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Continuous low-dose chemotherapy plus inhibition of cyclooxygenase-2 as an antiangiogenic therapy of glioblastoma multiforme.

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Abstract

PURPOSE: Glioblastoma multiforme (GBM) represents the prototype of an angiogenic tumor. Recently, the **continuous low-dose** scheduling of chemotherapeutic drugs in combination with an **inhibition of cyclooxygenase-2 (COX-2)** has been suggested as a novel **anti-angiogenic** approach. The aim of this study was to evaluate the safety and activity of **continuous low-dose** temozolomide (TMZ) **plus** the COX-2 inhibitor rofecoxib in patients with newly diagnosed GBM.

METHODS: In vitro, endothelial cells were characterized by a tenfold higher sensitivity to TMZ than glioma cells. Consequently, a subgroup of patients with incompletely resected GBM (n=13) was divided into three groups aiming at a dose escalation to 1/10 of the daily MTD for TMZ: (A) TMZ 10 mg/m² every third day and rofecoxib 25 mg/d; (B) TMZ 10 mg/m²/d and rofecoxib 25 mg/d; (C) TMZ 5 mg/m² twice a day and rofecoxib 12.5 mg twice a day. COX-2, VEGF, VEGF Receptor-2, and CD34 were assessed immunohistochemically, in the clinical setting.

RESULTS: The mean follow-up period was 15 months. We observed no severe toxicity attributable to the **therapy**. Quality of life was not impaired. For the whole study population, median time to progression and overall survival were 8 months and 16 months, respectively. Immunohistochemistry suggested that tumors with higher vessel densities were characterized by a significantly better control than those with lower vessel densities.

CONCLUSIONS: **Continuous low-dose** TMZ **plus** rofecoxib is feasible, safe, and maintains good quality of life. This study is indicative of an **anti-angiogenic** efficacy of **continuous low-dose** TMZ **plus** rofecoxib in GBMs, especially in those tumors that are characterized by a high angiogenic activity.

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