Author’s response to reviews

Title: Application effect of apatinib in patients with failure of standard treatment for advanced malignant tumours

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Author’s response to reviews:

Dear Editor:

We must thank you and all other reviewers for the critical feedback. We feel lucky that our manuscript went to these reviewers as the valuable comments from them not only helped us with the improvement of our manuscript, but suggested some neat ideas for future studies. Please do forward our heartfelt thanks to these experts.

Based on the comments we received, the format of the manuscript was carefully revised, and checked the references. All changes were marked in highlights colours in this text.

In addition, we also have a native English speakers double-checked the English for the revised version. We hope the new manuscript will meet your magazine’s standard.

Below you will find our point-by-point responses to the reviewers’ comments/ questions:

Reviewer 1:

1- The two VEGFR-2 mediates two signaling pathways is not clear. Please, clarify this sentence.

About this sentence, we mean that “VEGFR-2 mediates two signalling pathways: the protein kinase C–mitogen-activated protein kinase/extracellular signal-regulated protein kinase pathway and the phosphatidylinositol 3 kinase/protein kinase B pathway. The former affects the proliferation of endothelial cells, and the latter is associated with the survival of endothelial cells.”. These can be seen on line 8-12, page 4.
2- Could the authors explain this sentence: "The ECOG score was 1 point in 14 cases (34.1%), 2 points in 21 cases (51.2%), and 3 points in 6 cases (14.6%). The transfer site was < 3 cases in 24 cases (58.5%), and ≥3 cases in 17 cases (41.5%)." 

About this sentence, we mean that “Regarding the ECOG score, 14 patients scored 1 point (34.1%), 21 patients scored 2 points (51.2%), and 6 patients scored 3 points (14.6%). Regarding the patients’ numbers of metastatic sites, 24 patients had < 3 metastatic sites (58.5%), and 17 patients had ≥3 metastatic sites (41.5%).”. These can be seen on line 1-4, page 6.

3- Some numbers and percentages are written differently, please, correct them.

Thank you for the strict review by experts. We have corrected the writing of numbers and percentages. These can be seen on line 28, page 5; line 1, page8; line 18-20, page 9; line 20, page13.

4- It is not right to start a sentence with Arabic number, correct them.

I have made corrections as required. These can be seen on line 4, page 7; line 1, page8.

5- Tables should be better organized. Title should be justified. The values should be centralized. There is no table legend, please insert it.

Table legend has been re-corrected. Change to the following:

Table 1 Comparison of curative effects between patients with different clinical features [n (%)]

Table 2 Comparison of median PFS time after apatinib treatment between patients with different clinical features (months)

Table 3 Therapeutic effect of apatinib in different cancers

Table 4 Adverse reactions in patients treated with apatinib

Reviewer 2:

1. Pages of the Manuscript was not numbering

The manuscript has been marked with the page number.

2. Line 3 of the abstract Background of the abstract needs more information about the project.

In recent years, targeted therapy has received widespread attention. Among these therapies, anti-angiogenic targeted drugs have become one of the hotspots of research. Apatinib is a novel oral small molecule anti-angiogenic agent that has been clinically tested in a variety of solid
tumours. The aim of this study was to investigate the efficacy of apatinib in patients with advanced malignant tumours and failure of standard therapy. Already added as required, these can be seen on line 2-7, page 2.

3. Line 7 Methods should contain something about the type of clinical data

We collected 41 patients with advanced malignant tumours in our department; all tumours were pathologically confirmed as malignant. All patients received apatinib after failure of standard therapy: 500 mg/dose, one dose/d, orally 30 min after a meal, until progressive disease or intolerable adverse reactions occurred. When there was a second- or third-degree adverse reaction associated with apatinib during treatment, apatinib treatment could be suspended or reduced to 250 mg/dose. Clinical efficacy and progression-free survival were assessed according to RECIST1.1, and adverse reactions were observed. These can be seen on line 8-15, page 2.

4. Line 11 The Author did not mention the duration of the short-term efficacy and survival

Here we mean “assess clinical efficacy and progression-free survival”

5. Line 15 The efficacy assessment was available in 31 patients, what about the remaining 10 patients

Of the patients, 10 had not been treated for 1 month due to drug side effects or to economic or other reasons; the patients stopped taking the drug on their own, and its efficacy could not be evaluated. Therefore, efficacy could be evaluated in 31 patients.

6. Results Line 53 The treatment time of 41 patients was 0.2 ~ 15.7 weeks, months or years?

The patient's treatment time is 0.2 ~ 15.1 month.

7. Table 4 Needs more clarification regarding the groups. What they indicate and what means of weak as a adverse effect.

Hand-foot skin reaction, hypertension, and proteinuria were the most frequent ARs of antiangiogenic drugs. However, all of the ARs could be managed by reducing the dose of apatinib. Apatinib showed a high rate of hypertension and proteinuria, but the occurrence rate of grade 3–4 events was low. In view of the present reports, apatinib shows acceptable safety.

Reviewer 3:

1. The manuscript needs extensive language revision.

We re-correct the language and grammar of the manuscript, and have a native English speakers double-checked the English for the revised version.
2. The argument in the background section needs to be strengthened and to be more convinced.

We re-expand the background part, see the text section for details. Supplementary text that we mark them orange.

3. Other variables and cofounders should be mentioned. Then, a multivariate regression should be done to access the impact of these variables on the final outcomes.

Thanks for your advice. When designing the experiment, we considered other variables related to the data, and carry out multiple regression, obtain the impact of these variables on the final result. However, the data is too small to provide enough evidence to support the experimental results. Due to the limitations of this study, including a small sample size and a limited number of patients, also it is a single-center treatment, and there may be bias in the selection. In the future, it is necessary to further study and verify the effectiveness and safety under a sufficient sample size. Thank you very much for your pertinent advice.