FPN: 224P Cerebrospinal Fluid-Based Mutation Abundance Index (MAI) Correlated to Clinical Outcome in Leptomeningeal Metastasis of Non-Small Cell Lung Cancer with *EGFR* Mutations

Wenjie Zhu[1], Haiyan Xu[1,*]

1. National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

*Correspondence to: Haiyan Xu (studs@126.com), National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17# Panjiayuannanli, Beijing, 100021, China.

Introduction: Leptomeningeal metastasis (LM) is a devastating complication of advanced non-small cell lung cancer (NSCLC). Genetic profiling using cell-free DNA (cfDNA) from cerebrospinal fluid (CSF) may serve as a novel method for monitoring of LM.
Objective: Our study was designed to measure mutations in serially collected CSF specimens and investigate its correlation with clinical outcome in oncogene-driven NSCLC.
Methods: From March 2018 to June 2023, patients with cytologically confirmed LM who had epidermal growth factor receptor-mutated (*EGFR*m) NSCLC were enrolled at our institute. All of them underwent EGFR tyrosine kinase inhibitor (TKI) plus intrathecal therapy as initial treatment for LM disease. CSF samples were collected by lumbar puncture. cfDNA isolated from CSF was analyzed via gene-panel target-capture next-generation sequencing method. For each sample, mutation abundance index (MAI) was defined as the average value of mutant allele fractions (AF) which are greater than 5%. The primary endpoint was overall survival (OS) which referred to the interval from diagnosis of LM to death of any cause.
Results: 35 patients were included in the final analysis. Clinical and tumor-related information of the study cohort were shown in Table 1. The median time from diagnosis of NSCLC to LM was 18.3 months (95% confidence interval (CI): 14.1-22.4). Intra- and extra-cranial ORR was 14.3% and 8.6% respectively. By the date of last follow-up (July 10, 2023), 27 death events had occurred. The median survival after diagnosis of LM was 18.1 months (95% CI: 11.0-19.4). cfDNA was detectable in all 76 CSF samples. Type of *EGFR* mutation, presence of *TP53* mutation and baseline MAI (MAI 1) were not discriminating factors for OS. For each patient, MAI 2 was defined as the MAI measured while on treatment with EGFR TKI (1-2 months away from baseline). The pattern of MAI change was associated with clinical outcome. Neurological function improvement was identified in 72.7% (8/11) of cases with MAI decrease. Patients with MAI decrease (MAI 2 < MAI 1, N=11) had significantly better OS than patients with stable or increased MAI (median OS, 21.3 vs. 14.4 months, p=0.012, HR=0.293).
Conclusion: CSF-based MAI might be used as a prognostic indicator in LM in *EGFR*m NSCLC.
Key words: cerebrospinal fluid; mutation abundance index; leptomeningeal metastasis; non-small cell lung cancer; *EGFR* mutation

Table 1 Baseline characteristics and treatment patterns of patients with LM in *EGFR*m NSCLC (N=35)

Characteristics	N (%)
Age	
<65 years	13 (37.1)
≥65 years	22 (62.9)
Sex	
Male	12 (34.3)
Female	23 (65.7)
Smoking status	
Former/current	12 (34.3)
Never	23 (65.7)
ECOG score	
0-1	24 (68.6)
≥2	11 (31.4)
History of surgical resection	
Yes	12 (34.3)
No	23 (65.7)
TNM stage at initial diagnosis	
Stage I-III	13 (37.1)
Stage IV	22 (62.9)
Type of *EGFR*mutation at baseline	
Exon 21 L858R	17 (48.5)
Exon 19 deletion	10 (28.6)
Compound mutations	8 (22.9)
Coexisting intraparenchymal brain metastasis	
Yes	27 (77.1)
No	8 (22.9)
Previous lines of therapy before LM	
0	3 (8.6)
1	23 (65.7)
≥2	9 (25.7)
Intra-cranial response	
CR/PR	5 (14.3)
SD	30 (85.7)
PD	0 (0)
Extra-cranial response	
CR/PR	3 (8.6)
SD	32 (91.4)
PD	0 (0)
Treatment pattern for LM after failure of EGFR TKI	
Higher dose of EGFR TKI	7 (20.0)
EGFR TKI plus anti-angiogenic agents	7 (20.0)
Chemotherapy-based treatment	5 (14.3)
Best supportive care	16 (45.7)
Radiation therapy	
Yes	6 (17.1)
No	29 (82.9)

Note: CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease.

The authors declare no conflicts of interest.