Abstract

Introduction: Targeted therapy with low molecular-weight tyrosine kinase inhibitors (TKI) directed at inhibition of epidermal growth factor receptor (EGFR) is a novel effective option for systemic treatment of locally-advanced or metastatic non-small cell lung cancer (NSCLC). Finding biomarkers that predict the efficacy of targeted treatment may increase the treatment efficacy and also prolong survival of patients.

Aims: To assess the frequency of activating EGFR mutations and KRAS mutations in our patients and their role for prediction of EGFR-TKI treatment efficacy. To compare the efficacy and safety of EGFR-TKI and chemotherapy in the first-line treatment of patients harboring activating EGFR mutations.

Methods: 613 patients with cytologically or histologically confirmed NSCLC were tested for activating EGFR mutation, of which 448 patients were also tested for KRAS mutation. First-line therapy was evaluated in 54 patients harboring activating EGFR mutations. Mutations were detected using denaturing capillary electrophoresis, and verified by direct DNA sequencing. Survival of patients was assessed using the methodology of Kaplan-Meier, the comparison was calculated using log-rank test.

Results: Activating EGFR mutations were detected in 73 (11.9%) patients, more frequently in patients with adenocarcinoma ($p=0.008$), women ($p<0.001$) and non-smokers ($p<0.001$). KRAS mutations were detected in 69 (15.3%) patients, more frequently in patients with adenocarcinoma ($p=0.004$) and smokers ($p=0.006$). Median PFS and OS for patients harboring activating EGFR mutation was 7.2 and 14.5 *vs*. 2.0 and 7.5 months for patients harboring wild-type EGFR gene ($p<0.001$; $p=0.019$). Among patients harboring activating EGFR mutation, median PFS and OS for those with adenocarcinoma was 10.2 and 17.7 months *vs*. 4.7 and 6.8 months for those with squamous-cell carcinoma ($p<0.001$, $p=0.009$). The difference in PFS and OS according to presence of activating EGFR mutation was statistically significant for patients with adenocarcinoma ($p<0.001$; $p=0.010$), but not for patients with squamous-cell carcinoma ($p=0.141$, $p=0.749$). We observed no statistically significant difference in survival in relation to the specific type of EGFR mutation. Median PFS and OS for patients with known KRAS mutation was 1.3 and 3.0 months *vs.* 2.2 and 7.2 months in patients with wild-type EGFR and wild-type KRAS gene ($p=0.048$, $p=0.197$). Among patients harboring KRAS mutation, the median PFS and OS for those with type G12C mutation was 1.1 and 2.3 months *vs*. 2.3 and 3.0 months for patients with type nonG12C ($p=0.009$, $p=0.068$). When evaluating the first-line treatment in patients harboring activating EGFR mutation, median PFS and OS for patients treated with EGFR-TKI was 7.2 and 14.5 *vs*. 2.5 and 21.4 months for patients treated with chemotherapy ($p<0.001$, $p=0.729$). Chemotherapy was frequently accompanied with haematologic toxicity, nausea, vomiting, elevation of liver enzymes and parestheses. EGFR-TKI was frequently accompanied with skin rash and diarrhea.

Conclusion: Activating EGFR mutations were found in 11.9% patients, more frequently in patients with adenocarcinoma, women and non-smokers. KRAS mutations were found in 15.3% patients, more frequently in patients with adenocarcinoma and smokers. Activating EGFR mutations predict good treatment efficacy of EGFR-TKI in patients with non-squamous NSCLC. KRAS mutations predict low treatment efficacy of EGFR-TKI. The predictive significance has only G12C KRAS mutation type. When deciding on the treatment with EGFR-TKI in patients harboring KRAS mutation, it is necessary to take into account particular type of mutation. Patients harboring G12C KRAS mutation assume primary resistance to EGFR-TKI. First-line treatment with EGFR-TKI in patients harboring activating EGFR mutation is more effective, safe and less burdensome than first-line chemotherapy.