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World Cancer 2019: Efficacy of first and second generation-EGFR-TKIs in NSCLC patients with uncommon EGFR mutations: A literature-based pooled analysis: A Review Article- Yiyin Zhang and Jianxing He, Fudan University Shanghai Cancer Center, China

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Introduction: The approval of tyrosine kinase inhibitors (TKIs) to selectively target tumors with activating epidermal protein receptor (EGFR) mutations marked a revolutionary milestone within the management of non–small-cell carcinoma (NSCLC) and signaled the dawn of the precision medicine. Approximately 25% of patients with NSCLC who were never- or ex-light smokers were found to own activating EGFR mutations, and this number will be up to 50% to 60% in Asian non-smoker patients whose tumors have adenocarcinoma histology. There are multiple generations of EGFR TKIs approved for clinical use. First-generation EGFR TKIs, gefitinib and erlotinib, inhibit EGFR by competitive binding with ATP and demonstrate remarkable improvements in progression-free survival (PFS) over platinum doublet chemotherapy. Subsequent generations of TKIs were designed to beat treatment resistance. Second-generation TKIs, afatinib and dacomitinib, irreversibly inhibit all 4 ERBB receptors including EGFR. As such, they're more impregnable inhibitors of EGFR, but at the price of increased toxicity. Osimeritinib, the sole available third-generation TKI, is specifically designed to focus on the T790M resistance mutation that emerges with EGFR TKI treatment but also shows activity against tumors harboring the exon 19 deletion and exon 21 L858R point mutations. Emerging evidence supports a task for afatinib dacomitinib and osimertinib within the upfront management of EGFR-mutated NSCLC. Several prospective studies have compared the various generations of EGFR TKIs against each other in treatment-naive patients. within the phase IIB LUX-Lung study, afatinib demonstrated a non-significant improvement in median overall survival (OS) compared with gefitinib. The larger clinical trial ARCHER 1050 study compared dacomitinib with gefitinib and located a big improvement in PFS with the second-generation. This study also demonstrated a superior OS: median OS was 34.1 months within the dacomitinib group compared with 26.8 months within the gefitinib group. Osimertinib was compared with first-generation TKIs within the FLAURA study, and also demonstrated a superior PFS.15 Although the ultimate OS data remains immature, interim results favored osimertinib. Osimertinib has not been directly compared with second-generation TKIs within the first-line setting, and whether there's any benefit to using sequential therapy with a second-generation TKI followed by a third-generation TKI is unknown.

Background: NSCLC patients with common sensitive EGFR benefit remarkably from first and second-generation EGFR-TKIs. However, the efficacy of those agents in uncommon EGFR mutations has yet to be confirmed. Thus, we performed a meta-analysis to pool all current evidence.

Methods: We searched PubMed for eligible studies from the date of inception to 17th June, 2019. Overall objective response rate (ORR) and 6-month progression free survival (PFS) rates were pooled. Mutations within the identical exons were grouped, additionally to subgroup analyses of some notable mutation types.

Results: Of 10,951 patients from 35 included studies, 1,584 (14.5%) patients were diagnosed with uncommon EGFR mutations. the foremost frequent mutation types were G719X (11.9%), L861Q (6.3%) and exon 20 insertion (5.4%). In single-arm synthesis, the general ORR in patients with uncommon mutations was 30.1% (95% confidence interval (CI): 24.0 to 36.2) and 40.2% (95% CI: 21.3% to 59.0%) in first and second generation-EGFR-TKIs, respectively, compared with 67.0% (95% CI: 59.6% to 74.5%) in those with common mutations. The 6-month PFS rate was 46.4% (95% CI: 37.2% to 55.6%) and 78.3% (95% CI: 74.0% to 82.5%). In exploratory analyses, ORR was 29.4%, 11.8%, 23.6% and 42.4% in patients with rare mutations in EGFR exon 18, 19, 20 and 21, respectively. The ORR was 27.1% (95% CI: 20.3% to 34.0%), 47.7% (95% CI: 34.0% to 61.4%) and 69.7% (95% CI: 58.1% to 79.2%) in single rare mutations, rare+ rare mutations and rare+ sensitive mutations.

Conclusions: Both first and second-generation EGFR-TKIs presented considerable benefits among patients with uncommon mutations and remained an option for treatment, especially in mutations.

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