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Platinum Opinion

Higher Risk of Fragility Fractures in Prostate Cancer Patients Treated with Combined Radium-223 and Abiraterone: Prednisone May Be the Culprit

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Radium-223 dichloride (radium-223) is the first targeted α-particle therapy approved for treatment of patients with castration-resistant prostate cancer (CRPC). Since the drug has a specific targeted effect on bone metastases, the combination with modern hormone therapies is a reasonable and testable hypothesis.

The ERA 223 trial (NCT02043678) is a randomized phase 3 trial in which abiraterone, at the standard dose of 1000 mg daily plus 5 mg of prednisone twice daily, was administered in combination with radium-223 or placebo to asymptomatic or mildly symptomatic men with chemotherapy-naïve CRPC and bone metastases (>2 bone metastatic lesions).

The final results of this trial, recently presented at the 2018 European Society for Medical Oncology (ESMO) congress [1], show that addition of radium 223 to abiraterone plus prednisone failed to translate to an improvement in survival free from symptomatic skeletal events (SSEs), the primary endpoint of the study, with respect to abiraterone plus prednisone alone.

These data are quite unexpected, since a previous randomized phase 3 clinical trial (ALSYMPCA) [2] demonstrated that in a population of patients with symptomatic bone metastatic CRPC, administration of radium-223 was associated with a significant improvement in overall survival (OS) and a delay in time to first SSE when compared to placebo. Therefore, the ERA 223 results raise several questions. (1) Are these data influenced by a failure of increased antineoplastic efficacy of the addition of radium-223 to abiraterone or are they due to an increase in bone fragility? Stratifying the primary endpoint according to the event type, it should be noted that addition of radium-223 to abiraterone plus prednisone was associated with a lower proportion of spinal cord compression (5% vs 10%) and a lower need for bone radiation therapy (37% vs 42%), whereas there was an increase in the risk of bone fracture (18% vs 9%) [1]. Moreover, the majority of bone fractures in the radium-223 arm occurred in nonmetastatic bone sites, a finding that is consistent with the increase in bone fragility associated with radium-223 administration instead of disease progression in bone. (2) Why does radium-223 favor bone fragility? The previous randomized clinical trial [2] clearly showed that administration of radium-223 is associated with a reduction in osteoblast activity, as demonstrated by a significant decrease in bone alkaline phosphatase in the experimental arm. Therefore, radium-223 administration induces a bone remodeling imbalance favoring osteoclast activity. (3) Why then was the bone remodeling imbalance induced by radium-223 so detrimental in the ERA 223 trial? A plausible explanation is a negative interaction with abiraterone and/or prednisone. Abiraterone induces androgen depletion and thus increases bone fragility [3], but all the patients included in ERA 223 were already on androgen deprivation therapy and therefore serum testosterone levels were in the castration range, so it is unlikely that a further reduction in androgen levels induced by abiraterone could have influenced fracture risk. By contrast, addition of a glucocorticoid could result in excess bone fragility [4]. Prednisone administration during abiraterone therapy is needed to compensate drug-induced inhibition of glucocorticoid synthesis and prevent mineralcorticoid excess due to ACTH increase [5]. However, the dose of prednisone administered in this trial (eg, 5 mg twice daily) is excessive [6], especially considering that glucocorticoid administration, even at low doses, is associated with rapid bone loss and fragility. In fact, glucocorticoids negatively affect bone health via a complex mechanism that includes both a

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decrease in bone formation and an increase in bone resorption. Glucocorticoid-induced inhibition of bone formation involves multiple pathways, including a reduction in osteoblast proliferation via suppression of the growth factors BMP2 and TGFβ1 [7], upregulation of Wnt antagonists (Dkk-1, Wif-1, and Sost), and downregulation of the Wnt receptor complex (frizzled 4, 7, Dsh1, and Axin1) [7,8]. This results in strong suppression of osteoblast differentiation, maturation, and activity [9]. The combination of radium-223 and prednisone in ERA 223 could have induced synergistic inhibition of osteoblast activity with potentially significant worsening of uncoupled bone remodeling, and thus leading to an increase in bone fragility. A pertinent point is that glucocorticoid supplementation in hypopituitary patients with growth hormone deficiency (GHD), a condition characterized by reduced osteoblast activity, was associated with a dramatic increase in vertebral fracture risk, whereas the prevalence of vertebral fractures was not influenced by cumulative glucocorticoid doses in GHD patients under GH replacement therapy [10]. This observation is consistent with a synergistic effect of GHD and glucocorticoid excess in inhibiting osteoblast maturation and function, leading to an increase in vertebral fracture risk. It is likely that this pathophysiologic condition was reproduced in the ERA 223 trial and could have been responsible for the failure of radium-223 in preventing SSE.

In our opinion, radium-223 remains an efficacious option in the management of metastatic CRPC. The results from the ERA 223 trial, however, provide a warning regarding concomitant administration of radium-223 and prednisone, a combination that is likely to be detrimental to bone health and in principle should not be prescribed. In the ESMO presentation of the ERA 223 trial it was shown that the use of bone health agents (bisphosphonates or denosumab) was associated with lower fracture rate in both treatment groups. Therefore, if the combination of radium-223 and glucocorticoids is deemed necessary in clinical practice for palliative reasons, bone resorption inhibitors should be introduced to counteract the increase in fracture risk. The ongoing EORTC PEACE III trial (NCT02194842) is testing radium-223 combined with enzalutamide versus enzalutamide alone. This trial will provide data on whether the combination of radium-223 and a modern hormone therapy agent is safe and efficacious or not. In our opinion, use of high glucocorticoid doses in CRPC patients with a long-term survival perspective should always be carefully balanced against the risk of potentially serious side effects. We therefore suggest that if the dose of prednisone combined with abiraterone had been lower (eg, 5 mg daily as in the hormone-sensitive setting) and administration of bone resorption inhibitors had been preplanned for all patients in the ERA 223 trial, the study might have led to different results.

Conflicts of interest: Alfredo Berruti has participated in paid advisory boards for Janssen Cilag and Bayer.

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