Reviewer's report

Title: Administration of Zoledronic Acid Enhances the Effects of Docetaxel on Growth of Prostate Cancer in the Bone Environment

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Reviewer: Philippe Clezardin

Reviewer's report:

General
This manuscript by Brubaker and colleagues reports the investigation of the effects of docetaxel (20 mg/kg every 2 weeks) alone or in combination with the bisphosphonate zoledronic acid (0.1 mg/kg, given s.c. twice weekly) on the in vivo growth of prostate cancer LuCaP 23.1 tumors in bone. These authors have previously shown that zoledronic acid (0.25 mg/kg, given s.c. twice weekly) reduces the formation of osteoblastic lesions induced by LuCaP 23.1 cells and decreases tumor burden in the bones of animals (Corey et al., Clin Cancer Res, 2003). Others have shown that zoledronic acid (0.025 mg/kg, s.c. twice daily) alone or in combination with paclitaxel (8 mg/kg, once weekly) reduces the formation of osteolytic lesions caused by PC-3MM2 prostate cancer cells and decreases skeletal tumor burden (Kim et al., Cancer Res 2005). The present study is the first to describe the effects of a combined treatment of zoledronic acid with docetaxel on the formation of prostate cancer osteoblastic lesions and skeletal tumor growth. Based on a series of in vivo and in situ studies, the investigators conclude that zoledronic acid enhances the antitumor effect of docetaxel on growth of LuCaP 23.1 prostate cancer cells in bone. While experiments conducted by the investigators largely support this conclusion, there are some issues that need to be further addressed and/or clarified.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The measurement of the bone mineral density usually strongly correlates with that of the BV/TV. Here, the histomorphometric analysis indicates that the percentage of the BV/TV increased almost twofold in the group treated with docetaxel + zoledronic acid when compared to that observed in the control group. In contrast, the bone mineral density (BMD) did not significantly differ between the two groups. How do the authors explain this discrepancy between the BMD and histomorphometric data?

2. As illustrated in Fig.1B and 1D, bone in osteoblastic lesions is very chaotic in structure. This is likely explained by the fact that osteoblasts rapidly deposit new bone so that the bone formed in these lesions is of poor quality and is disorganized rather than lamellar in character as it is observed in normal bone. Figs 1C and 1E suggest that the treatment of animals with zoledronic acid, alone or in combination with docetaxel, has improved the bone structure. Thus, beyond the effects of zoledronic acid ± docetaxel on the BMD and BV/TV, a major effect of this combined treatment could be on bone quality. I suggest the authors to examine metastatic bone sections under polarized light to examine if bone has a more lamellar structure upon a combined treatment. In addition, because bone sections are stained with Goldner's trichrome, the osteoid surface and osteoid thickness should be measured.

3. In Fig. 3, there is a correlation between the inhibition of tumor growth and the decrease of circulating PSA levels upon docetaxel treatment. In Fig. 2, only docetaxel in combination with zoledronic acid significantly reduces circulating PSA levels. In contrast, zoledronic acid alone or in combination with docetaxel inhibits skeletal tumor burden (Table 1). How do the authors explain that the decrease in skeletal tumor burden is not associated with a decrease in PSA levels?
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. In Table 1 and Fig. 2, the P values for the BV/TV and TUV/TV should be the same (that's not the case). Similarly, in the Results section on page 8, P values for the osteoclast number are different from those in Table 1. In addition, I wonder if it is necessary to show the same results in Table 1 and panels A and C of Fig. 2.
2. page 7, subcutaneous tumors: the size of tumors is expressed in mg, whereas results shown in Fig. 3 are expressed in mm3.
3. page 10, Discussion section (last paragraph): « Docetaxel has been shown to be effective ... [49,50]». In ref 50, they are using paclitaxel instead of docetaxel.
4. page 12, Abbreviations section: Add the meaning of abbreviations OB.PM./BPM and N.OC./BS

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

There is a non-financial competing interest in relation to this paper. The reviewer is also working on the therapeutic effects of bisphosphonates (alone or in combination with cytotoxic drugs) on bone metastases.