Author's response to reviews

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

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Version: 2 Date: 10 October 2013

Author's response to reviews: see over
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Title: Impairment of cognitive functioning during sunitinib or sorafenib treatment in cancer patients: a cross sectional study

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We would like to thank the reviewers for their comments. We have tried to answer questions in an appropriate way.

In the meantime our institute changed its name so all the (email) addresses have been altered in the manuscript
Reviewer's report

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

Version: 1 Date: 1 March 2013

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.

Answer: We agree with reviewer 1 that this is not a 'case control' study but a cross-sectional study with control groups, so we changed that in the manuscript

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.

Answers:
One of the inclusion criteria was that patients with sorafenib/sunitinib had to be on treatment for at least 8 weeks. The reason for this was that we wanted them to be exposed for a longer period of time to the TKI. We have chosen for 8 weeks for the following reasons: 1 at that time patients were at least on their second cycle of treatment so all patients who stop due to toxicity or rapid progression in the first weeks were excluded; 2. for patients who were just started 8 weeks before the study with sunitinib in a 4 weeks on 2 weeks of schedule, those patients were not in their stop weeks at the time of the neuropsychological assessments.
We have chosen the cross-sectional study design in order to explore the cognitive functioning in patients on TKIs, and we recommend a longitudinal study for confirmation and further exploration of the results.

The dose schedules of sunitinib and sorafenib have been added to the revised manuscript in the results section.

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.

Answers:
In neuropsychological research it is common practice to recruit healthy controls with approximately the same socioeconomic background as the patients, in order to match patients and controls on four important characteristics (age, sex, estimated IQ and level of education) which in itself affect cognitive performance, and cannot be properly adjusted for statistically. This is even more important in relatively small samples as in our study. Note, however, that the matching was done at group level, i.e. to avoid statistically significant differences between groups, which makes it feasible.

We think that Berkson’s bias is not a concern in our study. Berkson’s bias is a concern in retrospective case-control studies with hospitalized patients but not in a cross-sectional study with patients who are not hospitalized.

As the reviewer remarked the references 18 and 19 were indeed incorrectly placed. This section has been altered accordingly.

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.

Answer: this has been clarified in the manuscript and table. Education levels were used (7 categories), in accordance with the Dutch educational system. See also reply on comment #3.

5. In table 1, why was median glucose tested with t-test? Were data normalized before t-test was performed?

Answer: All biomarker data were assessed for (log) normality and t-tests were used when applicable, the distribution of glucose values was normal so we used the t-test.

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.

Answer: Because we matched the groups for age, sex and level of education, the groups did not differ on these variables. In the revised table, we have added the p-values for the ANOVA examining age, as well as the nonparametric tests for sex distributions and education level.

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.

Answer: All neuropsychological tests are validated and published Dutch-language equivalents of widely used measures. References to all individual tests have been added, but we feel it is beyond the scope of the present paper to discuss these in more detail (as this would require several pages). We have added a sentence stating that we used validated, Dutch-language versions on p. 7: “An extensive neuropsychological assessment using validated, Dutch-language versions of widely used tests…”

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

Answer: For both the VEGF levels and the serum cytokines we have chosen the analysing techniques that our laboratories were most experienced with.

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

Answer: We describe what we found in our study: higher levels of ESR, CRP and neutrophils (all reflections of a systemic inflammatory response) were associated with worse objective cognitive functioning and with more depressive symptoms (CRP and LDH). These data are consistent with others who found a relation between cognitive impairment and pro-inflammatory cytokines (reference 4, 9 - 12 in the paper) and CRP and cognitive impairment and depression. (reference 40,41) We included the more recent references in the manuscript (40, 41).

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.

Answer: as suggested by reviewer 1 we adjusted the conclusions.

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.
Reviewer's report

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

Version: 1 Date: 10 September 2013

Reviewer: Martin Klein

Reviewer's report:
This is an interesting study into the effect of VEGFR TKI on cognitive functioning. While this study certainly has its value in this field of research, a number of issues should be addressed.

1. In the abstract under the header 'Background' no background information is provided, only what the authors will be studying. Why would anyone study this association becomes not clear from the abstract, while the introduction does provide solid evidence.

Answer: Changes have been made in the abstract.

2. The authors state that VEGFR TKI has a negative impact on cognitive functioning, but how does this finding translate into daily clinical practice? Are there any choices at all in treatment and how are the potential side effect of treatment balanced against survival?

Answer: The VEGF TKI are used in a palliative setting, when no cure is possible. Part of the patients will live for years while on treatment. In this phase it is important to outweigh the benefits of the treatment against the side effects. This is a constant dialogue between the patient and his or her physician. When side effects occur that have a relevant negative impact on quality of life, dose reductions or so called drug holidays (a short period of interrupting the treatment) can have a positive effect. By awareness of cognitive dysfunction as an adverse event patients and medical oncologists can make better choices.

3. The authors report no consistent correlations between the results of hematology and chemistry blood tests and objective or subjective cognitive functioning. Since this was not the primary endpoint of this study do the authors think this is due to a lack of power?

Answer: For most of the biomarkers we think that there really is no correlation between the blood tests and the objective or subjective cognitive functioning because all the correlation tests in the domain and subdomain scores and the questionnaires
were negative. For other tests like vitamin B12 and TSH level the study could be underpowered because correlations were found but not consistent in the domain and subdomain scores and the questionnaires.

4. What is the value of the reported subjective complaints against the reported cognitive performance?

Our results show that subjective complaints with respect to cognitive function can be substantiated by objective neuropsychological assessment, which is relevant as subjective cognitive complaints do not always correspond with cognitive test performance. In the revised conclusion, we have added a sentence to briefly address this (p.18): “In summary, our data suggest that treatment with VEGFR TKI has a negative impact on cognitive functioning, and that subjective complains can be corroborated by objective neuropsychological testing.”

5. The discussion is lengthy and is a bit off focus at times and thus should be shortened where possible.

Answer: The discussion has been altered as asked.

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: ‘I declare that I have no competing interests’