Although osimertinib enriches a longer survival time than first-generation EGFR-TKI for non-small cell lung cancer (NSCLC) harboring EGFR mutations, acquired resistance is inevitable. Since the time to acquire resistance to EGFR-TKI is shorter for cancers with a higher mutational burden and mutations increase after EGFR-TKI resistance is acquired, the acquired resistance mechanism depends primarily on acquired mutations. 1 Even so the cancer immunodominance theory indicates that the process of genetic mutation accumulation by cancer cells involves a conflict with T-cell immunoediting, which recognizes gene mutation products as neoantigens and destroys them, the relationship between TKI treatment effect and immunological responses in patients with EGFR-mutating NSCLC is unknown. Two prospective observational cohort studies, one focusing on first, second generation cohorts and the other on third generation osimertinib treated cases, were designed at different times to elucidate tumor immune responses in treatment with EGFR-TKI.

Patients and Methods

Each prospective cohort observational study included patients who were diagnosed with NSCLC harboring EGFR mutation at Saitama Medical University International Medicine Center in Saitama, Japan between February, 2016 and November 2017 (discovery cohort) and November 2018 and October 2020 (validation cohort). Peripheral blood samples were collected before and after 4 weeks starting of EGFR-TKI. Peripheral blood mononuclear cells (PBMC) samples from 22 patients who received 1st and 2nd EGFR-TKI (including 3 patients prescribed osimertinib at that time) were analyzed using LSR FortessaTM in discovery cohort and from 43 patients who received osimertinib were analyzed using CyTOFTM in Validation cohort. We are analyzed for CCR7 and CD45RA expression on gated CD3+. Among the CD4+ T-cell, we examined Th1 T cell expressing CXC4+CCR6+, Th2 T cell expressing CXC4+CCR6+, Th17 T cells expressing CXC4+CCR6+5, 6 and then we called the cluster of expressing CXCR3+CCR6+, CXCR3+CCR6+, CXCR3+CCR4+ and CXCR3+CCR6+7. The Th17 T cell was divided into Th17 low and Th17 high subgroups, respectively. Based on the Kaplan-Meier survival analysis, Th7R low and Th7R rich subgroups were analyzed as those with a cutoff value lower than 17% and those with a cutoff value higher than 17%. The cutoff value was calculated using ROC analysis with a cutoff value higher than 2.5% and lower than 2%.

Results

Figure 3. Correlation between Th7R CD4+ T cells and to EGFR-TKI resistance in the discovery cohort.

Figure 4. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) among Th7R low (n=12) and rich (n=10) patients who received EGFR-TKIs.

The Th7R low and Th7R rich groups were defined as those with a cutoff value lower than 2.5% and those with a cutoff value higher than 2.5%, respectively, as calculated using ROC analysis.

Figure 5. Comparison of the percentage of T cell subset based on CCR7 and CD45RA of gated CD8 T cell between before and after prescribing osimertinib (Osim).

The percentage of CCR7+CD45RA- T cell, that is central memory T cell, significantly decreased by administration of osimertinib.

Figure 6. Comparison of the percentage of T cell subset based on CXCR4/CXCR4 and CCR6 of gated CD4 T cell between before and after prescribing osimertinib (Osim). The percentage of CXCR4+CCR6+ T cell significantly decreased by administration of osimertinib.

Conclusions

➢ T-cell immunity influences the time to acquire resistance after EGFR-TKI treatment.

➢ Pre-treatment Th7R and Th17 assays before TKI treatment could predict PFS and OS of osimertinib.

References


Acknowledgements

This work was supported by grants from Boehringer Ingelheim. We would like to thank Mrs. Keiko Koizumi for technical assistance.

Disclosure

All authors have declared no conflicts of interest. HK received honorarium from Otsu Pharmaceutical Co. Ltd. All the authors declared receipt of funding from Otsu Pharmaceutical Co. Ltd.