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LETTER TO THE EDITOR

Considering bone health in the treatment of prostate cancer bone metastasis based on the results of the ERA-223 trial

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ERA-223, a phase III clinical trial, was conducted globally to investigate the usefulness of radium-223 (Ra-223) administered concurrently with abiraterone acetate and prednisolone (AAP) [1]. However, in this trial, the Ra-223 + AAP group did not exhibit increased survival and had a clearly higher incidence of bone fracture than the placebo + AAP group. In this paper, we would like to discuss the reasons why this study did not produce the anticipated outcomes, and how we should use Ra-223 in consideration of both efficacy and bone health.

Testosterone and its metabolic estrogen maintain bone health by preventing loss of bone mineral density. When serum estrogen decreases, the frequency of fracture rises [2]. Androgen-deprivation therapy (ADT) also induces loss of bone mineral density and muscle strength, leading to frailty and consequently increased frequency of fractures [3]. However, the antitumor effect of ADT outweighs its adverse effect on bone health, and for this reason it is considered an effective treatment for prostate cancer (Fig. 1a).

Administration of AAP for castration-resistant prostate cancer (CRPC) has been shown to improve survival [4]. However, in the COU-AA-301 clinical trial using AAP for docetaxel-refractory CRPC, AAP significantly increased the risk of pathological fracture compared to the control arm (prednisolone monotherapy) [4]. Abiraterone is a 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor, which results in even further depletion of serum testosterone and its metabolic estrogen. That is, although ADT alone usually worsens bone health, when combined with abiraterone, it may increase osteoclast activity, leading to even further deterioration in bone health. Moreover, inhibition of osteoblast activity by prednisolone, used together to prevent the side effects of abiraterone, could worsen bone health even more. However, the antitumor effect of ADT + AAP still outweighs the deleterious effects on bone health (Fig. 1b).

The ALSYMPCA trial showed significant improvement in prognosis with concurrent use of ADT with Ra-223 compared to ADT monotherapy. Radium-223 is an emitter of radioactive α-particles that, like calcium, is incorporated in the bone matrix at sites of active mineralization via osteoblasts. The emitted alpha particles irreversibly break double-strand DNA of prostate cancer cells near the bone matrix of the same site, thereby exerting an antitumor effect in bone metastases [5]. However, because Ra-223 also accumulates in normal bone matrix and inhibits osteoblast activity, it is considered an undesirable drug for bone health, like steroids. Nevertheless, the antitumor effect of Ra-223 combined with ADT still outweighs these negative effects on bone health (Fig. 1c).

In ERA-223, the concurrent use of Ra-223 with ADT and AAP did not improve overall survival (OS) [1]. Furthermore, the Ra-223 arm had an increased risk of bone fracture, especially in areas of bone without metastasis. Ra-223 with ADT and AAP concurrent therapy seemed to produce extremely poor bone health due to strong activation of osteoclasts by abiraterone, inducement of osteoblast apoptosis by Ra-223, and inhibition of osteoblast differentiation and maturity by prednisolone. Such extremely poor bone health might adversely affect patients' general condition. In these cases, the antitumor effect of the treatment might not outweigh the adverse effects of Ra-223 with ADT and AAP combination therapy. This might explain why OS did not improve and the frequency of bone fracture increased in the ERA-223 trial (Fig. 1d).

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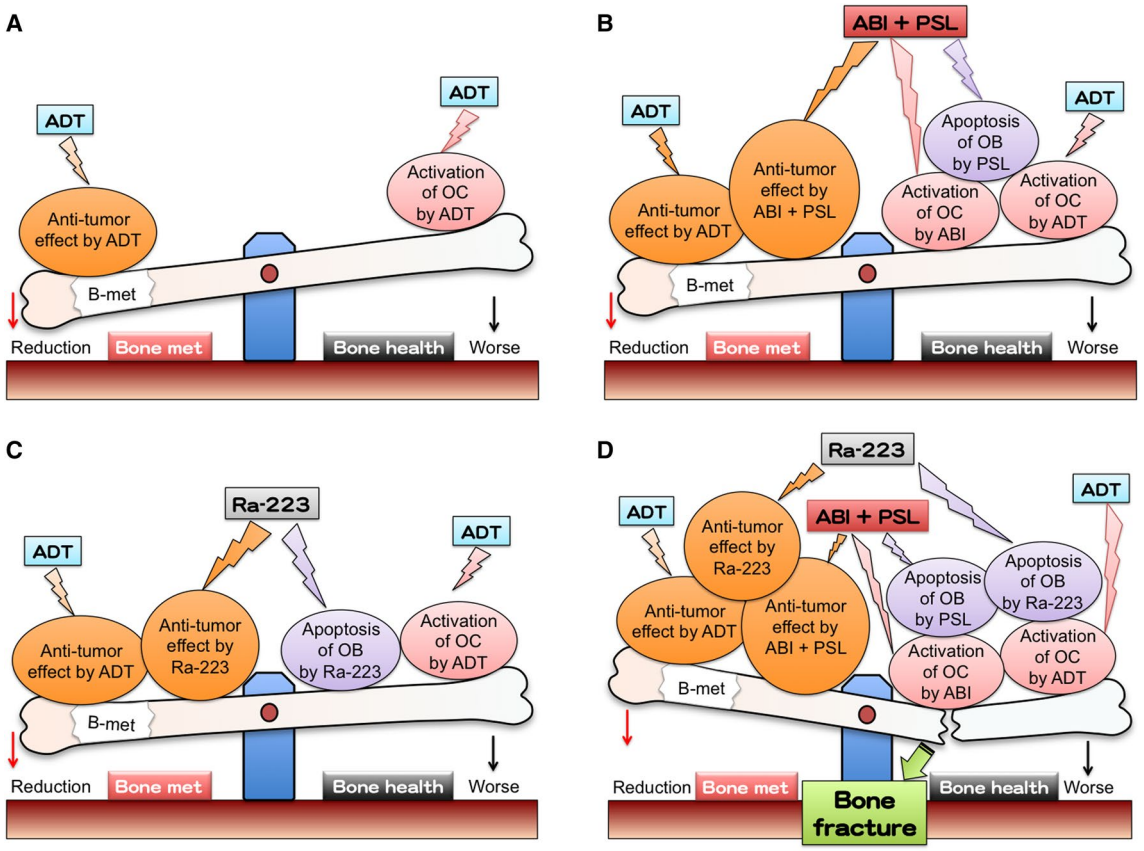

Fig. 1 Bone environment during hormonal therapy and/or Ra-223, and the countermeasures when physicians use Ra-223 in the treatment of bone metastases. **a** ADT and bone health, **b** ADT and abiraterone + prednisolone and bone health. **c** ADT and Ra-223 and bone health. **d** ADT, abiraterone + prednisolone, and Ra-223 and bone health, E. ADT and estrogen and bone health. *OC* osteoclast, *OB* osteoblast, *B-met* bone metastasis, *Ra-223* radium-223, *ADT* androgen-deprivation therapy, *ABI* abiraterone, *PSL* prednisolone

To solve the issue of increased bone fracture risk when using Ra-223, the authors of the trial recommended concurrent use of bone health agents (BHAs), such as bisphosphonates and denosumab [1], which inhibit differentiation and activation of osteoclasts. Recently, Tombal et al. reported that concurrent use of bone health agents (BHAs) on combination Ra-223 and enzalutamide treatment in metastatic CRPC patients decreased bone fracture risk (PEACE-III trial) [6]. However, it remains unknown whether the combination of Ra-223, enzalutamide, and BHAs has higher antitumor effect than the combination of enzalutamide and BHAs. Considering antitumor effects and bone health, estrogen might be an alternative drug candidate to use concurrently with Ra-223. Ethinylestradiol has in fact been shown to exhibit an antitumor effect for CRPC [7, 8]. Furthermore, a recent phase II study has reported that estrogen patches not only lower testosterone to castration levels in untreated advanced prostate cancer, but also improve bone density [9]. Of course, a prospective study is needed to demonstrate the activity of estrogen on both tumors and bone health in combination with Ra-223 in patients with mCRPC.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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