Letter to the Editor

Osimertinib in combination with bevacizumab in *EGFR*-Mutated NSCLC with leptomeningeal metastases

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Leptomeningeal metastases (LM) occur in approximately 5–15% of non-small-cell lung cancer (NSCLC) patients with *EGFR* mutations together with very poor prognosis, and there is no broadly accepted standard treatment (1). Although new-generation *EGFR*-TKIs have significantly prolonged both progression-free survival (PFS) and overall survival (OS) in patients with *EGFR*-mutated NSCLC (2,3), little is known about the efficacy of novel *EGFR*-TKIs (e.g., osimertinib) for patients with LM. Recently, Lee *et al.* compared the clinical outcomes of patients with *EGFR*-mutated NSCLC and LM received osimertinib with those not receive osimertinib in the *Journal of Thoracic Oncology* (4). Their data showed that patients with LM received osimertinib had significantly longer OS than those not treated with osimertinib (17.0 *vs.* 5.5 months, P<0.001), which suggested that osimertinib would be a good therapeutic option for patients with *EGFR*-mutated NSCLC and LM. Moreover, two recent publications suggested that combining *EGFR*-TKIs and bevacizumab may be efficacious for brain metastases (BMs) and protective against central nervous system (CNS) progression (5,6). Herein, we presented one case to further investigate the efficacy and tolerability of osimertinib plus bevacizumab for patient with *EGFR*-mutated NSCLC and cytologically proven LM.

This patient was a 47-year-old male smoker consulted our hospital with 3-week history of cough and chest distress in September 2019. The thoracic computed tomography (CT) scan found a mass in the lower lobe of the right lung (*Figure 1A*). Multiple BMs and abnormal signal on meninges of cerebellum were seen in magnetic resonance imaging (MRI) scan, but ^{18}F-deoxyglucose on positron emission tomography (PET) scan did not find other distant metastases. Bronchoscopy biopsy and cytology of cerebrospinal fluid (CSF) revealed lung adenocarcinoma (*Figure 1B*). Subsequent genotype of primary lesion revealed *EGFR* exon 19 deletion, which was confirmed by targeted next-generation sequencing (NGS) panel of 139 genes (PULMOCAN, GENESEEQ Technology Inc., Nanjing, China) of CSF cytologic specimen (*Figure 1B*). The patients suffered headache and violent vomiting during hospitalization. Then he received osimertinib (80 mg, once daily) plus bevacizumab (7.5 mg/kg, 21-day cycle) as the first-line treatment from October 2, 2019. Strikingly, the abnormal signal on LM disappeared (*Figure 1A*) and his LM-related symptoms significantly improved. A marked shrinkage of both primary lesion and BMs was also observed after 6 weeks of osimertinib plus bevacizumab treatment (*Figure 1A*). Moreover, the efficacy has been maintained more than 10 months (last follow-up: August 8, 2020). This regimen was well tolerated, with only grade 2 skin rash and grade 1 hypertension during regular follow-up.

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

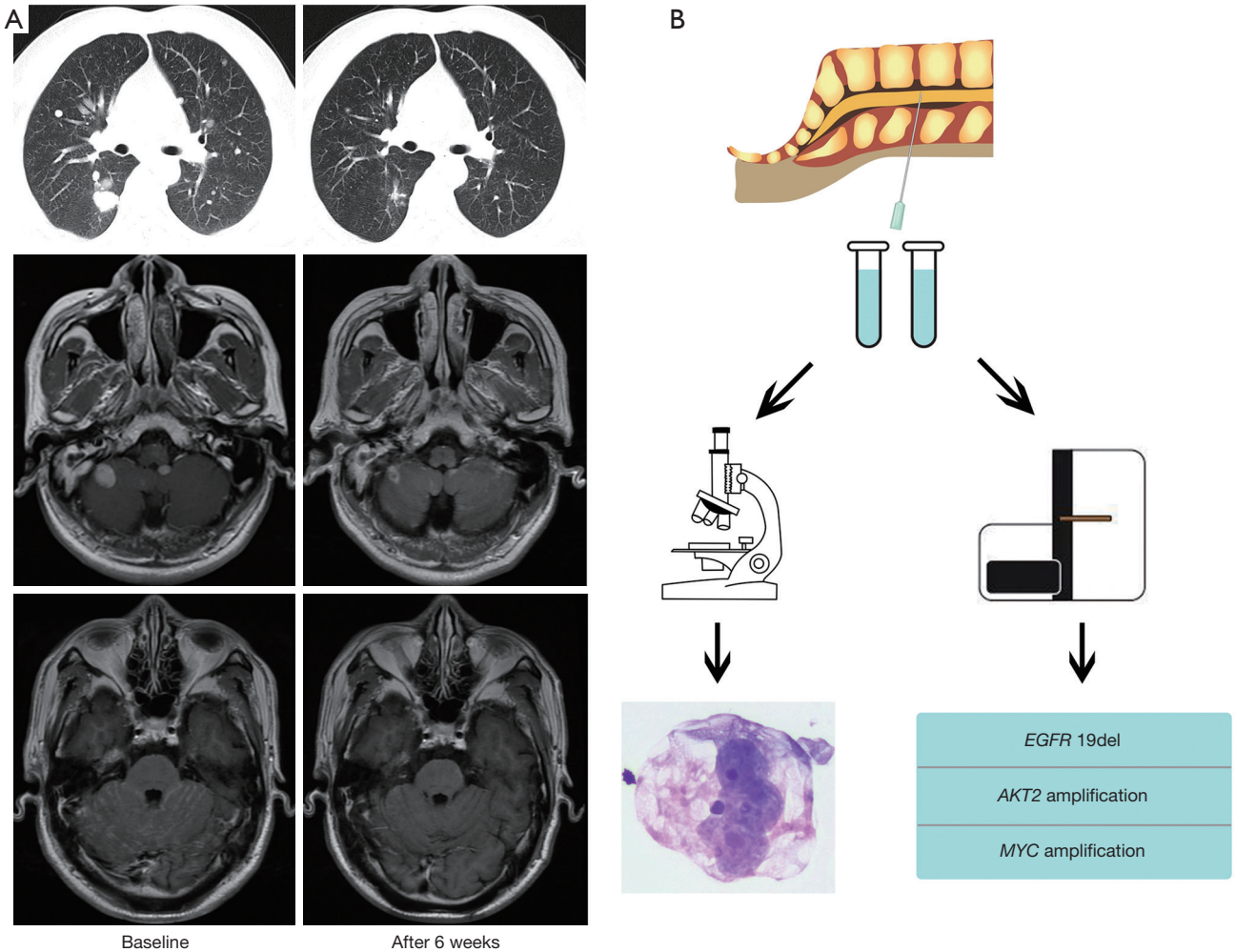

Figure 1 (A) Chest computed tomography and brain magnetic resonance imaging images before (at baseline) and after 6 weeks treatment of this case, which showed the excellent and durable response of both primary lesion, BMs and LM to this regimen; (B) flowchart of cerebrospinal fluid cytologic examination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

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 (7), which demonstrated that osimertinib showed promising therapeutic efficacy in patients with *EGFR*-mutated and LM (investigator-assessed ORR 41%, PFS 8.6 months, OS 11.0 months). Recently, Lee *et al.* reported that patients with *EGFR*-mutated NSCLC with cytologically proven LM received osimertinib treatment had significantly better OS (4). The median OS was 17.0 months in osimertinib treatment group, which is comparable to the data in the BLOOM study. These results together indicate that osimertinib is effective and a promising therapeutic option for patients with *EGFR*-mutated NSCLC and LM. However, patients with LM had significantly shorter the median OS than those without or with asymptomatic CNS metastasis in the FLAURA study, suggesting that alternative treatment strategies are still needed.

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 (7,8), 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 to 160 mg in patients with LM is warranted.

The biologically synergistic antitumor activity of EGFR inhibition in combination with VEGF/VEGFR pathway blockade have been demonstrated in preclinical studies (9). Several recent phase 2/3 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 (10,11). Subgroup analysis reported that the addition of bevacizumab to *EGFR*-TKIs seem to have better PFS for those with CNS metastases (hazard ratios =0.78). 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) (12). 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 (5). Moreover, a recent phase 1/2 trial reported that osimertinib pus bevacizumab could be efficacious and protective against central nervous system progression (6). 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 (NCT04425681). The result is anticipated. To date, we have at least three therapeutic choices, osimertinib 80 mg, osimertinib 160 mg and osimertinib 80 mg plus bevacizumab, for EGFR-mutated NSCLC with LM. Which regimen is better in LM treatment need future investigations.

In conclusion, the current findings suggest that osimertinib or osimertinib in combination with bevacizumab could be considered as a promising treatment option for patients with central nervous system metastases, including BMs and LM. Future prospective and well-designed studies with large cohort are needed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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