, the results of the meta-analysis of RCTs were different from those of the meta-analysis of all studies relevant to fracture incidence. This may be caused by the limited number of studies and group settings. Most RCTs focus on the comparison between combination therapy and NHA monotherapy, and a total of 1029 patients were involved in the only RCT meta-analysis relevant to fracture incidence;[15,25] however, all patients (19 patients) in the ^{223}Ra monotherapy group were included in Petrylak *et al.*'s study.[6] Therefore, there was an obvious bias involving ^{223}Ra monotherapy. More studies should be conducted to explore the differences in fracture incidence among different treatments with or without ^{223}Ra.

In the ERA223 trial, patients treated with ^{223}Ra plus AAP had a fracture incidence of 29% compared to 11% in the AAP monotherapy patients after 12 months of follow-up, and the combination therapy caused the result to be taken for granted.[15] However, subsequently, the radium-223 evaluation of activity and surrogate response (REASURE; ISRCTN17805587) trial compared the fracture incidence between patients with or without ^{223}Ra with a 1-year follow-up, and the results showed that ^{223}Ra increased the fracture incidence from 33% to 56%.[29] Similarly, the results of our study also showed that the increasing fracture frequency was strongly associated with the use of ^{223}Ra and should not be attributed to combination therapy.

Previous androgen deprivation therapy (ADT) and concomitant prednisone might also increase the fracture incidence. A total of 78% of fractures in the ERA223 trial occurred at nonmetastasis sites, and a similar rate was observed in the REASURE study (68% of fractures occurred at nonmetastasis sites); such fractures were most likely due to osteoporosis.[15,29] All patients had previously received ADT, which has been confirmed to cause osteoporosis, and ADT was associated with a significantly increased risk of any fracture (OR: 2.83, 95% CI: 2.52–3.17).[30,31] Patients in the ^{223}Ra+NHA combination group also

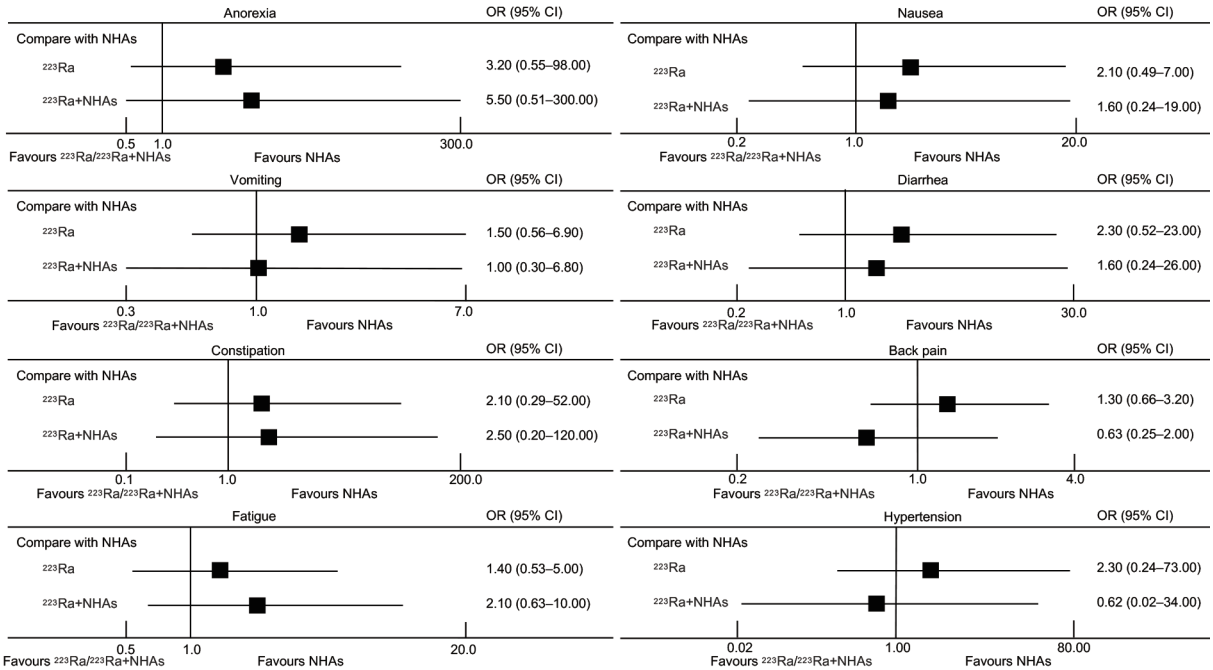

Figure 4: Forest plot of network meta-analysis in some common AEs. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; AEs: adverse events; OR: odds ratio; CI: confidence interval.

received prednisone or prednisolone, which was also shown to cause osteoporosis.[32] Therefore, it is necessary to improve osteoporosis and monitor bone density in patients treated with ^{223}Ra.

Compared to the ERA223 trial, the fracture incidence was much higher in the REASURE trial. This might be due to the BPA use rates in the REASURE trial, which were only 11% in the ^{223}Ra group and 6% in the control group compared to 39% and 42% in the ERA223 trial.[15,29] The ongoing PEACE III clinical trial also confirmed the importance of BPAs in mCRPC patients who received ^{223}Ra treatment. The dosage regimen of BPAs might have influenced its protective function.[25] In our study, a relevant meta-analysis was not conducted due to the impact of BPA administration timing on the fracture risk observed in the PEACE III trial and the unknown administration protocol of BPA in all studies that conducted BPA-related fracture risk.[25]

From the above outcomes, the destructive effect of ^{223}Ra, osteoporosis, underutilizing of BPAs, and prior treatment history might have been important reasons for the increased fracture incidence in patients treated with ^{223}Ra. Further clinical trials should be carried out on these influencing factors.

In addition to safety, the efficacy of ^{223}Ra combined with NHAs was also discussed in several studies, which should have been the primary measurement outcome of the combination therapy. While the survival benefit of the combination therapy is still controversial, compared with monotherapy, it has obvious advantages in curative effects against bone lesions.[6] Control of bone metastases can significantly impact OS in mCRPC patients.[33–35] Given the mechanism of ^{223}Ra and the results of the ALSYMPCA study, we should focus on the treatment efficacy of bone metastases when using ^{223}Ra.[3] Combination therapy might be better in patients with severe bone metastasis burden and symptomatic bone metastasis than in asymptomatic patients.

Moreover, two studies[5,9] divided combination treatment regimens into layered and concurrent regimens, but only Shore *et al.*[9] reported this categorization in detail. In that study, the concurrent group had a higher fracture incidence than the layered group, but they also achieved a longer OS. Given their impact on patient outcomes, these factors should be fully considered when conducting further clinical trials.

There are several limitations in our analysis. Due to the control settings and incomplete data, only a small number of studies were included in our meta-analysis, and the follow-up time and baseline characteristics of patients were not very uniform in these studies. Subgroup analysis related to some factors that may have influenced the results, such as BPA application, could not be performed due to incomplete data. These findings will be updated in the future once more relevant studies are published.

CONCLUSIONS

The combination therapy of ^{223}Ra with NHAs was well tolerated in bone mCRPC patients compared to ^{223}Ra monotherapy, even though the incidence of fracture was higher in patients who received ^{223}Ra than NHA monotherapy. Further evidence is needed on the safety and efficiency of ^{223}Ra combination therapy with different regimens, the use of bone protection agents, and prior treatment history.

AUTHORS CONTRIBUTIONS

MHW carried out the conceptualization, resources, writing, and editing. JDD carried out the data curation and review. XMZ carried out the data curation and review. JGZ, GXS, YHZ, Hong Z, and NWX carried out the data curation and resources. Hao Z and PFS carried out the review and edit. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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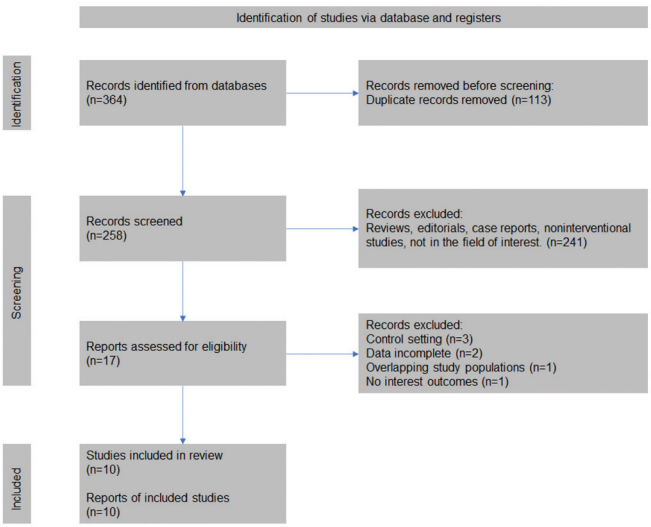
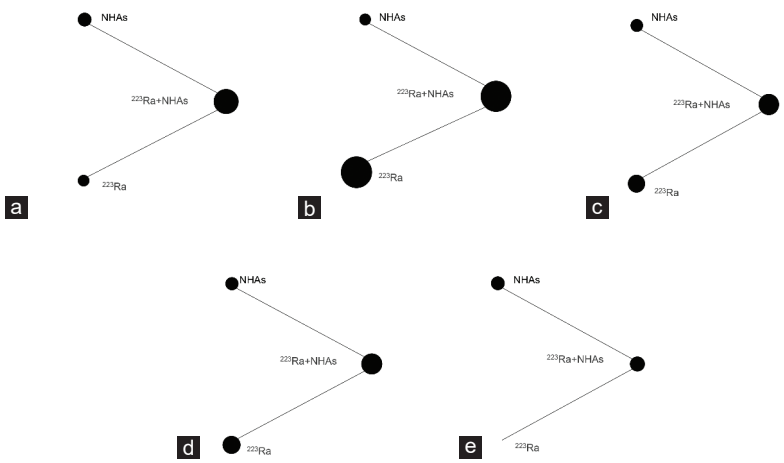
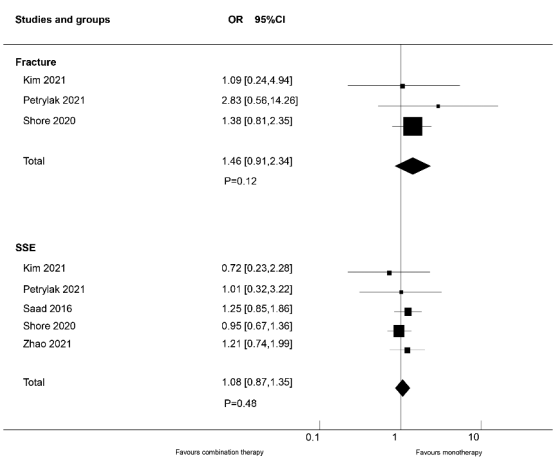


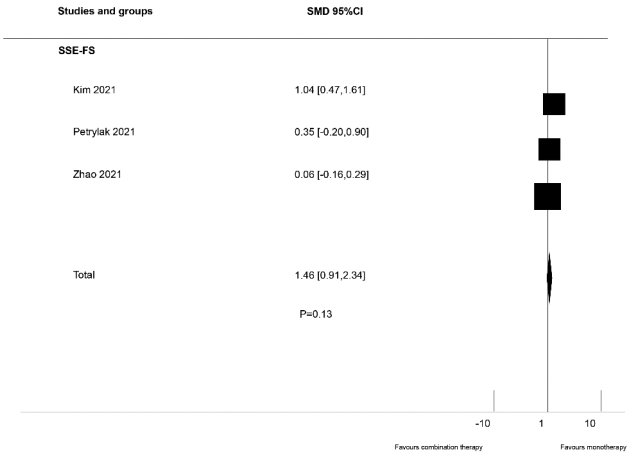
Supplementary Figure 1: PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.



Supplementary Figure 2: Net plot. (**a**) Net plot for fracture. (**b**) Net plot for SSE. (**c**) Net plot for fatigue, nausea, vomiting, constipation, and diarrhea. (**d**) Net plot for anorexia, hypertension, and back pain. (**e**) Net plot for fracture of RCT only analysis. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; SSE: skeletal symptom events; RCTs: randomized controlled trials.



Supplementary Figure 3: Forest plot of pairwise comparison between the ^{223}Ra+NHA combination therapy group and the ^{223}Ra monotherapy group in fracture and SSE. OR: odds ratio; CI: confidence interval; NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; SSE: skeletal symptom events.



Supplementary Figure 4: Forest plot of pairwise comparison between the ^{223}Ra+NHA combination therapy group and the ^{223}Ra monotherapy group in the SSE-FS. SMD: standard mean difference; CI: confidence interval; NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; SSE-FS: skeletal symptom event-free survival.

Supplementary Table 1: Results from network meta-analysis (league table)

Adverse outcomes	*Pairwise comparisons of outcomes among groups*		
Fracture	NHAs		
	0.45 (0.24–0.81)	^{223}Ra	
	0.31 (0.22–0.45)	0.70 (0.43–1.12)	^{223}Ra + NHAs
SSE	NHAs		
	1.01 (0.70–1.48)	^{223}Ra	
	0.93 (0.69–1.27)	0.92 (0.74–1.15)	^{223}Ra + NHAs
Fatigue	NHAs		
	0.48 (0.096–1.60)	^{223}Ra	
	0.72 (0.20–1.90)	1.5 (0.69–3.70)	^{223}Ra + NHAs
Anorexia	NHAs		
	0.18 (0.003–2.00)	^{223}Ra	
	0.30 (0.01–1.90)	1.70 (0.26–12.00)	^{223}Ra + NHAs
Nausea	NHAs		
	0.64 (0.06–4.10)	^{223}Ra	
	0.48 (0.06–2.00)	0.75 (0.21–2.50)	^{223}Ra + NHAs
Vomiting	NHAs		
	1.00 (0.15–3.3)	^{223}Ra	
	0.69 (0.15–1.70)	0.69 (0.31–1.70)	^{223}Ra + NHAs
Constipation	NHAs		
	0.37 (0.01–5.20)	^{223}Ra	
	0.44 (0.02–3.50)	1.20 (0.20–8.30)	^{223}Ra + NHAs
Diarrhea	NHAs		
	0.63 (0.04–4.30)	^{223}Ra	
	0.44 (0.04–1.90)	0.70 (0.19–2.90)	^{223}Ra + NHAs
Hypertension	NHAs		
	1.60 (0.03; 47.00)	^{223}Ra	
	0.43 (0.01–4.30)	0.27 (0.02; 2.20)	^{223}Ra + NHAs
Back pain	NHAs		
	1.60 (0.50–3.90)	^{223}Ra	
	0.77 (0.32–1.50)	0.48 (0.25–0.98)	^{223}Ra + NHAs

The value is OR and 95% CI, OR <1 favor the treatment in the column. NHAs: new-generation hormonal agents; SSE: symptomatic skeletal events; ^{223}Ra: radium-223; OR: odds ratio; CI: confidence interval

Supplementary Table 2: Results from network meta-analysis (rank probability)

Treatment	*Rank 1*	*Rank 2*	*Rank 3*
Fracture			
NHAs	0.88	0.11	0.01
^{223}Ra	0.12	0.81	0.07
^{223}Ra + NHAs	0	0.08	0.92
SSE			
NHAs	0.45	0.21	0.34
^{223}Ra	0.39	0.31	0.31
^{223}Ra + NHAs	0.16	0.48	0.35
Fatigue			
NHAs	0.80	0.14	0.06
^{223}Ra	0.04	0.12	0.84
^{223}Ra + NHAs	0.15	0.75	0.10
Anorexia			
NHAs	0.90	0.06	0.03
^{223}Ra	0.04	0.2	0.76
^{223}Ra + NHAs	0.05	0.74	0.21
Nausea			
NHAs	0.69	0.20	0.10
^{223}Ra	0.27	0.47	0.26
^{223}Ra + NHAs	0.03	0.33	0.64
Vomiting			
NHAs	0.49	0.34	0.16
^{223}Ra	0.47	0.38	0.15
^{223}Ra + NHAs	0.03	0.28	0.69
Constipation			
NHAs	0.70	0.16	0.14
^{223}Ra	0.17	0.3	0.53
^{223}Ra + NHAs	0.13	0.54	0.33
Diarrhea			
NHAs	0.68	0.23	0.09
^{223}Ra	0.29	0.47	0.24
^{223}Ra + NHAs	0.03	0.30	0.67
Hypertension			
NHAs	0.38	0.40	0.23
^{223}Ra	0.60	0.31	0.08
^{223}Ra + NHAs	0.02	0.29	0.69
Back pain			
NHAs	0.17	0.66	0.17
^{223}Ra	0.83	0.15	0.19
^{223}Ra + NHAs	0.01	0.19	0.81

NHAs: new-generation hormonal agents; SSE: symptomatic skeletal events; ^{223}Ra: radium-223

Supplementary Table 3: Results from only randomized controlled trials analysis in fracture (league table)

Adverse outcomes	*Pairwise comparisons of outcomes among groups*		
Fracture	NHAs		
	0.88 (0.17; 4.62)	^{223}Ra	
	0.31 (0.22; 0.45)	0.35 (0.07; 1.78)	^{223}Ra + NHAs

The value is OR and 95% CI, OR <1 favor the treatment in the column. NHAs: new-generation hormonal agents; ^{223}Ra: radium-223; RCTs: randomized controlled trials; OR: odds ratio; CI: confidence interval

Supplementary Table 4: Results from only randomized controlled trials analysis in fracture (rank probability)

Treatment	*Rank 1*	*Rank 2*	*Rank 3*	*PSCORE*
NHAs	0.02	0.45	0.54	0.2202
^{223}Ra	0.87	0.13	0.46	0.3315
^{223}Ra + NHAs	0.12	0.42	0.46	0.9484

NHAs: new-generation hormonal agents; ^{223}Ra: radium-223