Combination therapy of pi3k and egfr inhibitors in patient-derived gastroesophageal circulating tumour cell models

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Abstract

Gastroesophageal cancer (GOC) presents a significant global burden, with over 1.4 million cases identified in 2022, and over 1.1 million associated deaths. In GOC, the PI3K/AKT and EGFR/RAS/MAPK signalling networks are regularly mutated or amplified, and play a key role in driving epithelial-mesenchymal-transition (EMT) induced stemness of circulating tumour cells (CTCs). Dual blockade of these pathways presents an effective treatment strategy as it blocks compensatory crosstalk which often confers therapeutic resistance. In this study the circulating tumour cell line, UWG02CTC, derived from a patient with metastatic HER2 negative gastroesophageal carcinoma, was used as a model system for this disease. UWG02CTC is characterised by two activating mutations in the PIK3CA gene, encoding the PI3K p110α subunit, and expresses high levels of EGFR protein. EGFR and PI3K both present excellent targets for therapeutic intervention. This study aimed to determine the efficacy of dual PI3K and EGFR inhibition against UWG02CTC, employing sophisticated 2D and 3D preclinical CTC culture models. UWG02CTC sensitivity to PI3K inhibitor alpelisib, coupled with first, second, or third generation EGFR inhibitors gefitinib, afatinib, and osimertinib, respectively, was assessed under both two-dimensional (adherent monolayer) and ultra-low-attachment (suspension/loose aggregation of cells into clusters to simulate tumour cells in circulation) conditions. Our study revealed that the combination therapies effectively blocked the compensatory cross activation of signalling pathways leading to a strong synergistic cytotoxic response. Interestingly, suspension UWG02CTCs were significantly more sensitive to combination treatments than adherent subpopulations of cells, suggesting cells in the circulation would also be targeted by these treatments. Proteomic analysis through the Olink platform was pursued to provide mechanistic insights behind these differential cell phenotype responses, particularly the potential role of EMT markers and adherent-to-suspension transition (AST) factors. This study proposes a novel strategy for the treatment of HER2 negative metastatic gastric adenocarcinoma that is effective against both adherent and circulating cells, thereby combatting multiple stages of disease progression.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.