Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1481

Reviewer A

Comment 1: Please correctly specify the older group in the abstract. I assume it should be 70 or more. 147 patients were included. 94 (63.9%) were 70 years.

Reply 1: we fully agree that our syntax was not easily understandable. We did what was necessary to be as clear as possible.

Changes in the text: we have modified our text as advised (page 2 line 9 and 16, it was of course 70 years old or more).

Comment 2: Please provide a rationale for exclusion of patients who used other targeted therapies.

Reply 2: as mentioned in the discussion, sunitinib and sorafenib were during the inclusion period the only two molecules available in our center. This is why our study is limited to the use of these two molecules.

Changes in the text: "Regarding the molecule used, our cohort was mainly based on Sunitinib 83.7%. Only 16.3% of the patients received Sorafenib as first line treatment, this was due to a temporary authorization to use Sorafenib in 2006 in this indication at our institution while waiting for Sunitinib to be available from mid-2007. Sunitinib was then used as the standard treatment for first line mRCC." (page 7, line 18-23)

Comment 3: The study groups differ numerically for a number of baseline demographic and clinical characteristics (eg. Karnowsky performance scale, CCI, thrombocytosis, neutrophil counts). Please provide results from multivariable cox proportional hazard model for OS and PFS. Although results from KM curve for OS and PFS did not differ statistically, it is clear that OS and PFS looked better for older adults (especially OS), which was very surprising.

Reply 3: Indeed, several characteristics are significantly different between the two groups studied, as reported in the results section. A multivariate analysis might be of interest here. However, given the results obtained with a univariate analysis, and a small population size, a multivariate analysis would provide only limited additional information. Moreover, the comparison of the two groups on the IMDC prognostic score variable did not reveal any significant difference (p=0.057). Among the data that make up this score we find the Karnofsky performance status (KPS), time from diagnosis to first-line targeted therapy, hemoglobin concentration, neutrophil count, platelet count, and serum calcium concentration. We can therefore assume that univariate analysis is sufficient here.

Changes in the text: as mentioned in the manuscript: "significant differences between the two groups were found. Patients >70 years had a higher incidence of CKD (defined by GFR<60ml/min). More patients <70 years presented thrombocytosis and/or high neutrophil count than in the >70 years old age group (respectively 14.8% vs 3.77%, p=0.0431)" (page 5, line 25-26)

Comment 4: The rate of discontinuation due to toxicity and proportion of patients with severe toxicity was higher in older group than younger. Further, more older patients had

toxicities earlier (2-3 months) than younger patients. Although they are statistically non-significant, directionality of the results suggest that older patients have higher degree of toxicity. Therefore the conclusion suggesting similar efficacy between older and younger group does not hold correct.
Reply 4: regarding our results, the use of these drugs among elderly population does not seem to have a different efficacy despite a possible higher toxicity. This last point correlate with overall publications reporting better efficacy correlated to higher toxicity. In addition, we agree that there is a trend for higher toxicity among elderly patients. However, this difference remains not statistically significant. That not allowed us to make any other conclusion.
Changes in the text:

Comment 5: Authors suggest that higher occurrence of CKD as the reason for higher treatment related AEs in younger group. However, this is only one of the possibilities. There could be many other factors that make older adults susceptible to have more side effects. A multivariable model that control for such confounders and predicting the risk incidence of AEs and total number of AEs is needed.
Reply 5: we agree that the sentence was confusing. We changed it to make it more clearer. We meant to suggest that higher occurrence of CKD as a reason for higher toxicity in older group.
we agree that CKD is not the only explanation, however it is widely described in the literature and we find it again in our study.
Changes in the text: page 8, line 8-10 “This trend could be related to the higher rate of CKD in the older group. We previously reported the role of GFR less than 60 in mRCC as risk factor of TT-induced toxicities”.

Comment 6: The conclusion in the main body of the manuscript is more realistic than the one from the abstract. Based on the overall study results, it is not possible to conclude that safety was similar between older and younger mRCC patient groups.
Reply 6: we do indeed agree with your remark. We have modified the conclusion of the abstract in order to agree with our findings.
Changes in the text: we have modified our text as advised. “Safety results suggest that these drugs can be safely used for older patients with a need of caution regarding toxicity prevention.” (page 3, line 2-4).

Reviewer B
Comment 1: Please describe the IRB approval information in the discussion section.
Reply 1: No mention has been made in our text about IRB approval. Indeed, given the retrospective nature of our study, no authorization from the IRB was mandatory. However, the set of Principles of Helsinki were respected.
Changes in the text: page 4, line 30-31 “Due to the retrospective nature of this study, the Institutionnal Review Board was not mandatory. However, all the Principles of Helsinki were respected.”

Comment 2: Please use editing service. Especially, I have concern the proper use of comma and period. In Tables, as the radix point, the period should be used instead of comma.
Reply 2: we totally agree with your remark. all of our values and our tables and figures have been modified in order to comply with international editing rules.
Changes in the text: all numerical values contained in the manuscript as well as in the tables and figures have been modified.

Comment 3: When authors classified these patients using IMDC criteria. Please describe it in the Materials and Methods section with the suitable reference. Recently, we do not call it Heng criteria.
Reply 3: it is indeed an error on our part that we have corrected. The IMDC model is indeed the model currently used for metastatic kidney cancer. We have made sure that this appears in the methods section of the manuscript.
Changes in the text: we have modified our text as advised (page 4 line 23-27). “The prognostic score of each patient was calculated from the 6 clinical and biological data composing the International Metastatic Renal Cell Carcinoma Database Consortium model (IMDC). These data were Karnofsky performance status (KPS), time from diagnosis to first-line targeted therapy, hemoglobin concentration, neutrophil count, platelet count, and serum calcium concentration”.

Comment 4: In Table 2, please describe the number of Grade 3/4 toxicity because the clinical impact of Grade 1/2 and Grade 3/4 are always completely different.
Reply 4: Our table was indeed not precise enough on the proportion of Grade 3/4 toxic events. We have modified the first line to be clearer.
Changes in the text: Table 2, line 3 “grade ¾ toxicity events”.

Comment 5: In Table 1 and Table 2, both tables have different 2 titles. Please revise them. I think that Table 1 is not a flow chart.
Reply 5: indeed, it was a mistake on our part, table 1 is obviously not a flow chart. We have made new simplified and standardized tables in order to gain clarity.
Changes in the text: the titles of the tables have been modified:
- table 1: clinical and tumor baseline characteristics
- table 2: detailed toxicity according to patient age
- table 3: main publications about targeted therapies for mRCC among elderly patients