Reviewer's report

Title: Efficacy of Temsirolimus in Metastatic Chromophobe Renal Cell Carcinoma

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Reviewer: Brian Shuch

Reviewer's report:

Well-written manuscript. Important in that there are only a limited number of reports of this kind for metastatic chromophobe.

Needs several areas touched up prior to publication.

1. Discretionary Revision
Hale’s colloidal iron is often positive and immunohistochemical markers are usually negative for cytokeratin 20 and vimentin but positive for cytokeratin 7. Should cite this

2. Discretionary Revision
Following this, the decision was then taken to proceed to a left cytoreductive nephrectomy.

Just for sake of completeness, please state surgical approach. Laparoscopic? radical? Node dissection?

3. Discretionary Revision
The phase III trial reported by Hudes et al which compared patients with metastatic RCC who received temsirolimus alone or temsirolimus plus interferon or interferon alone included patients with metastatic RCC who had at least three of the six predictors of short survival namely: haemoglobin less than lower limit of normal, serum lactate dehydrogenase (LDH) levels greater than 1.5 times the upper limit of normal, metastases at multiple organs, Karnofsky performance status score of 60 or 70, time from diagnosis to randomization less than a year or corrected serum calcium more than 2.5 millimole per litre.[4]

Do not need to restate the prior trials criteria. Just state that your patient had 3 high-risk features (anemia, poor performance status, and synchronous metastatic disease) as defined in the trial of Hudes et al.

4. Discretionary Revision
When was poor performance status defined? Those with debilitating bone metastases that area treated can have improvement in performance status. Should make it clear if the radiation didn't improve her performance status.

5. Discretionary Revision
At this point, the patient required physical aids to mobilise due to painful lytic bony metastases of the femur.

Did you prescribe any bone agents such as zoledronic acid or denosumab.

6. Minor Essential Revisions

The prognosis of RCC varies significantly depending on histological sub-type, with non-clear cell histology portending a favourable prognosis compared with clear cell RCC. Amongst the non-clear cell variety, patients with chRCC demonstrate significantly higher median overall survival compared to both clear cell and papillary RCC.

You have to make it clearer- first off several studies have demonstrated that histology may not be an independent predictor of outcome. The poor outcome is more associated with stage, size, and grade. Is the survival difference you are trying to refer to for metastatic patients? Cite the studies you wish to reference. You introduce that these series were prior to the introduction of targeted agents, however if you are talking about all patients- I disagree that median survival would be that different as most papillary or chromophobe patients will not develop metastatic disease.

7. Discretionary Revision

It is accepted that abrogation tumour suppressor function of the Von Hippel-Lindau (VHL) gene

This sounds awkward. Also I believe VHL should be italicized.

8. Discretionary Revision

In this trial, there was only one patient with chRCC but the outcome of this specific patient is unknown.

Is this true? I have never seen this broken down and I believe they didn't have that data. Please check

9. Minor Essential Revisions

Of the 12 patients with metastatic chRCC, only three had a partial response (two patients treated with sorafenib and one treated with sunitinib). This suggests that VEGF targeted tyrosine kinase inhibitors may only have modest activity against chRCC.

I don’t agree that the study suggests anything, especially modest activity. The partial response rate of sorafenib in clear cell is nothing special either (10% in NEJM article). Can we definitively say that this is worse? I would tone this down. It perhaps shows that the papillary RCC patients didn't have a dramatic response rate.

10. Minor Essential Revisions

One additional highly relevant report in the literature should be included:
Targeting the mTOR pathway in Chromophobe Kidney Cancer.
PMID: 22481981

I would incorporate this and also discuss the registry-based findings regarding the extreme rarity of this cancer (accounting for approximately 1% of all RCC deaths). This can be cited again about the difficulties performing a trial for this patient population at the end of the paper.

10. Minor Essential Revisions

Tables and Figures
1) I would state it's a hematoxylin and eosin stained slide at “X” magnification
2) I would label a panel “a” and “b” and reference it in the text this way.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests.