Temozolomide preferentially depletes cancer stem cells in glioblastoma.


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Abstract
The prognosis of patients suffering from glioblastoma (GBM) is dismal despite multimodal therapy. Although chemotherapy with temozolomide may contain tumor growth for some months, invariable tumor recurrence suggests that cancer stem cells (CSC) maintaining these tumors persist. We have therefore investigated the effect of temozolomide on CD133(+) and CD133(-) GBM CSC lines. Although differentiated tumor cells constituting the bulk of all tumor cells were resistant to the cytotoxic effects of the substance, temozolomide induced a dose- and time-dependent decline of the stem cell subpopulation. Incubation with sublethal concentrations of temozolomide for 2 days completely depleted clonogenic tumor cells in vitro and substantially reduced tumorigenicity in vivo. In O(6)-methylguanine-DNA-methyltransferase (MGMT)-expressing CSC lines, this effect occurred at 10-fold higher doses compared with MGMT-negative CSC lines. Thus, temozolomide concentrations that are reached in patients were only sufficient to completely eliminate CSC in vitro from MGMT-negative but not from MGMT-positive tumors. Accordingly, our data strongly suggest that optimized temozolomide-based chemotherapeutic protocols might substantially improve the elimination of GBM stem cells and consequently prolong the survival of patients.

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