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1: [Cancer Chemother Pharmacol.](#) 2007 Oct;60(5):643-50. Epub 2007 Jan 26.



Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model.

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PURPOSE: Dose-limiting adverse effects of thrombocytopenia and leukopenia prevent augmentation of current temozolomide (TMZ) dosing protocols; therefore, we hypothesized that the direct intracranial delivery of TMZ would lead to improved efficacy in an animal model of malignant glioma in an animal model. **METHODS:** Temozolomide was incorporated into biodegradable polymers and the active drug was released over 80 h. Intracranial toxicity was assessed in F344 rats and a maximally tolerated dose was not achieved. **RESULTS:** In vivo drug biodistribution demonstrated that intracranial concentrations of TMZ increased threefold compared with orally delivered TMZ. In a rodent glioma model, animals treated with a single TMZ polymer (50% w/w) had a median survival of 28 days ($P < 0.001$ vs. controls, $P < 0.001$ vs. oral treatment), whereas animals treated with oral TMZ had a median survival of 22 days compared to control animals (median survival of 13 days). Animals treated with two TMZ polymers (50% w/w) had a median survival of 92 days ($P < 0.001$ vs. controls, $P < 0.001$ vs. oral treatment). The percentage of long-term survivors (LTS) for groups receiving intracranial TMZ ranged from 25 to 37.5%; there were no LTS with oral TMZ treatment. Animals treated with radiation therapy (XRT) and intracranial TMZ (median survival not reached, LTS = 87.5%) demonstrated improved survival compared to those with intracranial TMZ alone (median survival, 41 days; LTS = 37.5%), or oral TMZ and XRT (median survival, 43 days, LTS = 38.9%). **CONCLUSIONS:** The survival of tumor-bearing animals was improved with local delivery of TMZ compared with systemic administration. XRT in combination with intracranial TMZ did not cause additional toxicity and prolonged the survival even further.

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PMID: 17256133 [PubMed - indexed for MEDLINE]
