given an intended AD-WNTLT value. We decided to fix the limits to keep the liver decompensation risk lower than 15%. Just to clarify the difference, our receiver-operating-characteristic curve analysis with this bilirubin stratification gave optimal thresholds of 59 and 65 Gy, whereas the normal-tissue complication probability-based limits are 50 and 90 Gy.

In the lobar treatment group, Watanabe et al. reported 4 of 78 toxicity cases (5%) and 74 nontoxic cases. In the whole-liver approach, they had 16 of 98 liver decompensations (16%) versus 82 nontoxic treatments. Note that the difference in toxicity incidence was found to be significant using the exact Fisher test (P = 0.03). The mean AD-WNTLT was 42 Gy in the lobar treatment group (lower than our more conservative limit of 50 Gy), whereas it was 70 Gy in the whole-liver group. In addition, without a second contralateral treatment, radioinduced hypertrophy was free to develop. Therefore, the combination of lower AD-WNTLT and partial treatment resulted in a significantly lower toxicity incidence in the lobar approach. It was so low that the authors could not obtain statistical significance, nor was a meaningful threshold found, given the small number of toxic treatments, as was our experience with lobar treatment (4).

In conclusion, the voxel dosimetry method by Watanabe et al. might be an important advance to safely plan radioembolization. However, before being used in clinics by other centers, the proposed safety thresholds for whole-liver treatment (hybrid) should be revised according to the above comments, mainly introducing analysis of causes, stratification on the basal bilirubin value, and normal-tissue complication probability analysis.

DISCLOSURE

In the last 3 y, Carlo Chiesa and Marco Maccauro were consultants for Boston Scientific, the producer of ⁹⁰Y glass microspheres; for Terumo, the producer of ¹⁶⁶Ho microspheres; and for AAA, the producer of Lutathera (¹⁷⁷Lu-DOTATATE). He received a research grant from Boston Scientific. Matteo Bagnalasta is a resident supported by a scholarship from Boston Scientific. No potential conflict of interest relevant to this article was reported.

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Unraveling the Hypocalcemic Response to ¹⁷⁷Lu-Prostate-Specific Membrane Antigen Therapy

TO THE EDITOR: We read with great interest the recent article by Kumar et al. published in *The Journal of Nuclear Medicine (1)*. The authors presented an intriguing finding of clinically significant hypocalcemia and osteosclerosis as rare but important side effects of ¹⁷⁷Lu-PSMA-I&T therapy in patients with high-volume osseous metastatic disease who showed a significant treatment response. The paper provides valuable insights and stimulates thought; however, there are still certain aspects that require further clarification and discussion. Although Kumar et al. shed light on the potential side effects of ¹⁷⁷Lu-PSMA-I&T therapy, additional investigation is necessary to fully comprehend the underlying mechanisms and optimize patient management.

Hungry bone syndrome was initially described by Albright and Reifenstein in relation to the removal of parathyroid adenomas (2). This procedure triggers an increase in osteoblastic activity, resulting in excessive deposition of calcium and phosphate in the bones (3). The calcium sink effect in metastatic prostate cancer, which is also associated with hungry bone syndrome, is actually caused by tumor-induced osteoblastic activity (4). These cases generally do not respond well to aggressive medical treatment but may show improvement after successful tumor control (1,5,6).

We posit that the findings of Kumar et al. may differ from the tumor-induced calcium sink effect. According to their study, patients who were previously normocalcemic experienced hypocalcemia after ¹⁷⁷Lu-PSMA therapy, specifically when there was significant tumor suppression. The authors hypothesized that the remaining minority of tumoral cells may have increased the release of osteoblastogenic growth factors. However, we propose that the underlying pathophysiology might be explained by considering the fact that prostate cancer cells have the ability to secrete parathyroid hormone-related peptide, thereby stimulating osteoclast activity. Tumor suppression consequently results in significant suppression of parathyroid hormone-related peptide in the microenvironment, leading to hypocalcemia that closely resembles hungry bone syndrome (7,8). Unfortunately, Kumar et al. did not provide any data regarding the levels of parathyroid hormone-related peptide in the cases to assess this hypothesis. Furthermore, it would have been

valuable to evaluate whether changes in calcium levels correlate with changes in prostate-specific antigen and prostate-specific membrane antigen levels in the bone-only metastatic subgroup.

Kumar et al. have also introduced intriguing concepts regarding the Tyr phenomenon and its potential impact on bone marrow reserve. However, their report lacks supportive data on this matter. The authors propose that an excessive osteoblastic reaction may lead to a decrease in the bone marrow reserve. To substantiate this assertion, it would have been beneficial if they had presented the changes in hemoglobin levels among patients experiencing albumincorrected hypocalcemia after ¹⁷⁷Lu-PSMA therapy and compared them with the original dataset.

In their approach to mitigate the undesired exaggerated osteoblastic reaction, the authors used glucocorticoid therapy, which appears to be a reasonable strategy. However, it is worth considering ²²³Ra therapy as a potential alternative since it can inhibit osteoblastic activity and has demonstrated its efficacy in controlling refractory tumor-induced hypocalcemia (9,10).

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REPLY: We have reviewed the letter to the editor entitled, "Unraveling the Hypocalcemic Response to ¹⁷⁷Lu-Prostate-Specific Membrane Antigen Therapy," which refers to our published article, "The Tyr Phenomenon: A Hypocalcemic Response in High-Volume Treatment Responders to ¹⁷⁷Lu-Prostate-Specific-Membrane Antigen Therapy" (1). We thank the authors for their interest in our article.

We describe a novel phenomenon of severe hypocalcemia in patients with high-volume bone metastatic prostate cancer who respond to ¹⁷⁷Lu-prostate-specific membrane antigen (PSMA) treatment. Patients who developed hypocalcemia (<2.10 mmol/L) during ¹⁷⁷Lu-PSMA had significantly higher markers of pretreatment disease burden, including baseline SPECT total tumor volume (median, 3,249 cm³ [interquartile range (IQR), 1,856–3,852 cm³] vs. 465 cm³ [IQR, 135–1,172 cm³]; P = 0.002), baseline prostate-specific antigen concentration (median, 471 ng/mL [IQR, 108–1,380 ng/mL] vs. 76 ng/mL [IQR, 22–227 ng/mL]; P = 0.008), and baseline alkaline phosphatase concentration (median, 311 U/L [IQR, 195–2,046] vs. 114 U/L [IQR, 69–184 U/L]; P < 0.001). Patients who developed hypocalcemia also demonstrated a greater prostate-specific antigen response between the first- and third-dose ¹⁷⁷Lu-PSMA (median, 85% [IQR, 53%–91%] vs. 47% [IQR, 1%–77%]; P = 0.022).

We suspect that an exaggerated osteoblastic response drove the hypocalcemia in our 2 most severe cases given the markedly elevated alkaline phosphatase and procollagen type 1 N-propeptide concentrations at hypocalcemia onset and the rapid response of serum calcium and bone formation markers to high-dose prednisone therapy, which is known to suppress osteoblastogenesis and promote osteoblast apoptosis (2,3). It is unclear whether this osteoblastic response is specifically occurring in the osteoblastic bone metastases or is a more generalized skeletal response. Interrogation of further cases with transiliac bone biopsy, including histomorphometric indices of bone turnover and micro-CT assessment of trabecular and cortical bone morphology, will likely provide important insights. We agree that our cases differ from those with hypocalcemia in the setting of progressive bone metastases (4), as the hypocalcemia occurred in association with excellent responses to treatment.

The authors postulate whether parathyroid hormone-related protein suppression in the tumor microenvironment and subsequent reduction in osteoclastic activity may have been the driving factor for hypocalcemia. This is a reasonable hypothesis, which we did not examine. However, given the evidence for an exaggerated osteoblastic response, we suspect parathyroid hormone-related protein suppression was not a major underlying factor for the hypocalcemia, particularly given that the 2 more severe cases had recent high-dose denosumab, which is already a potent suppressant of osteoclast activity (5). Indeed, one of our patients had a low-normal serum C-terminal telopeptide of type 1 collagen at the onset of hypocalcemia (113 μ g/L; normal range, 100–750 μ g/L). Further, we were unable to identify any cases in the literature describing hypocalcemia secondary to parathyroid hormone-related protein suppression. Most patients in our cohort had underlying bone metastases (>95%), and we demonstrated that onset of hypocalcemia during ¹⁷⁷Lu-PSMA treatment correlated with greater prostate-specific antigen response.

Patients who developed hypocalcemia in our cohort had a significantly lower hemoglobin nadir between the first and third doses of ¹⁷⁷Lu-PSMA (median, 95 g/L [IQR, 76–114 g/L] vs. 112 g/L [IQR, 102–122 g/L]; P = 0.029). There is concern that an osteoblastic hypersclerotic reaction may compromise marrow reserve; however, various factors can contribute to anemia in such patients. Further, whereas our data suggest a short-term decline in hemoglobin, a long-term persistent hemoglobin reduction is more clinically relevant and would require a longer follow-up period.

We commenced high-dose prednisone in the 2 most severe cases of hypocalcemia to suppress the exaggerated osteoblastic response. ²²³Ra is a calcium mimetic that facilitates α -radiation preferentially to osteoblastic bone metastases exhibiting high bone turnover (6). However, as mentioned, the hypocalcemic phenotype we describe occurred in excellent treatment responders, and hence, administering