JS-K, a glutathione S-transferase-activated nitric oxide donor with antineoplastic activity in malignant gliomas.


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Abstract

BACKGROUND:

Glutathione S-transferases (GSTs) control multidrug resistance and are upregulated in many cancers, including malignant gliomas. The **diazoniumdiolate JS-K generates nitric oxide (NO) on enzymatic activation by glutathione and GST, showing promising NO-based anticancer efficacy.**

OBJECTIVE:

To evaluate the role of NO-based antitumor therapy with JS-K in U87 gliomas in vitro and in vivo.

METHODS:

U87 glioma cells and primary glioblastoma cell lines were exposed to JS-K and a variety of inhibitors to study cell death by necrosis, apoptosis, and other mechanisms. GST expression was evaluated by immunocytochemistry, polymerase chain reaction, and Western blot, and NO release from JS-K was studied with a NO assay. The growth-inhibitory effect of JS-K was studied in a U87 xenograft model in vivo.

RESULTS:

Dose-dependent inhibition of cell proliferation was observed in human U87 glioma cells and primary glioblastoma cells in vitro. Cell death was partially induced by caspase-dependent apoptosis, which could be blocked by Z-VAD-FMK and Q-VD-OPH.
Inhibition of GST by sulfasalazine, cGMP inhibition by ODQ, and MEK1/2 inhibition by UO126 attenuated the antiproliferative effect of JS-K, suggesting the involvement of various intracellular death signaling pathways. Response to JS-K correlated with mRNA and protein expression of GST and the amount of NO released by the glioma cells. Growth of U87 xenografts was reduced significantly, with immunohistochemical evidence for increased necrosis and apoptosis and reduced proliferation.

CONCLUSION:

Our data show for the first time the potent antiproliferative effect of JS-K in gliomas in vitro and in vivo. These findings warrant further investigation of this novel NO-releasing prodrug in gliomas.

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