Patterns of Tyrosine kinase inhibitors -Associated Pneumonitis in *EGFR*-Mutated and Other Driver-Positive NSCLC

Barliz Waissengrin[1], Kamya Sankar[1], Eric Vail[2], Matt Leong[2], Ben Barrena[2], Karen Reckamp[1]

1. Cedars Sinai Cancer Center, Cedars-Sinai, Los Angeles, California
2. Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Background:

Tyrosine kinase inhibitors (TKIs) have improved outcomes for patients with non-small cell lung cancer (NSCLC) subtypes with actionable genomic alterations (AGAs), but also exhibit unique toxicities, including pneumonitis. Pneumonitis secondary to TKIs treatment, particularly in compromised lungs of NSCLC patients, might jeopardize treatment and survival. We aimed to characterize these patients in order to identify potential predictors for pneumonitis among patients who are treated with TKIs.

Methods:

This was a retrospective study including patients with NSCLC with AGAs and metastatic disease at time of diagnosis who were treated with first-line TKI therapy at Cedars-Sinai Cancer Center between 2019 and 2024. We excluded patients who had previous radiotherapy. Data collected included demographic characteristics, genomic information, and radiologic and clinical diagnoses of pneumonitis based on CT scans and physician notes. Patient characteristics were compared using two-sample t-tests, and co-mutation analyses were performed using Fisher's exact test.

Results:

We reviewed electronic medical records of 476 patients with AGA metastatic NSCLC. Among them, 27 patients (5.67%) developed pneumonitis of varying grades (1-3). The majority of patients, 348, had *EGFR* mutations. Among them, 19 patients (5.45%) had pneumonitis. Pneumonitis was also diagnosed in patients with MET Exon 14 skipping mutation (capmatinib four patients of 40, 10%), RET (selpercatinib two patients and pralsetinib one patient of 12, 25%), and ROS1 (entrectinib one patient of 12, 8.3%).

Among the 19 patients with *EGFR*-mutant NSCLC who developed pneumonitis, 11 (57.9%) were diagnosed with asymptomatic radiologic pneumonitis (grade 1), while two (10.5%) experienced severe pneumonitis (grade 3). There were no pneumonitis-related deaths in this cohort. No statistically significant differences were observed in demographic characteristics, including gender, race, ethnicity, or smoking status. Co-mutation analysis showed that *FGFR* co-mutations were significantly more common among patients with pneumonitis (p= 0.0001), and *SMARC* co-mutations showed a trend of association (p = 0.058).

Discussion:

Although TKIs are relatively well tolerated, they are not without toxicity. In this study, we characterized pneumonitis cases, predominantly among patients with *EGFR* mutations. Most cases were asymptomatic radiographic only, while a small proportion developed severe pneumonitis. No demographic predictors were identified. However, *FGFR* co-mutations were significantly enriched among patients who developed pneumonitis, a finding that may relate to the known involvement of FGFR signaling in fibrotic processes, including idiopathic pulmonary fibrosis, suggesting a potential role in priming the lung parenchyma for injury or impaired repair in the setting of TKIs exposure.