Carcinoma colo-retal. É importante inibir o IGF-IR: NVP-AEW541 é derivado sintético do NDGA

Possíveis tratamentos para inibir o IGF-1 e ou o IGF-1R

a- Silibinina: diminui o receptor do IGF-1 e o IGF-1beta e aumenta muito a proteína carregadora do IGF-1 a IGFBP-3 diminuindo assim a concentração plasmática do IGF-1

b- Ativadores da AMPK (AMP activated protein kinase):
   1- antocianinas: arroz preto (Oryza nigra), groselha preta (Black currant), uva preta, feijão preto, Sinadenium
   2- dieta com restrição de carboidratos com cetose
   3- metformina

c- Colecalciferol: aumenta IGFBP-3
d- Epigalocatequina-galato (inibe IGF-1R)
e- Resveratrol (inibe IGF-1R)
f- Genisteína: inibe IGF-1 e para outros os derivados da soja aumentam IGF-1
g- Inibidores da Angiotensina II (inibe IGF-1R)
h- Inibidores da Aldosterona (inibe IGF-1): Inspra (eplerenone), aldactone (espirolactona)
i- Amiloride: inibe o IGF-1 e o IGF-1R
j- NDGA: ácido nordihidroguaiarético, derivado da Larrea tridentata ou Larrea divaricata, “arbusto de creosoto” sendo conhecida erroneamente como “chaparral”: inibe o IGF1-R. José de Felippe JUnior

Tyrosine kinase of insulin-like growth factor receptor as target for novel treatment and prevention strategies of colorectal cancer.

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Source

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Abstract

AIM:

To investigate the antineoplastic potency of the novel insulin-like growth factor 1 receptor (IGF-1R) tyrosine kinase inhibitor (TKI) NVP-AEW541 in cell lines and primary cell cultures of human colorectal cancer (CRC).
**METHODS:**

Cells of primary colorectal carcinomas were from 8 patients. Immunostaining and crystal violet staining were used for analysis of growth factor receptor protein expression and detection of cell number changes, respectively. Cytotoxicity was determined by measuring the release of the cytoplasmic enzyme lactate dehydrogenase (LDH). The proportion of apoptotic cells was determined by quantifying the percentage of sub-G1 (hypodiploid) cells. Cell cycle status reflected by the DNA content of the nuclei was detected by flow cytometry.

**RESULTS:**

NVP-AEW541 dose-dependently inhibited the proliferation of colorectal carcinoma cell lines and primary cell cultures by inducing apoptosis and cell cycle arrest. Apoptosis was characterized by caspase-3 activation and nuclear degradation. Cell cycle was arrested at the G1/S checkpoint. The NVP-AEW541-mediated cell cycle-related signaling involved the inactivation of Akt and extracellular signal-regulated kinase (ERK) 1/2, the upregulation of the cyclin-dependent kinase inhibitors p21(Waf1/CIP1) and p27(Kip1), and the downregulation of the cell cycle promoter cyclin D1. Moreover, BAX was upregulated during NVP-AEW541-induced apoptosis, whereas Bcl-2 was downregulated. Measurement of LDH release showed that the antineoplastic effect of NVP-AEW541 was not due to general cytotoxicity of the compound. However, augmented antineoplastic effects were observed in combination treatments of NVP-AEW541 with either 5-FU, or the EGFR-antibody cetuximab, or the HMG-CoA-reductase inhibitor fluvastatin.

**CONCLUSION:**

IGF-1R-TK inhibition is a promising novel approach for either mono- or combination treatment strategies of colorectal carcinoma and even for CRC chemoprevention.

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