Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1860

Reviewer A

The current paper reports on the outcome of a phase 2 trial with apatinib plus chemotherapy (docetaxel or pemetrexed) in previously treated patients with metastatic NSCLC and multiple brain metastases. Thirty-five patients who had been pretreated with two or more lines of treatment were enrolled. The overall response rates for measurable and non-measurable brain metastases were 10% and 15%, respectively. The disease control rate for intracranial lesions was 66%. Median progression-free survival and median survival were 4 and 9 months, respectively.

Comments

1n my opinion, brain radiotherapy (stereotactic or whole brain irradiation) can be considered as a treatment option also for patients who have previously been pre-treated with more than two lines of systemic therapy.

Reply: Undoubtedly, radiotherapy is one of the main treatment modalities for brain metastases in advanced lung cancer. In this study, approximately 30% of patients received radiotherapy (whole brain radiation therapy or stereotactic body radiation therapy) prior to enrollment, while the remaining 70% of patients did not receive radiotherapy, with a majority of them having either subtle or asymptomatic symptoms at the time of brain metastasis.

The disease control rate for intracranial lesions of 66% was seen at what time?

Reply: In the efficacy evaluation section of the research methodology, it was explicitly stated that the efficacy would be assessed every 4 weeks (as described in lines 171-173 on page 6). The disease control rate for brain metastases was calculated after 12 weeks of treatment commence.

Did the patients experience symptom relief with regard to their brain metastases?

Reply: Due to the majority of enrolled lung cancer patients with brain metastases being either asymptomatic or having mild symptoms in this study, the assessment of symptom relief was not included as a criterion for evaluating efficacy. Only imaging techniques such as MRI were used to assess treatment response.

Reviewer B

Below are some of the items that need significant revision.

Use of word accepted should be changed to completed when referencing treatment. Ex page 1

line 18.
Page 2 line 34 -change “big” to “large”
Page 2 Highlights section – inappropriate use of abbreviations (pts, nab-ptx), did not capitalize nsclc. Need a lot of editing. How are you defining efficiency? Or do you mean efficacy?
Reply: The suggested modification has been made in accordance with the reviewer's comments. Additionally, due to a spelling error, "efficacy" was mistakenly written as "efficiency". The change has been made in accordance with the reviewer's comments.

Validity of results – How are the authors concluding that the OS and PFS were due to the apatinib without a control arm?
Reply: Due to the limited ability of chemotherapy drugs to penetrate the blood-brain barrier, the efficacy of traditional chemotherapy agents such as pemetrexed and docetaxel is not high in lung cancer brain metastases. Literature reports suggest a monotherapy response rate of only 3%, with median progression-free survival (PFS) and overall survival (OS) of merely 3 months and 6 months, respectively. Through indirect comparisons, it can be inferred that the combination of apatinib and chemotherapy significantly improves the treatment efficacy for lung cancer brain metastases.

Conclusion section is missing.
Reply: The conclusion has been added as per the reviewer's request (see lines 294-304 on page 9).

Reviewer C

The authors retrospectively examined 35 cases of non-small cell lung cancer with brain metastases to assess the significance of adding Apatinib to Docetaxel or Pemetrexed. While the overall response rate may appear favorable, there are concerns that need to be addressed and clarified, especially regarding the limited reporting on the outcomes specific to the effects on brain metastases. The following points of concern require resolution or revision:

#1
The efficacy of monotherapy with Docetaxel or Pemetrexed in treating brain metastases should be documented using historical controls. In other words, it is necessary to include information from past clinical trials regarding the extent of effectiveness achieved with Docetaxel or Pemetrexed monotherapy for brain metastases. This information is crucial to assess whether Apatinib exhibits an additive or synergistic effect.
Reply: Due to the limited ability of traditional chemotherapy drugs to penetrate the blood-brain barrier, currently there are no specific studies on the efficacy and safety of monotherapy with docetaxel or pemetrexed for brain metastases in non-small cell lung cancer (NSCLC). However,

since both monotherapy with docetaxel or pemetrexed are standard treatment regimens for second-line therapy in NSCLC, some large clinical studies such as NCT04303780 and LUME-Lung 1 have shown that the efficacy of monotherapy with docetaxel or pemetrexed in the brain metastasis subgroup is only around 3%, with a median progression-free survival (PFS) of no more than 3 months and a median overall survival (OS) of no more than 6 months. In this study, the combination therapy with apatinib plus docetaxel or pemetrexed achieved an efficacy rate of 10% in measurable brain lesions of NSCLC patients with brain metastases, and 15% in patients with unmeasurable lesions. The overall PFS and OS were 4 months and 9 months, respectively. These results indicate that compared to monotherapy with docetaxel or pemetrexed, the combination of apatinib with docetaxel or pemetrexed significantly improves the efficacy for NSCLC patients with brain metastases.

#2

Line 182-188

If the authors aim to present data specifically focused on brain metastases, it is essential to disclose how many cases within the total population of 35 showed measurable brain metastatic lesions. Then, the intracranial response rate is 10%, with a progression-free survival (PFS) 4 months, indicating a less favorable outcome compared to the overall population. The data of the effectiveness of combination therapy with Apatinib against brain metastases is limited and not impressive.

Reply: In this study, 80% of the enrolled patients had measurable brain lesions, while 20% had unmeasurable lesions. Although the efficacy rate for brain lesions was only 10%, further subgroup analysis revealed that the combination of apatinib with docetaxel or pemetrexed resulted in a median progression-free survival (PFS) and overall survival (OS) of 6 months and 12 months, respectively, in patients with measurable lesions. This indicates that combination therapy, compared to monotherapy with docetaxel or pemetrexed, can still provide significant survival benefits for NSCLC patients with brain metastases.

#3

Line72

ALK is an abbreviation for anaplastic lymphoma kinase, and the mention appears to be incorrect.

Reply: In response to the reviewer's request, the abbreviation for ALK has been changed to anaplastic lymphoma kinase.

#4

Line176

Since Osimertinib is a widely approved drug globally, AZD9291 should be referred to as Osimertinib

Reply: In response to the reviewer's request, AZD9291 has been changed to osimertinib.