Pulse Dose Erlotinib and Zuckerguss Improvement in EGFR-Mutant NSCLC

Pareen Mehta, MD, a Omid Hamid, MD, b,c Samuel J. Klempner, MD b,c,*

aDepartment of Radiology, The Angeles Clinic and Research Institute, Los Angeles, California
bThe Angeles Clinic and Research Institute, Los Angeles, California
cSamuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California

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An 80-year-old Asian female never-smoker presented with neurologic symptoms consisting of slurred speech, ataxia, diplopia, and weakness and somnolence. Contrast-enhanced magnetic resonance imaging (MRI) demonstrated extensive leptomeningeal carcinomatosis (LMC) (Fig. 1 A–C), and staging computed tomography revealed multiple lung nodules. MRI imaging of the spine did not identify additional leptomeningeal foci. A computed tomography–guided left upper lobe lung biopsy revealed an acinar predominant moderately differentiated adenocarcinoma that was strongly positive for thyroid transcription factor 1, positive for mucin, and negative for p63 (data not shown), which is consistent with NSCLC adenocarcinoma. Molecular testing confirmed the presence of an EGFR exon 21 mutation, L858R. The results of testing for other oncogenic drivers were negative, and programmed death ligand 1 staining was 0% (22C3 antibody). A baseline circulating tumor DNA assay did not identify EGFR L858R; the only detected genomic alteration was a variant of unknown significance in BRCA2, DNA repair associated gene (BRCA2) (BRCA2 S708T). The patient declined lumbar puncture for cytologic and circulating tumor DNA analyses. Because of symptomatic leptomeningeal disease, the patient began receiving pulse dose erlotinib, 1 g weekly by nasogastric tube and then orally as her mental status improved over 2 weeks. The patient received initial steroids, which were tapered over 2 weeks. She demonstrated symptomatic improvement, and MRI 8 weeks after she had started therapy showed resolution of the Zuckerguss appearance that was consistent with disease response (Fig. 1 D–F). Treatment response was ongoing for 5 months at the time of submission of this article. Initial whole brain radiotherapy was held because of published activity of pulsatile erlotinib and inability to comply with radiotherapy owing to altered mental status.

Management of oncogene-driven NSCLC with brain metastases continues to evolve. Intracranial disease will develop in nearly 40% of patients with NSCLC, with LMC developing within a subset of them.1 Central nervous system response in EGFR-mutant NSCLC treated with erlotinib ranges from 55% to 89%, although LMC is not included and outcomes are poor in LMC.2,3 Pulsatile dosing of erlotinib to improve central nervous system penetration and cerebrospinal fluid (CSF) concentration has demonstrated clinical activity in EGFR-mutant NSCLC with LMC.4–6 Later-generation EGFR tyrosine kinase inhibitors, including osimertinib, have demonstrated leptomeningeal activity in the phase I BLOOM trial and may not require pulsatile dosing to achieve adequate CSF concentration.7

Diagnosis and response assessment in LMC is problematic, and Response Assessment in Neuro-oncology and Response Assessment in Pediatric Neuro-oncology criteria suggest MRI, CSF, and neurologic examination in accordance with 2017 guidance.8,9 Less commonly, the degree of leptomeningeal disease creates a Zuckerguss or “cake-icing” pattern, as observed in our patient.10 Our patient meets the proposed leptomeningeal Response Assessment in Neuro-oncology criteria for response, and overall, our case adds further support to the activity of pulsatile erlotinib in EGFR-mutant NSCLC.
with LMC. Appreciation of LMC patterns and objective response assessment is important in assessing the central nervous system activity of tyrosine kinase inhibitors across molecularly defined NSCLC subgroups.

References

Figure 1. Zuckerguss appearance of leptomeningeal carcinomatosis in EGFR-mutant NSCLC. Brain magnetic resonance imaging demonstrated extensive leptomeningeal enhancement on the postcontrast T1-weighted images, especially within the left Sylvian fissure and the bilateral cerebellar hemispheres (A-C [red arrows]). Resolution of Zuckerguss appearance after pulse dose erlotinib weekly (D-F [red arrows]).