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Platinum Priority – Editorial

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. . .But Words Will Never Hurt Me

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It turns out that the saying is not true. We always fixate on the adverse effects of sticks and stones on bones, but words can definitely hurt you, and some of the worst culprits might be the words not spoken. A missed conversation about bone protection in people receiving androgen deprivation therapy (ADT) for prostate cancer is an example of missing words that can lead to a world of hurt.

ADT for prostate cancer leads to detectable bone loss within a few weeks after commencement of therapy [1]. The enormous impact of poor bone health on patient well-being, particularly for those who are more frail, is known to us all. Fractures are painful and disabling, and most people experiencing hip fracture do not regain prefracture mobility by 120 days [2]. Perhaps less well appreciated is their lethality: 12-month mortality for hip fracture in Australia is over 22% [2], worse than many cancers. Clinical guidelines are clear and explicit about what should be done [3]. Best multidisciplinary care for people with prostate cancer undergoing ADT should involve endocrinologists, andrologists, nurses, and exercise professionals, among many others. We should already be mitigating iatrogenic poor bone health as effectively as current knowledge allows.

If we are honest, however, many oncologists might admit that conversations and therapeutic interventions about bone health might not be a major component of their routine consultations [4]. We are often caught up in talking about the cancer and its direct effects, and the optimal approach for best cancer outcomes for each individual patient based on evidence. Ironically, this could mean that our efforts to provide the best personalised treatment for prostate cancer might sometimes overlook other aspects of care vital to the future well-being of our patients.

That makes the report from the PEACE-3/European Organisation For Research And Treatment Of Cancer (EORTC) GUCG-1333 trial, published in this month's issue of *European Urology* [5], even more important. The main results of PEACE-3 are yet to be published, but data were presented at the European Society for Medical Oncology Congress in September 2024 [6]. The rationale for PEACE-3 was logical. At the time it was conceived, androgen receptor pathway inhibitors (ARPIs) such as enzalutamide were known to improve overall survival in metastatic castrate-resistant prostate cancer (mCRPC); and radium-223 dichloride (Ra-223) also improved overall survival in people with mCRPC and symptomatic metastatic disease confined to the bones. Perhaps the combination might be additive or even synergistic.

PEACE-3 participants had mCRPC and bone metastases without visceral metastases, were asymptomatic or mildly symptomatic, had good performance status, and had no prior enzalutamide or Ra-223. They were randomised 1:1 in an open-label fashion to receive Ra-223 55 kBq/kg every 4 weeks for six cycles plus enzalutamide 160 mg daily, or enzalutamide alone. The primary endpoint was radiologic progression-free survival (rPFS), with the key secondary endpoints of safety, overall survival, time to next treatment, time to pain progression, and time to first symptomatic skeletal event (SSE). The trial met its primary endpoint of improved rPFS (hazard ratio: 0.69, 95% confidence interval [CI]: 0.54–0.87, p = 0.0009), with no evidence of any subgroup performing differently. Time to next systemic

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treatment was improved, but time to pain progression and time to SSE appeared similar between the two arms. The overall survival curve displayed evidence of nonproportional hazards, and although an apparent signal of benefit was observed, the study will continue until the final planned analysis to confirm the findings.

These results of themselves are remarkable and cement PEACE-3 as an important trial of combination ARPI and radionuclide therapy. The broader applicability of this regimen remains unclear in 2025 and beyond, as the patient population (no prior ARPI) becomes rarer with the increasing use of these agents in metastatic hormone-sensitive prostate cancer (mHSPC).

That is not the subject of the brief report you will read in this month's issue of *European Urology* [5]. This paper contains information that, in our opinion, is far more important than improved rPFS in a dwindling population, and that is relevant to everyone experiencing or treating mCRPC. ERA-223 was a phase 3 study of similar design to PEACE-3 [7]. The results of the ERA-223 study became available during the course of PEACE-3, with a very clear signal of fractures in both treatment groups that occurred only in participants not receiving bone-protecting agents (BPAs). The PEACE-3 sponsor, EORTC, therefore mandated in March 2018 that all current and future participants in PEACE-3 receive BPAs, and that bone densitometry be performed at study entry to exclude osteoporosis. The protocol was amended to require either zoledronic acid or denosumab, administered at the more intense regimen used for prophylaxis of prostate cancer–associated skeletal-related events (SREs), rather than the less intense regimens used for the prevention or treatment of osteoporosis.

The results, first presented as an interim safety analysis at the American Society of Clinical Oncology Annual Meeting in 2021 [8], were striking and clinically impactful. Prior to the protocol amendment, the cumulative fracture rates after 1 yr of treatment in participants not receiving any BPA were 15.6% (95% CI: 5.6–30.3%) in the enzalutamide arm and 37.1% (95% CI: 21.3–53.0%) in the combination arm, alarmingly high in a population with a median age of 70 yr. The combination appeared worse for this outcome, but the control standard-of-care group was also impacted significantly. Implementation of the mandatory use of BPAs reduced the cumulative incidence of fractures at 1 yr to 2.6% (95% CI: 0.5–8.3%) in the enzalutamide arm and 2.7% (95% CI: 0.5–8.5%) in the combination arm. This is well below the expected rate [9], and now with no apparent difference between the treatment arms.

Some questions remain. The doses and schedules of BPAs in PEACE-3 were those used for SRE/SSE prophylaxis; could we see the same benefits using the much less intense osteoporosis regimens? PEACE-3 is yet to report long-term follow-up of its participants receiving BPAs; what will be the impact when the known complications of these treatments inevitably emerge?

Previously, bone protection in mCRPC was mainly considered in the context of preventing SREs or SSEs. Not all clinicians at our health service were convinced that the relatively small benefits in these endpoints outweighed the cost or toxicity of the routine use of BPAs for this specific purpose. More effective anticancer agents such as ARPIs had emerged since the original SRE/SSE prevention studies. We had also seen the dreaded complications of osteonecrosis of the jaw or refractory hypocalcaemia, and so did not use BPAs routinely for SRE/SSE prophylaxis in all our patients. BPAs for the other indication of prevention of osteoporosis and fractures were used in a subset of patients and, to our shame, not very consistently until we began working effectively with our endocrinologists and prostate cancer support nurses.

There are situations where BPAs are not safe or appropriate, and we must as always personalise these decisions for the benefit of our patients. When did you last inspect your patient's dentition adequately? Is their renal function optimal? Are their vitamin D levels replete, to reduce the risk of hypocalcaemia? However, PEACE-3 now makes it clear, and there is no excuse: we must routinely consider whether BPAs should be included for patients receiving ADT and ARPIs. We have changed our practice at our site.

Perhaps we should go further as we apply this information in practice and extrapolate beyond the PEACE-3 evidence. The prostate cancer disease state should not matter: anyone undergoing ADT, especially in combination with ARPIs but also as monotherapy, should be considered for BPAs. This would include those with mHSPC and CRPC as well. The sites of disease should not matter: BPAs should not be restricted only to those with bone metastases. The issue is about osteoporosis rather than the cancer itself, and unrelated to SREs and SSEs; perhaps it would be reasonable in the absence of direct evidence to use osteoporosis doses and schedules of BPAs [10]. Assessment of markers of bone turnover may be of value.

Sticks and stones are bad enough. It is time to make sure our words, including the ones unspoken, do not also do harm.

Conflicts of interest: Ian D. Davis has published with several of the authors of the paper under discussion but had no involvement in the PEACE-3 trial. Ian D. Davis is the global co-chair of the ENZAMET trial (ANZUP 1304), led by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) of which Ian D. Davis is the Director and Chair. ANZUP has received funding for clinical trials from both Astellas and Bayer. Ian D. Davis has received institutional funding from Astellas and Bayer for clinical trials involving enzalutamide or radium-223 dichloride; has been a member or chair of advisory boards for Astellas and Bayer; receives no remuneration for any of this activity; is employed by Monash University and Eastern Health; and is supported in part by an Australian National Health and Medical Research Council Investigator Grant L3 (2016274). Angelyn Anton has received honoraria from Astellas, AstraZeneca, Bayer, and Johnson & Johnson; has received institutional research funding from Astellas, Amgen, AstraZeneca, Bayer, Johnson & Johnson, MSD, Mundipharma, and Pfizer; and is employed by Eastern Health, and Walter and Eliza Hall Institute of Medical Research. Edmond M. Kwan has consulted or served in an advisory role for Astellas, Ipsen, and Janssen; has received travel funding from Astellas, Ipsen, Pfizer, and Roche; has received honoraria from Astellas, Ipsen, and Janssen; is employed by Monash University and Eastern Health; and is supported by a Prostate Cancer Foundation Young Investigator Award and an ANZUP Synchrony Fellowship.

References

[1] Cheung AS, Zajac JD, Grossmann M. Muscle and bone effects of androgen deprivation therapy: current and emerging therapies. Endocr Relat Cancer 2014;21:R371–94.

[2] Australian and New Zealand Hip Fracture Registry. Annual report of hip fracture care 2022. https://anzhfr.org/registry-reports/. Accessed 16 December 2024.

[3] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Prostate cancer, version 1.2025.

[4] Anton A, Wong S, Shapiro J, et al. Real-world incidence of symptomatic skeletal events and bone-modifying agent use in castration-resistant prostate cancer—an Australian multi-centre observational study. Eur J Cancer 2021;157:485–92.

[5] Gillessen S, Tombal B, Turco F, et al. Decrease in fracture rate with mandatory bone-protecting agents in the EORTC 1333/PEACE-3 trial comparing radium-223 combined with enzalutamide versus enzalutamide alone: a safety analysis. Eur Urol. 2025;87:285–8.

[6] Gillessen S, Choudhury A, Saad F, et al. LBA1 A randomized multicenter open label phase III trial comparing enzalutamide vs a combination of radium-223 (Ra223) and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer (mCRPC): First results of EORTC-GUCG 1333/PEACE-3. Ann Oncol 2024;35:S1254.

[7] Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:408–19.

[8] Gillessen S, Choudhury A, Rodriguez-Vida A, et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: an updated safety analysis. J Clin Oncol 2021;39(15_suppl):5002.

[9] Suarez-Almazor ME, Pundole X, Cabanillas G, et al. Association of bone mineral density testing with risk of major osteoporotic fractures among older men receiving androgen deprivation therapy to treat localized or regional prostate cancer. JAMA Network Open 2022;5:e225432.

[10] Motlaghzadeh Y, Wu JY. Approach to bone health in the patient with breast cancer. J Clin Endocrinol Metab 2024;109:e1902–10.