Tipifarnib prevents emergence of resistance to osimertinib in EGFR-mutant NSCLC

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Background

Drug-tolerant “dominant” cells (DTC) have emerged as one of the major non-mutanogenic mechanisms driving resistance to targeted therapy in lung cancer1, 2, although the sequence of events leading to exit and exit from dormancy remains poorly described. Here, we provide a step-by-step phenotypic and molecular characterization of the differences involved during the adaptive response to osimertinib using several EGFR-mutated lung cancer models. This strategy led to the identification of a common vulnerability of drug-tolerant cells which could be efficiently and safely targeted by a clinical stage drug.

Methods

We report that adaptive response to osimertinib is a highly dynamic process which invariably involves a dedifferentiation process through an alveolar type phenotype with contractile features. Using a screen of Rho/ROCK pathway inhibitors, we found that tipifarnib, a clinically active farnesyltransferase inhibitor, efficiently and durably prevented relapse to osimertinib in vitro and in vivo by inducing an AT4-dependent apoptotic response, with no evidence of toxicity in mice. Collectively, our data strongly support the use of tipifarnib in combination with osimertinib in the clinic to effectively and durably prevent relapse.

Conclusions

A panel of EGFR-mutated NSCLC cell lines was subcloned to minimize/avoid the presence of potential pre-existing resistant cells (1), and transduced with the FUCCI (fluorescence ubiquitination cell cycle indicator) system (2) to perform real-time monitoring of the cell cycle dynamics in response to 1 µM erlotinib or osimertinib (3). (G1 vs G2) and (S+G2) cells were sorted during the early stage of the adaptive response to EGFR-TKI (4) and isoRNAseq experiments were performed to identify the molecular mechanisms underlying entry and exit from dormancy (5). GSEA analysis was performed to determine molecular pathways invariably activated among the cell lines (6), and in vitro drug screening was conducted to target identified pathways (7). The most relevant combinations were validated in vivo using EGFR-mutated NSCLC xenografts and PD1 (Patient-Derived Xenografts) (8).

Results

We report that adaptive response to osimertinib is a highly dynamic process which invariably involves a dedifferentiation process through an alveolar type phenotype with contractile features. Using a screen of Rho/ROCK pathway inhibitors, we found that tipifarnib, a clinically active farnesyltransferase inhibitor, efficiently and durably prevented relapse to osimertinib in vitro and in vivo by inducing an AT4-dependent apoptotic response, with no evidence of toxicity in mice. Collectively, our data strongly support the use of tipifarnib in combination with osimertinib in the clinic to effectively and durably prevent relapse.

Figure 1. Osimertinib resistance emerges from an alveolar-like phenotype with contractile features

Figure 2. Drug-tolerant cells display cytoskeletal remodeling and Rho/ROCK pathway activation

Figure 3. The farnesyltransferase inhibitor tipifarnib prevents relapse to osimertinib in vitro

Figure 4. Osimertinib + Tipifarnib treatment impairs mitosis and induces an integrated stress response (ISR)-mediated apoptotic pathway

Figure 5. Tipifarnib prevents relapse to EGFR-TKI in vivo

References


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