Reviewer's report

Title: Impairment of cognitive functioning during sunitinib or sorafenib treatment in cancer patients: a cross sectional study

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Reviewer: Alexandre Chan

Reviewer's report:

This report reports the occurrence of cognitive dysfunction among patients receiving sunitinib or sorafenib in cancer patients. Although the research question deems importance, there are major flaws with the design of the study, which can affect the interpretation of the data.

Major Essential revisions:

1. The authors made a major error to call this study a 'case control' study. Recommend authors to understand what is the definition of a case control study from epidemiology textbook. In this study, 'cases' should refer to cognitive dysfunction cases, whereas 'control' should refer to patients who did not experience cog dysfunction. Unfortunately, authors assume cases are 'TKI' receiving patients and 'controls' are those who were not receiving TKIs. This is a major error.

2. Why included sorafenib/sunitinib for at least 8 weeks? Is this purely out of convenience because the shortest follow up time is 8 weeks for a patient (as presented as the minimum of a range under results) I understand that this is a cross-sectional study, but if the assessment of cognitive functioning occurs at different time points, will the data be consistent? I highly question the validity of the results.

What is the dose schedule of sunitinib? 4 weeks on 2 weeks off? Cyclic doses? 37.5 mg/day? 50 mg/day? How about sorafenib? This is poorly addressed in the manuscript.

3. Although ambitious, it sounds impossible to match four individual characteristics (age, gender, estimated IQ, level of education) among 30 patients into 30 health controls. Is Berkson bias a concern with the selection of mRCC patients? Why were references 18 and 19 cited for matching purpose? Doesn't make a lot of sense.

4. In table 1, it is unclear what is defined as mean education of 4.83 and 5 (without units provided). Are those years of education? Seems very low to me. Remember audience worldwide does not necessarily understand the way how Dutch presents its education system.

5. In table 1, why was median glucose tested with t-test? Were data normalized before t-test was performed?
Also why was p value not presented, comparing age of all 3 groups, as well as gender? Krukal Wallis would be an appropriate test to perform, assuming the data is non-parametric in nature.

6. Under methods, the authors poorly presented the tools that were utilized in this study. How many items? Were they all presented in Dutch? Back-forward translated? Validated? None of these details were presented.

7. In terms of analysis, why plasma VEGF and serum cytokine? Why not all serum, or all plasma?

8. Under discussion (p/17) - the authors presented how markers of systemic inflammatory response which is a symptom of tumor progression correlates with more depressive feelings. The association of all these subject matters is illogical and lack clinical sense. Were there any evidence to justify these statements?

9. Conclusion needs to be reworded. TKI has a negative impact on cognitive functioning, in comparing to which population? In terms of what domains? The conclusion is inappropriate as data is immature and seems to have lacked problems with the interpretation.

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.