

Novel dual targeting strategy with vandetanib induces tumor cell apoptosis and inhibits angiogenesis in malignant pleural mesothelioma cells expressing RET oncogenic rearrangement.

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Malignant pleural mesothelioma (MPM) is an aggressive malignancy with a poor prognosis, therefore development of novel effective therapies is urgent. In the present study, we investigated the therapeutic efficacy of vandetanib (ZD6474), an inhibitor of VEGFR-2, EGFR and RET tyrosine kinases, in an orthotopic model of MPM. We found that a human MPM cell line, EHMES-10, expressed RET/PTC3 oncogenic rearrangement and a large amount of VEGF. Vandetanib induced the apoptosis and inhibited the proliferation of EHMES-10 cells *in vitro* (IC₅₀)=0.3 μM). Once-daily oral treatment with vandetanib inhibited tumor angiogenesis, and reduced significantly the growth of thoracic tumors and the production of pleural effusions, resulting in the prolonged survival of mice in EHMES-10 orthograft model. In contrast, the selective EGFR tyrosine kinase inhibitor, gefitinib, had no effect against EHMES-10 cells both *in vitro* and *in vivo*. Our results suggest that using vandetanib to target RET-dependent tumor cell proliferation and survival and VEGFR-2-dependent tumor angiogenesis may be promising against MPM expressing RET oncogenic rearrangement and VEGF.