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The utility of vitamin K3 (menadione) against pancreatic cancer.

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Abstract

BACKGROUND: To evaluate the efficacy of vitamin K3 (VK3) against pancreatic cancer, the molecular mechanism of VK3 or gemcitabine (GEM)-induced inhibition of proliferation was characterized.

MATERIALS AND METHODS: The cell viability was determined using the 3-[4,5-dimethylthiazol]-2,5-diphenyl tetrazolium bromide (MTT) test method. The expressions of cellular proteins were evaluated by Western blot analysis. For morphological studies of the in vivo transplanted cancer cells, the tissues were stained with hematoxylin and eosin.

RESULTS: The IC50 of VK3 for pancreatic cancer cells was calculated for 42.1 +/- 3.5 microM. Western blot analysis showed that VK3 induced rapid phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK) 30 minutes after application. ERK but not JNK phosphorylation was maintained for at least 12 hours. Activation of apoptosis by VK3, as shown by molecular weight shifts of the pro-activated 32-kDa form of caspase-3 and poly(ADP-ribose)polymerase (PARP) cleavage of the 112-kDa form, was found. Treatment with the thiol antioxidant, L-cysteine (>0.2 mM), completely abrogated the VK3-induced phosphorylation of ERK, but not the JNK, and inhibition of proliferation. A caspase-3 inhibitor antagonized caspase-3 activation, but had no inhibitory effect on the proliferative activity of VK3. GEM at concentrations >0.1 microg/ml was found to inhibit cell proliferation after 24 hours. GEM also induced phosphorylation of JNK, activation of caspase-3 and accumulation of cyclin B1. Local application of VK3 was found to induce extensive tumor tissue necrosis, but slight hematemesis without necrosis was observed 48 hours after GEM injection. In Western blot, ERK but not JNK phosphorylation, was clearly detected in response to VK3 injection into the tumor tissue.

CONCLUSION: The action of VK3 may lead to a favorable outcome against pancreatic cancer, and the detection of ERK phosphorylation in the tissue is important for predicting this effect.

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