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LETTER TO THE EDITOR

Osteonecrosis of the jaw (ONJ) in renal cell cancer patients after treatment including zoledronic acid or denosumab

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Dear Editor,

The paper by Henry et al. published by *Supportive Care in Cancer* comparing efficacy of denosumab versus zoledronic acid in patients with bone metastases of advanced solid tumours [1] comes to integrate the original reports of three pivotal large randomized phase 3 trials [2–4], the publication by Saad et al. about osteonecrosis of the jaw (ONJ) in those three trials [5], and the combined outcome analysis by Lipton et al. [6].

Henry et al. [1] reported outcomes of the single trial conducted on patients with solid tumours (except breast or prostate cancers, object of other two trials) [2, 3], excluding patients with multiple myeloma: This ad hoc analysis confirmed the superiority of denosumab in delaying or preventing skeletal-related events [1]. Amongst side effects, after a median (Q1, Q3) time on study of 6.7 (3.2, 13.0) and 6.4 (3.1, 12.9)months in the two groups, ONJ was reported in six denosumab arm patients (0.8 %) and in nine zoledronic acid arm patients (1.1 %).

We wish to underline some sparse data reported in the cited papers, focusing attention on occurrence of ONJ in patients with renal cell cancer (RCC) included in the trial.

In the summary ONJ analysis [5] of the above-mentioned three randomized trials comparing zoledronic acid and denosumab in patients with several cancer types and conducted between 2006 and 2009, it appears that an "Oral Event Identified as Potential ONJ" was registered in 276 patients out of 5,723 (4.8 %). Finally, cases of positively adjudicated ONJ according to very strict criteria were only 89 (1.6 %)—37 (1.3 %) on zoledronic acid and 52 (1.8 %) on denosumab. Notably, in the three trials, there were 14 ONJ cases among 464 patients treated with an antiresorptive agent (zoledronic acid or denosumab) and antiangiogenic agents (3.0 %) versus 75 ONJ cases among 5,259 patients receiving zoledronic acid or denosumab without any antiangiogenic agents (1.4 %) [5]: This kind of data seems to enforce recent literature data suggesting possible higher ONJ risk from combination of antiresorptive and antiangiogenic agents [7, 8].

According to the paper by Saad et al. [5], among 89 total adjudicated ONJ patients (treated either with zoledronic acid or denosumab) there were six RCC patients, out of a total number of enrolled RCC patients of 155 [1, 4]. This 6/155 (3.9 %) ONJ frequency in RCC patients is more than twice as high, if compared with the entire patient population (1.6 %).

In recent years, bone metastatic RCC patients received routinely targeted therapy, as monoclonal anti-VEGF antibody (bevacizumab), tyrosin-kinase inhibitors (sunitinib, sorafenib, pazopanib), mTOR inhibitors (temsirolimus, everolimus). Several types of recent reports suggest a relatively high ONJ risk in RCC patients after a combination of bisphosphonates (mostly zoledronic acid) and antiangiogenic agents (mostly sunitinib) [9–12].

The question is: could the antiangiogenic treatment have played a role in the 3.9 % ONJ rate among RCC patients in the trial illustrated by Henry et al.? Unfortunately, according to the reports of the trial [1, 4], it is neither arguable how many of those six RCC patients developing ONJ had received antiangiogenic agents, nor which bone antiresorptive agent was administered.

Furthermore, we can extrapolate from the cited reports of the trials [2–5] that, among 21 ONJ adjudicated cases, an antiangiogenic drug had been administered in six out of

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eleven ONJ patients in the zoledronic acid arm versus one out of ten ONJ patients in the denosumab arm. This seems to suggest a possible higher risk of ONJ in patients who had received zoledronic acid together with an antiangiogenic agent, in comparison to the association of denosumab with a targeted therapy.

We think that the details of the treatment received by RCC patients in the trial reported by Henry et al. [1, 4] (preferably if updated with longer follow-up) would be of value to clarify the role of a targeted therapy (i.e., antiangiogenic drugs) together with zoledronic acid or denosumab in developing ONJ.

Disclosure/conflict of interest None.

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