Peer Review File

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Reviewer A

This is a case report regarding combination of osimertinib plus bevacizumab in EGFR mutant NSCLC with LM. The author described very promising clinical outcomes with this regimen. Although this is quite interesting data, several issues should be concerned.

Reply: Thanks very much for your appreciation.

- The first patient received WBRT with combination of osimertinib plus bevacizumab. Given the potential efficacy of WBRT in LM patient, it is hard to differentiate which treatment played a major role in this patient. Given that, this case should be removed to better define the pure role of combination therapy.

Reply: Thanks. Following your good comment, we have deleted the Case 1.

- Since high penetration of osimertinib in CNS, osimertinib alone might be enough to control LM. And there is no evidence to show combination strategy is better than single agent. This should be discussed. Also, Bloom study used 160mg of osimertinib in LM and it is not still clear whether 80mg vs 160mg of osimertinib has similar efficacy in LM. This issue also should be discussed.

Reply: Thanks for your good suggestion. We are totally agree with your opinion that osimertinib has high CNS penetration of NSCLC, and osimertinib alone might be enough to control LM. However, on the one hand, patients with NSCLC and LM had very dismal prognosis and therapeutic strategies are very limited. On the other hand, EGFR-mutant NSCLC patients with LM received osimertinib had significantly shorter the median OS than those without or with asymptomatic CNS metastasis in the

FLAURA study. These findings suggest that alternative treatment strategies beyond osimertinib are still urgently needed for these population. Mechanistically, EGFR inhibition in combination with VEGF/VEGFR pathway blockade had biologically synergistic antitumor activity in preclinical model. Then, several recent phase II/III trials have demonstrated that EGFR-TKIs plus bevacizumab could significantly improve PFS than EGFR-TKIs monotherapy in first-line treatment for patients with EGFR-mutated NSCLC. Moreover, a recent phase I/II trial reported that osimertinib pus bevacizumab could be efficacious and protective against CNS progression. Therefore, we presented one case with EGFR-mutated NSCLC and LM received osimertinib plus bevacizumab. Our result firstly reported the excellent and durable response of both primary lesion, BMs and LM to this regimen, suggesting the potential efficacy of osimertinib plus bevacizumab in LM.

As you mentioned, whether 80 mg vs 160 mg of osimertinib has similar efficacy in LM remains unclear so far. Preclinical pharmacokinetic and pharmacodynamic modeling and retrospective analysis from the AURA studies with LM patients suggest that more than 50% of patients are expected to have sufficient LM-free drug exposure to achieve maximal tumor growth inhibition at 80 mg of osimertinib. However, a recent study reported that 160 mg of osimertinib controlled the disease in six of eight patients who developed LM during 80 mg of osimertinib therapy. These findings suggest that 160 mg of osimertinib could have better efficacy than 80 mg in controlling LM. Due to the limited sample size, further investigation with osimertinib 80 mg vs 160 mg in patients with LM is warranted. Here is the added text.

“Theoretically, the objective response of LM should be more sensitive to the CSF concentration of osimertinib because of metastatic tumor cells spreading to CSF, leptomeninges, and subarachnoid space. In the BLOOM study and a phase II trial, double dose of osimertinib (160 mg once daily) showed striking efficacy in controlling LM. Furthermore, a recent study reported that 160 mg of osimertinib could control the

disease in six of eight patients who developed LM during 80 mg of osimertinib therapy. Collectively, these findings suggest that 160 mg of osimertinib could have better efficacy than 80 mg in controlling LM. However, due to the limited sample size, further investigation to compare the efficacy of osimertinib 80 mg to 160 mg in patients with LM is warranted."

Reviewer B

This paper titled "Osimertinib in combination with Bevacizumab in EGFR-Mutated NSCLC" by Tao Jiang, et al shows 2 cases of NSCLC with cytologically confirmed leptomeningeal metastases (LM) effectively treated with osimertinib plus bevacizumab. This regimen is challenging for NSCLC patients with LM. Although cases described in this article are interesting, I would like to indicate some points as below to improve the article. I hope these comments will be helpful.

Major comments.

1. I can understand the authors would like the title to have an impact, but the present title could be misleading. I recommend to reconsider the title. "Two cases of NSCLC with leptomeningeal metastasis treated with osimertinib plus bevacizumab" would be better.

Reply: Thanks for your good suggestion. We have revised the title as "Osimertinib in combination with Bevacizumab in EGFR-Mutated NSCLC With Leptomeningeal Metastases: a case report".

2. The patient No.1 was treated with osimertinib plus bevacizumab for only 2-3 months at date cutoff . Therefore, I do not think that the response in patient 1 is not enough to mention as "durable response".

Reply: Thanks. Following your and Reviewer A's comment, patient No.1 received concurrent WBRT and short time of osimertinib plus bevacizumab. The representability of this case is limited. Thus, we decided to remove this case.

3. Possible duration of response when treated with osimertinib in patients with LM should be discussed. Date from BLOOM and retrospective analysis of AURA studies are available.

Reply: Thanks. We have added the text on the data form BLOOM and retrospective analysis of AURA studies. Here is the added text.

"In previous study, 22 NSCLC patients (previously received EGFR-TKIs, from the AURA program) with EGFR T790M mutation and radiologically-detected LMs were treated with osimertinib (80 mg once daily). LM ORR was 55% according to RANO-LM radiologic criteria, a median LM PFS was 11.1 months, and a median OS was 18.8 months. Then, Yang et al. reported the BLOOM study, which demonstrated that osimertinib 160 mg showed promising therapeutic efficacy in patients with EGFR-mutated and LM (investigator-assessed ORR 41%, PFS 8.6 months, OS 11.0 months)."

4. I recommend to discuss about which regimen is better in LM treatment: osimertinib alone or osimertinib plus bevacizumab. I also recommend to discuss about future clinical trials. Phase 2 study of osimertinib plus bevacizumab for LM is already ongoing (https://clinicaltrials.gov/ct2/show/NCT04425681).

Reply: Thanks. We have added the text on which regimen is better in LM treatment and the ongoing trial. Here is the added text.

"Here, we presented one case with EGFR-mutated NSCLC and LM received osimertinib plus bevacizumab. Our results firstly suggested the excellent and durable response of both primary lesion, BMs and LM to this regimen. Notably, the phase II study of osimertinib plus bevacizumab for LM is already ongoing. The result is anticipated. To date, we have at least three therapeutic choices, osimertinib 80 mg, osimertinib 160 mg and osimertinib 80mg plus bevacizumab, for EGFR-mutated NSCLC with LM. Which regimen is better in LM treatment need future investigations."

Minor comments.

1. Adverse events observed in 2 cases should be noted.

Reply: Thanks. Since we removed Case 1 according to the Reviewer #1' comment, we have added the adverse events of Case 2 in the revised manuscript.

2. Please mention the reason 7.5mg/kg of bevacizumab was chosen. Previous trials adopted bevacizumab 15mg/kg.

Reply: Thanks. Although previous clinical trials adopted 15mg/kg of bevacizumab, it is not recommended in Chinese population. 7.5mg/kg of bevacizumab is the recommended dose in Chinese patients with non-squamous NSCLC. Importantly, previous study revealed that 7.5mg/kg of bevacizumab showed the similar antitumor efficacy to 15mg/kg of bevacizumab when combined with chemotherapy as first-line therapy for non-squamous NSCLC (Martin Reck et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol. 2009 27(8):1227-34.).

3. Detailed explanation on radiological and cytological findings are warranted in figure legends.

Reply: Thanks for your comment. We have added the detailed explanation on radiological and cytological findings in figure legends. Here is the new Figure legend.

*"**Figure 1. A.** Chest computed tomography and brain magnetic resonance imaging images before (at baseline) and after 6 weeks treatment of this case, which showed the excellent and durable response of both primary lesion, BMs and LM to this regimen; **B.** flowchart of cerebrospinal fluid cytologic examination and genotype results of this case, which showed the leptomeningeal metastatic cells in cerebrospinal fluid with EGFR exon 19 deletion, AKT2 and MYC amplification."*

4. The detail of NGS kit should be described (name of the product, enterprise). The

paper by Yang JCH (BLOOM study) does not appear in the reference list.

Reply: Thanks for your suggestion. We have added the details of NGS kit and the paper by Yang JCH (BLOOM study) in the reference list.

5. There are some typos to be corrected (Line 91, 95. 104, 117).

Reply: Thanks. We have corrected these typos. Some grammar and spelling errors have also been corrected. Please seen in the revised manuscript.

6. Although the author's previous study showed survival benefit in EGFR-TKI plus bevacizumab, other studies, such as NEJ026 and JO25567, failed to show survival benefit. I recommend to discuss on this disconcordance. A comprehensive meta-analysis is also available (PMID 32714857).

Reply: Thanks for your comment. The current manuscript aimed to investigate the the efficacy and tolerability of osimertinib plus bevacizumab for patient with EGFR-mutated NSCLC and cytologically proven LM. The discrepancy between our previous findings and two previous trials (NEJ026 and JO25567) was beyond the research scope of our present study. Thus, we did not discuss on this topic. Following your good advice, we have added this meta-analysis (PMID 32714857) in the reference list.

"A recent meta-analysis also indicated that patients with BMs at baseline in the EGFR-TKIs plus bevacizumab group had a trend toward better PFS (hazard ratios = 0.55, P = 0.001). Analogously, our previous publication indicated that EGFR-TKIs in combination with bevacizumab could significantly prolong both PFS and OS in those with EGFR-mutated NSCLC with multiple BMs. Moreover, a recent phase 1/2 trial reported that osimertinib pus bevacizumab could be efficacious and protective against central nervous system progression."