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1: [Cancer Immunol Immunother.](#) 2009 Feb 17. [Epub ahead of print]



## **Treg depletion with a low-dose metronomic temozolomide regimen in a rat glioma model.**

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**BACKGROUND:** CD4+CD25+ regulatory T cells (Treg), which constitute about 2-3% of CD4+ human T cells, are the main contributors to the maintenance of immune tolerance. Cancer patients, including glioblastoma patients, bear increased number of circulating and tumor infiltrating Treg that exert functional inhibition on tumor-specific T cells. Temozolomide (TMZ) is one of the most effective chemotherapeutic agents in glioblastoma (GBM). Lymphopenia is a common side effect of TMZ treatment, but to what extent the Treg compartment is affected by this chemotherapy has been poorly investigated. We therefore studied the impact of various TMZ regimens on Treg cell population in a TMZ-resistant rat model of glioma. **METHODS:** RG2 glioma cells were implanted s.c. in Fischer rats. Twelve days after tumor implantation, TMZ was administered orally with schedules designed to mimic the TMZ regimens currently used in humans: 30 mg/kg per day for 5 days, or 10 mg/kg per day for 21 days. In addition, two metronomic regimens with low-dose TMZ (2 and 0.5 mg/kg per day for 21 days) were evaluated. Splenocytes and tumor infiltrating lymphocytes were analysed by flow cytometry using CD3, CD4, CD25, and Foxp3 mAbs. Statistical significance was determined by the Mann-Whitney U test, the Student's t test or the ANOVA test. **RESULTS:** In the spleen of tumor-bearing animals, low-dose TMZ metronomic regimens (0.5 and 2 mg/kg for 21 days) induced a significant decrease of Treg/CD4+ ratios (13 +/- 2; p < 0.01, 14 +/- 3; p < 0.05, respectively, vs. 19 +/- 5 for controls). On the contrary, high-dose TMZ regimen (10 mg/kg per day for 21 days or 30 mg/kg for 5 days) did not significantly modify the percentage of Treg/CD4+. Within tumors, treatment with the 0.5 mg/kg TMZ regimen induced a slight and nearly significant decrease in the percentage of Treg/CD4+ after a 2 to 3-week treatment (24 +/- 9 vs. 35 +/- 11; p = 0.06). Treg depletion induced by the low-dose metronomic TMZ regimen was accompanied by a decreased suppressive function of the remaining Treg cells as assessed by an in vitro functional test. Treatment with 0.5 mg/kg metronomic TMZ reduced tumor progression when compared to untreated animals but the effect did not reach statistical significance, indicating that Treg depletion alone is not sufficient to significantly impact tumor growth in our model of fully established tumor. **CONCLUSIONS:** A low-dose metronomic TMZ regimen, but not a standard TMZ regimen, reduced the number of circulating Tregs. These results can have clinical applications for immunotherapeutic approaches in GBM.

PMID: 19221744 [PubMed - as supplied by publisher]

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