Effects of insulin-like growth factor-1 receptor inhibition in mesothelioma. Thoracic Surgery Directors Association Resident Research Award.

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Abstract

BACKGROUND:

Malignant mesothelioma is a devastating disease with a poor prognosis. Recent data have shown that insulin-like growth factor-1 receptor (IGF-1R) may play a role in oncogenic signaling. Our aim was to...
evaluate the effect of a novel IGF-1R inhibitor, NVP-AEW541, on cell growth and IGF associated pathways.

METHODS:

Malignant mesothelioma cell lines, H2373 and H2461, previously shown to activate the IGF pathway were grown in culture. The adherent cells, initially plated at 5 x 10(5) cells/plate, were treated for 72 hours, in triplicate, with varying concentration of NVP-AEW541 (0, 1, 5, 10, 20, and 50 microM). Viable cells were counted every 24 hours. Additionally, separate cultures in serum-free medium were treated with NVP-AEW541, then stimulated with IGF and lysates collected for immunoblot analysis.

RESULTS:

In both cell lines, 0, 1, 5, and 10 microM showed an inhibitory or static effect, while 20 and 50 microM were cidal. Immunoblot analysis demonstrated that phosphorylation of IGF-1R was inhibited by NVP-AEW541 at higher concentration. Phosphorylation of mitogen-activated protein kinase and Akt, downstream IGF pathway mediators, were also shown to be repressed by drug treatment.

CONCLUSIONS:

NVP-AEW541 has a concentration-dependent inhibitory effect on mesothelioma cells in culture. NVP-AEW541 acts by inhibition of IGF-1R phosphorylation. Inhibition effects phosphorylation of downstream mediators in a dose-dependent fashion. Inhibition of the IGF pathway decreases viability of mesothelioma cell culture. Further evaluation of NVP-AEW541, and other selective IGF-1R inhibitors, may play an important role in multimodal treatment of malignant mesothelioma.

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