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The topoisomerase II inhibitor, genistein, induces G2/M arrest and apoptosis in human malignant glioma cell lines.

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Abstract

The protein tyrosine kinase inhibitor, genistein, has been reported to inhibit proliferation and to induce cell death in various non-solid and solid cancer cell lines. Herein, we examined the effects of genistein in several human malignant glioma cell lines. We found that genistein inhibited the proliferation of LN-18, LNT-229, LN-308 and T98G cells at EC50 concentrations of 25-80 microM (72 h of exposure). The growth of a non-neoplastic immortalized human astrocyte cell line, SV-FHAS, was inhibited at similar concentrations. There was a reduction in [3H]-methylthymidine incorporation and a moderate lactate dehydrogenase release as a sign of cell death in genistein-treated glioma cells. Electron microscopy showed morphological changes with mitochondrial swelling and apoptosis in glioma cells treated with high concentrations of genistein. Genistein-induced cytotoxicity was associated with an increased DNA/topoisomerase II complex formation. Furthermore, genistein induced cell cycle arrest in G2/M. There was an increase in the p53 and p21 levels in response to genistein. However, there was no difference in genistein sensitivity between p21-deficient colon carcinoma cells and isogenic control cells. Genistein-induced cell death in LN-18 and LNT-229 was unaffected by the ectopic expression of the preferential caspase 1/8 inhibitor, crm-A, or co-exposure to the pan-specific pseudosubstrate caspase inhibitor, zVAD-fmk. The ectopic expression of the anti-apoptotic BCL-2 protein attenuated the cytotoxic effects of genistein. Moreover, the ectopic expression of temperature-sensitive p53V135A, which acts as a dominant-negative p53 mutant at 38.5 degrees C but assumes p53 wild-type properties at 32.5 degrees C, in LN-18 or LNT-229 cells, had no effect on genistein cytotoxicity at either temperature. Genistein did not act in synergy with CD95 ligand-induced apoptosis or various cancer chemotherapy drugs in cytotoxic or clonogenic cell death assays. Thus, genistein-like protein kinase inhibitors are promising agents for the experimental treatment of malignant gliomas.

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