Peer Review File

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Reviewer A

Comment 1: The analysis should be performed in the ITT population, not in a subset of 25 patients that took apatinib for >1 month. All 30 patients who received at least one dose of apatinib should be included. There is no reason to arbitrarily subset the study to select the 25 patients treated beyond one month.

Reply 1: Thank you very much for these insightful and constructive comments. We have re-analyzed the data and came to the conclusion that the PR rate and SD rate was 20.0% and 40.0% respectively, and DCR was 60.0% in intent-to-treat (ITT) analysis. The relevant content has been added in our manuscript. (see Page 3, line 45-46; Page 8. line 157-158)

Changes in the text: Page 3, line 45-46; Page 8. line 157-158

Comment 2: What is the rationale to use a low dose of apatinib? What is the expected target engagement for apatinib at low doses? Does it inhibit VEGFR2 effectively? It's unclear why the authors used the described doses, other than to "lower toxicity". Is expected target engagement at this exposure enough to inhibit VEGFR2? Why efficacy would be better in SCC than ADC patients? Can the authors speculate?

Reply 2: We really appreciate the reviewer for his/her careful reading of our manuscript. Low-dose apatinib was used because of its safety and efficacy in end stage patients. A clinical study of low-dose apatinib (250 mg) monotherapy as a third-line treatment in patients with metastatic colorectal cancer (mCRC) was carried out recently. The results showed that the ORR and DCR were 4.0% (2/50) and 70% (35/50), and the median PFS and OS were 4.7 months and 10.1 months, which demonstrated that low-dose apatinib had comparable survival outcomes and limited adverse reactions(1). In our study, we also have observed definite effects of low-dose apatinib in elderly end-stage patients, including significant tumor regression, improvement of quality of life, and tolerable adverse effects. Above all, we used low-dose apatinib in the consideration of safety and efficacy.

It has been reported that apatininb could inhibit of VEGFR2 at very low dose *in vitro* and *in vivo*. YN968D1 (apatinib mesylate) completely blocked VEGFR2 activation at a concentration of 0.1 μM, which was comparable to sunitinib. The phosphorylation of ERK1/2, a downstream of VEGF signaling, was inhibited concomitantly(2). This study suggested that low-dose apatinib could also inhibit VEGFR2 effectively.

ADC patients usually carry more driver genes than SCC patients, which may be the reason why efficacy is better in SCC than ADC patients.

Reference

1. Zhao L, Yu Q, Gao C, et al. Studies of the Efficacy of Low-Dose Apatinib Monotherapy as

Third-Line Treatment in Patients with Metastatic Colorectal Cancer and Apatinib's Novel Anticancer Effect by Inhibiting Tumor-Derived Exosome Secretion. Cancers (Basel) 2022;14.

2. Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci 2011;102:1374-80.

Reviewer B

Comment 1: This study is retrospective analysis of patients with end-stage cancer treated with Apatinib between 2014 to 2016. Phase III trials of Afatinib has already been performed, therefore current results are not useful for development of Apatinib.

Reply 1: We thank the reviewer for raising this point. However, we thought the manuscript is useful and worthwhile publishing. The first-line or phase III clinical trial of apatinib cannot instead of results of patients in end-stage. For example, the goal of treatment of end-stage patients is DCR, not ORR. The patients in the end stage have poor tolerance to the standard dose, so low doses are more popular. This article explores the efficacy and safety of low-dose apatinib and demonstrates that apatinib is a satisfactory option for the end-stage cancer patients.

Comment 2: Entry criteria of patient were uncertain.

Reply 2: We thank the reviewer for this comment. The entry and exclusion criteria of patient are as follows: The end-stage cancer patients who was heavily pretreated and received low-dose apatinib. All patients suffered from uncontrollable progressive lesions, making them unsuitable for surgery, radiotherapy, and chemotherapy (intolerant or PD after combined chemotherapy). We excluded patients treated with a combination of Apatinb and other therapies, such as chemotherapy, radiotherapy, or targeted therapy. The patients who were not at end-stage but received mono-apatinib treatment were also excluded. The relevant content could be found in our manuscript. (see Page 5, line 91-96).

Changes in the text: Page 5, line 91-96

Comment 3: A variety of cancers such as head and neck cancer, gynecological cancers, and digestive cancers were included in this analysis. Details of cancer type of gynecological cancers and digestive cancers, such as uterine cancer, ovarian cancer, stomach, colorectal, pancreatic cancers, or others should be clarified.

Reply 3: Thank you very much for your careful reading of our manuscript. Details of cancer type and pathology were shown in Supplementary table 2 (Detail information of each patient).

Comment 4: Afatinib were used from 125 to 500mg in this study. It is not scientific that dose determination of Afatinib was uncertain.

Reply 4: Thank you very much for raising this interesting question. Our research is a retrospective study. Heavily pretreated patients with end-stage cancer who received oral administration of apatinib were enrolled, and the clinical outcomes were analyzed retrospectively. The dose of apatinib was decided according to the patient's clinical feature and personal tolerance. Therefore, the dose of apatinib should not be certain.

Comment 5: Overall response rate should be shown according to intent-to-treat analysis, therefore PR rate and DCR would be 20% and 60%, respectively.

Reply 5: I appreciate your helpful comment so much. We have re-analyzed the data and came to the conclusion that the PR rate and SD rate was 20.0% and 40.0% respectively, and DCR was 60.0% in intent-to-treat (ITT) analysis. The relevant content has been added in our manuscript. (see Page 3, line 45-46; Page 8. line 157-158)

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