Combination of Temozolomide and Nanotaxol inhibits cell invasion, angiogenesis and tumor growth in glioblastomas through cell cycle arrest

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Abstract

Temozolomide (TMZ) is a new oral alkylating agent introduced for the treatment glioblastoma multiforme. However, the prognosis remains poor even after combination treatment with radiotherapy. Nanotaxol (NTX) is a modified form of paclitaxel with better absorption rate and is used for the suppression of various tumors. Here we examined the combined effect of TMZ and NTX to inhibit cell invasion, angiogenesis, and tumor growth of T98MG and U87MG human glioblastoma cell lines. Inhibition of cell proliferation and cell migration was evaluated using MTT assay and spheroid migration assay, respectively. The rate of cell invasion was assayed on matrigel coated transwell inserts. In-vivo angiogenesis study was carried out using diffusion chambers under the dorsal skin of athymic nude mice. In vivo imaging was performed for intracerebral and subcutaneous tumorigenesis. We observed marked inhibition of cell proliferation, migration, and invasion after the combination treatment with TMZ and NTX. Treatment with TMZ and NTX also demonstrated significant cell cycle arrest at G2/M phase. Intracerebral and subcutaneous tumorigenesis and solid tumor formation were remarkably decreased after the treatment with combination of TMZ and NTX. Western blotting demonstrated significant reduction of PCNA, VEGF, CDK2, CDK4, and cyclin D1 and upregulation of cell cycle inhibitors, p21Waf1 and p27Kip1 in solid tumor samples after the combination therapy. Taken together, our results indicate that the combination of TMZ and NTX effectively inhibits cell proliferation, migration, invasion, angiogenesis and intracranial as well as subcutaneous tumor growth through cell cycle arrest. Therefore, the combination of TMZ and NTX is a promising novel and potential therapeutic strategy for effective control of the aggressive growth of human glioblastomas.