Author's response to reviews

Title: Hypercalcemia in metastatic GIST caused by systemic elevated calcitriol: A case report and review of the literature.

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Author's response to reviews: see over
Dear Editor Dr. Masahide Ikeguchi.

Thank you for the constructive comments given by the reviewers and sent to us on August the 13th 2015.

Please find enclosed a revised version of the manuscript “Hypercalcemia in metastatic GIST caused by systemic elevated calcitriol: A case report and review of the literature”. Changes are marked in red.

We are looking forward to your final evaluation.

Yours sincerely

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Response to reviewers:

Reviewer 1:

Comment 1
It is probably worth pointing out that there are many tumours, not just myeloma, that induce bone disease/hypercalcemia via the RANK/RANKL system. This is important for recognizing situations where hypercalcemia is due to excessive osteoclast activity that will likely respond best to potent inhibitors of osteoclast function. Along those lines, it is interesting that the present patient’s hypercalcemia didn’t really respond to the zoledronic acid treatment. There are
no pre-treatment markers of bone resorption such as C or N telo-peptide to help know whether bone resorption played a major role in the patient’s presentation but the non-response to zoledronic acid would support a non-bone related mechanism for the hypercalcemia. Thus, the message might be that non-bone mechanisms of cancer-related hypercalcemia should always be considered if there is failure to respond to bisphosphonate or denosumab.

**Our response**
We agree with the reviewer that not only multiple myeloma but also breast cancer, prostate cancer, and renal carcinoma induce osteoclast activation via the RANK/RANKL system, line 118. The importance of the lack of response to treatment with intravenous bisphosphonates has been emphasized, lines 142-143.

**Comment 2**
It is perhaps similarly surprising that the hypercalcemia failed to respond to glucocorticoid therapy which traditionally is thought to be highly effective in calcitriol mediated hypercalcemia. The literature supporting and reporting this is not of especially high quality and so perhaps the non-response was due to a dose that was too low or perhaps the response rate is just less than traditionally thought. Either way, it is probably worth mentioning this somewhat atypical observation.

**Our response**
We agree with the reviewer that this finding is surprising and could be caused by a dose too low of glucocorticoids, lines 143-147.

**Comment 3**
The definitive treatment of the hypercalcemia was the tyrosine kinase inhibitor and it therefore bears mentioning that this therapy should perhaps be considered for control of severe tumoural hypercalcemia even in cases where it is not otherwise being used for anti-cancer purposes and bisphosphonate therapy has failed.
Our response
We agree with the reviewer and the manuscript has been changed, lines 147-151.

Comment 4
I agree with your point that high tissue 1-alpha-hydroxylase activity would need to be demonstrated for the most convincing clinical evidence of mechanism.

Our response
We agree with the reviewer.

Comment 5
Minor note – in abstract, should probably specify the enzyme you mean.

Our response
Thank you for the comment. The abstract has been changed, line 38.

Reviewer 2:

Comment
My one suggestion for the authors is to make a table with the lab values and also a graph of the levels of calcium and calcitriol as a function of therapy.

Our response
Please see Figure 1 (uploaded separately) and Table 1, line 245.