EGFR-TKI acquired resistance in lung cancers harboring EGFR mutations in immunocompetent C57BL/6J mice

Abstract

Objectives

Lung cancers harboring epidermal growth factor receptor (EGFR) mutations inevitably develop resistance to EGFR tyrosine-kinase inhibitors (EGFR-TKIs). Therefore, we sought to establish clinically relevant lung-cancer mouse models to achieve deep remission of cancers.

Materials and Methods

We previously established two transgenic lung-cancer mouse models harboring human EGFR exon 21 L858R substitution (hLR) and mouse Egfr exon 19 deletion (mDEL) in the C57BL/6J background. Lung tumors from these two transgenic mouse strains were transplanted subcutaneously into BALB/c-nunu mice or C57BL/6J mice.

Results

The transplanted tumors developed the ability to grow on the subcutaneous tissue, peritoneum, or lung of C57BL/6J mice. While hLR tumors could grow only in C57BL/6J mice carrying the transgene, mDEL tumors could grow in wild-type C57BL/6J mice. The tumors maintained EGFR-dependency, and, thus, the EGFR-TKI gefitinib inhibited tumor growth; however, similar to human lung cancers, hLR and mDEL tumors acquired resistance in 60 and 200 days, respectively, following gefitinib administration. Secondary EGFR T790M mutation in hLR tumors and secondary Egfr T792I mutation in mDEL tumors developed; however, no MET activation was detected. Accordingly, the third-generation EGFR-TKI osimertinib effectively inhibited gefitinib-resistant tumors in vivo.

Furthermore, gefitinib-resistant tumors developed resistance to osimertinib in 100 days.

Conclusion

These syngeneic lung-cancer mouse models harboring EGFR mutations are suitable for studying the drug-resistance mechanisms and the role of the tumor microenvironment. Further investigation with these mouse models is warranted for developing next-generation treatment strategies for lung cancer.

Key words: acquired resistance, EGFR mutations, NSCLC, osimertinib, transgenic mice