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Reviewer A

Comment 1: There are several resistant mechanisms for 1st-line EGFT-TKI. In this report, the patient was resistant to afatinib, but sensitive to BE. The authors should describe potential resistant mechanisms that existed in this case.

Reply 1:

2nd generation TKIs have resistant mechanisms including T790M mutation as do 1st generation TKIs. There are off-target mechanisms of cMet, Her2, transforming to small cell lung cancer and so on, but a smaller percentage compared to 3rd generation TKIs. In this case, we checked EGFR mutation of plasma and CSF before BE treatment. T790M resistant mutations could not be detected. We have no data about off-target mechanisms. We believe that there is no T790M mechanism in this meningitis, whereas liquid biopsies often include false negatives. It is known that the mechanism of resistance in brain, spine, and meningeal metastasis is different from that in extracranial metastasis because concentrations of EGFR-TKIs in CSF are lower than in extracranial sites. It was reported that there are no T790M mutations in intracranial lesions in most patients with extracranial lesions exhibiting T790M resistance. (Hata et al. J Thorac Oncol. 2015 Nov;10(11):1553-9.) We do not know the exact mechanisms of resistance to afatinib in this case. However, this resistance mechanism might be related to a low concentration of TKI, and might be overcome by a high concentration of EGFR-TKIs.

Change in the text : We have modified our text as advised (see Page 11, line 7-11).

Comment 2: The meningitis worsened again after BE treatment. Was there any newly developed resistant mechanisms, such as T790M mutation? The authors should describe the mechanisms for the second resistance to BE. If the authors did not have relevant data, please describe potential mechanisms.

Reply 2: In liquid biopsy after failure of BE treatment, plasma EGFR testing was positive for the exon 19 deletion mutation and negative for the T790M mutation. At that time, the cerebrospinal fluid had not been tested for EGFR. Although there are no data on the resistance mechanism of BE treatment beyond the PCR-based EGFR mutation test, on-target mechanisms other than T790M and various off-target

mechanisms were suspected as resistance mechanisms. Data from NEJ024 show that patients receiving BE and those receiving erlotinib have the same rate of plasma T790M resistance mutations. (Fukuhara et al. Ebio Medicine)
The BE resistnace mechanism needs to be resolved by further studies with BE.
Change in the text : We have modified our text as advised (see Page 8, line 9-11).

Reviewer B

Comment 1: First of all, the medical English writing of this manuscript needs revision. There are many grammar errors.
Reply 1: We asked a native English speaker to check our manuscript again.
Change in the text: We edited our manuscript as advised.

Comment 2: The patient had disseminated pleural seedings and a few parietal pleural nodules were biopsied for confirmation of the metastatic nature. But why didn't the patient get any treatment after the surgical process regarding his residual pleural lesions, especially when you knew his lung cancer had an actionable EGFR mutation?
Reply 2: After we discussed treatment options with the patient, he wished to be followed without treatment for cancer.
Change in the text: We modified our text as advised (see Page 6, line 10-11).

Comment 3: What is the exact EGFR mutation in the first-hand biopsy specimen? Please clarify it.
Reply 3: He had EGFR exon19 deletion mutation.
Change in the text: We added "exon19 deletion" (see Page 6, line 9-10)**.**

Comment 4: Why then did the patient take a head MRI examination? Please describe his neurological symptoms and signs.
Reply 4: We perform head MRI every 4 months for early detection of brain metastasis. This is approved in Japan.
Change in the text: no change.

Comment 5: The MRI showed both brain parenchymal metastasis and leptomeningeal carcinomatosis over the cerebellum. As the authors described, the leptomeningeal lesions responded poorly to whole brain radiation, but how about the brain parenchymal lesions? The patient's loss of appetite and slurred speech seemed not compatible with cerebellar involvement alone.

Reply 5: The cerebellar parenchymal lesion showed shrinkage. Slurred speech is a form of dysarthria and is a typical symptom of cerebellar ataxia. We have considered loss of appetite as a symptom of meningeal carcinomatosis.
Change in the text: no change.

Comment 6: It would be better if readers could see pictures of CSF cytology.
Reply 6: We newly added a photo of the atypical cells in the CSF as Figure 3 in this manuscript. We added a pathologist Dr. Sugai to the authors due to prepare the figure.
Change in the text: We added Figure3, and we added a pathologist Dr. Sugai to the authors.

Comment 7: There is some regression of the leptomeningeal metastasis over cerebellum on bevacizumab plus erlotinib therapy but the response is not very remarkable. How about the other lesions? Had the pulmonary, pleural and brain parenchymal lesions already remitted under afatinib treatment?
Reply 7: The lesion in the brain parenchyma also shrank. We modified Figures2 and 3. Other lesions had already remitted under afatinib treatment and hadn't recurred.
Change in the text: We changed Figure 2 and 4.

Comment 8: The leptomeningeal metastasis was refractory to afatinib. Please compare the blood-brain barrier penetration rates of afatinib and erlotinib. So far as I know, their penetration rates are in the same level. So why is there a difference in treatment results? Comparison between erlotinib and gefitinib seems unnecessary because the patient had not taken gefitinib at all.
Reply 8: As newly indicated in the text, there is no significant difference in BBB penetration between erlotinib and afatinib. One of the mechanisms of bevacizumab that acts as an antitumor effect is to increase the tumor concentration of an antitumor drug given simultaneously with bevacizumab by normalizing immature blood vessels in the tumor. (Jain. Nature Med; 7 (9): 987–9). Heyan et al. showed that the addition of bevacizumab increased erlotinib concentrations in high VEGF-expressing tumors in a mouse model compared to erlotinib alone. (Cancer Chemother Pharmacol (2014) 74: 1297-1305)
We speculate that this mechanism also causes an increase in erlotinib concentrations in CNS metastases. Actually, one case report showed a higher penetration rate of erlotinib in BE treatment. (Sakata et al. Lung Cancer 2016 Sep;99:120-2.)

We deleted the sentence about comparison between erlotinib and gefitinib and described the CSF concentration and penetration rate of afatinib.
Change in the text: We added some sentences in our text (see Page 9-10, line 12-4).

Comment 9: In the NEJ026 study (listed as reference number 16 in the manuscript), bevacizumab plus erlotinib did not do better than erlotinib alone regarding therapeutic efficacies on non-small cell lung cancer harbouring actionable EGFR mutations. Then why didn't you adopt erlotinib alone for leptomeningeal metastasis? What is the role of bevacizumab in this combination protocol? Do the three possible mechanisms you mentioned explain the issue well?
Reply 9:
The NEJ026 trial failed to show the benefit of PFS in the BE group compared to the erlotinib group. Patients with brain metastases could only participate in this study if they had no associated symptoms. Therefore, the additional effect of bevacizumab has been evaluated only in a small number of early-stage brain metastases without edema, and this result may be questionable for similar results in advanced brain metastases. We have no idea of the mechanism of high concentration of erlotinib in CFS induced by BE treatment, although the mechanisms might be related to anti-angiogenesis, normalization of tumor vessels, and modulation of immune systems to some extent.
Change in the text: We added a sentence (see Page 11, line 7-11).

Comment 10: That is, for treating cancer cells floating freely in the CSF without need of tumour vessels, how does an anti-VEGF monoclonal antibody exert its effect?
Reply 10: BE treatment increases the CSF concentration of erlotinib according to the report by Sakata et al. BE treatment may have efficacy in tumor cells in CSF through a higher level of erlotinib in CSF.
Change in the text: We added a sentence (see Page 11, line 7-11).

Comment 11: Why didn't you choose a high dose, pulsatile erlotinib or gefitinib regimen to treat this patient?
Reply 11: High doses of EGFR-TKI treatments were not selected because the addition of bevacizumab is thought to increase erlotinib levels in CNS lesions.
Change in the text: no change.

Comment 12: In the title and the last paragraph, the authors mentioned that bevacizumab plus erlotinib was considered to be an effective treatment for severe

EGFR-TKI-resistant meningeal carcinomatosis. I certainly doubt it. Do you think bevacizumab could help reverse the resistance to erlotinib?

Reply 12: The concentrations of EGFR-TKIs in CSF were nearly one-hundredth lower than plasma concentrations. Resistance of CNS metastasis to TKIs are associated with this low concentration of TKIs in CNS. The bevacizumab combination with TKIs could increase the CSF concentration of EGFR-TKIs. This mechanism of BE treatment might act to overcome the resistance to afatinib.

Change in the text: no change.

Reviewer C

Comment 1: In clinical practice, BE treatment may often be tried in EGFR-positive, T790M-negative lung adenocarcinoma with symptomatic central nervous system involvement. Please tell us about the novelty and teaching points in this case report.

Reply 1: The outcome of patients with meningeal carcinomatosis is always poor. If afatinib treatment is administered in the late line to patients with malignant meningitis, some doctors may consider this afatinib treatment to be the last treatment for T790M negative tumors. In this report, BE treatment was effective for afatinib-resistant meningitis. In fact, in case reports, BE treatment achieved about half a year of PFS in the patient with meningitis. This case report may offer another effective treatment option for malignant meningitis.

Change in the text: no change.

Comment 2: The explanation of figures is difficult to understand. If possible, please indicate the lesion site with arrows.

Reply 1: Thank you for pointing that out. We changed figures to make it easier to see. We also added red arrows to the lesions.

Change in the text: We changed Figure 2 and 3.