The anti-proliferative effect of anti-EGFR tyrosine kinase inhibitor in combination with mitotane on H295R adrenocortical cancer cells

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Introduction: Adrenocortical carcinoma (ACC) is a rare disease with a poor prognosis and limited therapeutic options. Mitotane is considered as a first-line therapy but only 30% of the patients showing an objective tumour response.

Erlotinib and gefitinib (tyrosine kinase inhibitors - TKI) inhibit the epidermal growth factor receptor (EGFR), which is highly expressed and occasionally mutated in various cancers. EGFR expression was found to be a good discriminator between malignant and benign adrenal tumours. EGFR mutations in exons 18-21 have been found in 3-10% of ACC cases (but not in the H295R ACC cell line) although their functional significance remains unknown.

Aim: The aim of this study was to assess whether erlotinib or gefitinib (used alone or in combination with mitotane) inhibit ACC cell proliferation in a pre-clinical setting.

Materials and methods: The proliferation rate of the H295R ACC cell line was assessed by Alamar blue assay: optimal time points for determination of cytotoxic effect of the inhibitors were 72 and 96 h of incubation.

Results: Mitotane at a concentration of 10 μ M decreased the proliferation rate by 23%.

Erlotinib inhibited cell proliferation more effectively than gefitinib, causing a cytotoxic effect of 32 and 43%, vs 6 and 12% for gefitinib, after 72 and 96 h of incubation respectively ($P < 0.001$). The combination of mitotane with the EGFR inhibitors showed an additive effect on cell proliferation (41 and 45% for mitotane+erlotinib, and 29 and 32% for mitotane+gefitinib, at 72 and 96 h, respectively).

Conclusions: Erlotinib inhibits cell proliferation more potently than gefitinib, and causes higher H295R cells cytotoxicity in combination with mitotane. Combined therapy with agents targeting the EGFR and standard treatments may have the potential to improve the treatment of ACC patients. Given the lack of somatic mutations in this cell line, the potential mechanism(s) of sensitivity to anti-EGFR TKI is currently being investigated.

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