

ZD6474 (ZACTIMA), AN INHIBITOR OF VEGFR AND EGFR TYROSINE KINASES, INHIBITS GROWTH OF PANCREATIC CANCER CELLS AND DOWNSTREAM SIGNALING PATHWAYS.

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Background: Treatment with the standard chemotherapeutic drugs has only a marginal effect against pancreatic cancer with a 5-year survival rate of only 4%. Targeting key signaling pathways involved in pancreatic cancer offers an opportunity to improve response to standard therapies. The epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor-2 (VEGFR-2) are upregulated in pancreatic adenocarcinoma (PDA). ZD6474 was recently developed to target cell proliferation and angiogenesis. This study investigated the potential effectiveness of ZD6474 in human pancreatic cancer cells and evaluated the downstream signaling mechanisms associated with this treatment.

Experimental Design: PK-9 and AsPC-1 cells were treated with several concentrations of ZD6474, gemcitabine, and oxaliplatin for 72 hours for measurement of cell survival. Protein expression of the apoptotic proteins was measured by Western immunoblotting. The effect of ZD6474 on epidermal growth factor receptor (EGF)-stimulated activation of downstream signaling proteins was also evaluated.

Results: ZD6474 inhibited survival of PK-9 cells in a concentration-dependent manner. At clinically relevant concentrations, ZD6474 inhibited cell survival (31%) to a greater extent than gemcitabine (9.6%) or oxaliplatin (5%). The growth-inhibitor effect of ZD6474 was associated with decreased protein expression of Bcl2 and total poly (ADP-ribose) polymerase (PARP). Phosphorylation of the VEGFR-2, EGFR, extracellular signal-regulated kinase $\frac{1}{2}$, and Akt were downregulated in a concentration-dependent manner in ZD6474 treated pancreatic cancer cells.

Conclusions: These findings indicate that the VEGF receptor-2 and EGFR tyrosine kinase are important targets for pancreatic cancer cells. Combining ZD6474 with standard treatments may improve survival of patients with PDA.