Peer Review File

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Reviewer A

The overall contents of the manuscript do not provide clinically valuable information. The study purpose and the outcomes are not clearly connected to reach the conclusion. It appears the meta-analysis was conducted based on the literature review of mostly single arm studies, but not based on the patient level data. It brings significant limitations in the results interpretation, although the individual studies' heterogeneity was adjusted statistically. The figures and table are not clearly presenting meaningful data with accurate units, which cannot explain why it reaches the conclusion. In addition, at least two randomized clinical trials proved no survival benefit, although some other trials earlier showed promising response and survival data. With the consideration of additional risk of toxicity, international guidelines do not recommend adding bevacizumab for the treatment of ED-SCLC. With the reasons above, it is not convincing why bevacizumab in combination with chemotherapy provides better clinical benefit compared to chemotherapy alone. If authors still have desire to publish this article, my recommendation is to add the analysis of clinical benefit with bevacizumab by each different genomic biomarker group and other clinical characteristics, which is not likely feasible in publicly available data based meta-analysis.

Reply: Thank you so much for your advice. Your suggestion is very inspiring and objective. As you have mentioned, the utility of bevacizumab in SCLC is still a dilemma. In the previous studies, it seems that no improvement of OS could be yielded from the additional bevacizumab treatment. Meanwhile, neither ORR nor DCR was found better in the studies. Therefore, it appears that the current study provides no valuable clinical information. But it also shows that SCLC patients, though slightly, could benefit from it in terms of PFS.

At the very beginning, we tended to perform a comparative meta-analysis to figure out whether bevacizumab could be added to the standard regimen in treating ED-SCLC. However, only 3 analyzable articles were finally included in the primary cohort. We agree with you that meta-analysis comprising of only 3 comparative studies is not convincing enough. Therefore, we tried to investigate other clinical outcomes and adverse effects to provide more evidence for clinical decision. Besides, the subgroup analysis was also performed to look into the difference response from treatment-naïve and relapse patients. We noticed that the additional bevacizumab is well-tolerated with a slightly higher rate in hypertension. In order to further investigate whether the adverse effects are dose-related. We also separated the patients into different dosage groups. No significant adverse effect rate was observed.

In conclusion, we intended to provide evidence from a systemic review and meta-analysis. The single-arm analysis could indicate the estimated clinical outcomes and adverse effect rates. We are not trying to recommend using bevacizumab in ED-SCLC patient. According to the current publications, we agree that using anti-angiogensis treatment in combination with standard regimens are of limited effects.

Thank you again for your suggestions.

Reviewer B

The manuscript “effectiveness and safety of bevacizumab in extensive-disease small cell lung cancer: a systemic review and meta-analysis” by He et al.

Despite the hard work of the authors, there are several limitations and deficiencies in the work.

1. Majority of the studies included in the analysis were single arm with different doses of bevacizumab and different chemotherapy regimens. Even in the 3 randomized trials included in this analysis, there was significant variations in the chemotherapy doses, regimes and follow up. All these factors could impact the long-term outcome. The authors need to have robust methodology to address risk of bias assessment, particularly the single arm studies. There are several tools available to conduct risk bias assessment for non-randomized trials (e.g. Slim et al 2003, Dreek et al 2003).

Reply: Thank you very much for your advice. After screening from the publication candidates, we noticed that very few two-arm trials, no matter they were randomized or non-randomized, could be identified or included in the further analysis. There were only 3 candidates were finally selected for analysis after exclusion, the others were single-arm studies. We totally agree with you that different chemotherapy regimens or dosages can generate enormous differences to the clinical outcomes. We, therefore, looked up and read some previous reports before performing further investigations. We noticed that no significant survival outcomes were reported between the comparisons of cisplatin vs carboplatin or etoposide vs irinotecan (Kubota et.al 2014, Azar et.al 2020). Only some tendencies of higher complication rate were found in irinotecan groups. Based on this information, we did the meta-analysis of these two-arm studies. In terms of bias evaluations, Begg’s and Egger’s tests are commonly recommended for publications bias evaluation. Besides, those tools you have mentioned are also applied. But these methodologies are not normally required if only 3 candidates were included. Meanwhile, the finally analysis showed no significant heterogeneity between the candidates.
We want to provide evidence for clinical practitioners to make their decision whether bevacizumab is suitable for treating SCLC as additional component. In our findings, it showed that patients might benefit from the additional bevacizumab in PFS but they could experience a slightly higher risk of complications. Given, we would recommend clinical practitioners should be careful if they want to administer it to SCLC patients.
We really appreciate your suggestion.

2. The authors need to elaborate on their methodology and should include detailed description of their literature-search strategy and data extraction.

Reply: Thanks for your suggestion. We have added the extra description about the literature selection procedure in the text.

3. There are several errors in the manuscripts. For example, the numbers described in Figure 1 are totally different to what described in the results section on page 5. There are several grammatical and syntax errors in the manuscript.

Reply: Thank you for pointing out the errors. We have reviewed the manuscript again and corrected the errors.

4. The true effect size is very small, in fact there is no improvement in overall survival with the addition of bevacizumab in ES SCLC, so the authors conclusion that 'bevacizumab improved OS" is hard to accept. Moreover, the authors failed to recognize some facts, for example the HR of 0.80 for OS favoured the chemotherapy alone group, not bevacizumab in Pujol et al.

Reply: Thanks for your suggestion. We also found that the previous conclusion was slightly inappropriate. We intend to provide objective evidence for clinical practitioners in deciding whether adding bevacizumab in combination with traditional regimen for SCLC patients. Justifying the usage of bevacizumab is not our intention. Therefore, we rewrite the conclusion and make it more objective. We carefully read the Pujol's article. It turned out to the conclusion of the authors was not compliant to their figure in their article. As you can see the KM curve of the OS, the CT plus Bev obviously has a better median OS than CT alone. However, Pujol et. al reported that CT alone had HR 0.8. In order to solve this discrepancy, we decided to extract the survival data from the KM curve. But the combined results seem to be unaffected.
Thank you for pointing out such error, which also bothers us for a while. We really appreciate that.

5. Authors need to get familiar with the current standard of care treatment for small cell lung cancer. The treatment for limited stage is chemoradiotherapy with PCI, while for the extensive stage is combination chemotherapy and atezolizumab, with the current median OS of around 12 months.

Reply: Thank you so much for reminding us the standard of care. We agree that the IO has become a strong assistant to the traditional chemotherapy for extensive-disease SCLC. The purpose of this study is to provide evidence to figure out whether it is appropriate to add bevacizumab to the tradition regimen for ED-SCLC patients. The result turns out to be negative. We would try to further study the effect of IO in ED-SCLC patients in the up-coming days.

Reviewer C

He and colleagues report a systemic review and meta-analysis of effectiveness and safety of bevacizumab in extensive-disease small cell lung cancer. The main message is that bevacizumab may be effective for ED-SCLC, but the effects are not completely clear. This

manuscript is a well written. I have few Replys.

General comment's
- The standard treatment for ED-SCLC is now a combination of chemotherapy and immunotherapy, rather than chemotherapy alone. However, the effect is not satisfactory, and I think there is still room for further investigation of the combination of angiogenesis inhibitors. In fact, a phase III, double blind, randomized study of bevacizumab in combination with carboplatin or cisplatin + etoposide + atezolizumab compared with carboplatin or cisplatin + etoposide + atezolizumab in patients with untreated ES-SCLC (BEAT-SC study, JapicCTI-195034) in Asian region. I recommend that authors add to the discussion section the current standard of care for ED-SCLC including immunotherapy, basic data on the combination of angiogenesis inhibitors and immunotherapy and data on other carcinomas, and ongoing trials of angiogenesis inhibitors combined with immunotherapy/chemotherapy in ED-SCLC.

Reply: Thank you so much for your compliment and suggestion. The ED-SCLC is still poorly responsive to the chemotherapy. Clinical practitioners are always willing to find out new regimens to improve the clinical outcomes of these patients. The role of bevacizumab in NSCLC has been proved effective to prolong survival. Therefore, doctors are trying to verify the role of it in SCLC patients. However, there is no consensus on its effect in SCLC.
We agree with you that anti-angiogenesis treatment in combination of traditional chemo and IO would be effective somehow. But such benefit would not be universal to all SCLC patients but some specific ones. Meanwhile, the survival benefits might be also various.
We have added some info about the new standard regimen in the discussion section.
Hopefully that would be more convincing. Thank you again for your suggestion.