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TITLE:
Standard temozolomide reduces the survival benefit of immune checkpoint inhibition in high grade glioma that can be overcome with variations in dose

HYPOTHESIS:
In this study, we hypothesize that dose modification of TMZ may improve response to immune check point blockade (PD-1 inhibition) by priming host immunity and Tumor microenvironment in GBM.

BACKGROUND/AIMS:
Glioblastoma (GBM) is an aggressive type of brain cancer in adults, which is hard to treat, and have almost no cure. Temozolomide (TMZ) is the frontline therapeutic for GBM, although it is essentially ineffective in about 50% of patients. Therefore, novel immunotherapeutic strategies are under investigation for GBM. TMZ induce changes in host immunity and tumor microenvironment that can change responses to immunotherapy.

METHODS:
C57BL/6 tumor (GL-261) bearing mice were treated with standard (50 mg/kg for 5 days) and metronomic dose (25 mg/kg for 10 days) of TMZ alone and in combination with PD-1 blockade and different cell populations and their activation/exhaustion markers were evaluated in a time dependent manner. Survival was compared between groups.

RESULTS & CONCLUSIONS:
Both standard and metronomic TMZ slightly prolonged survival of GL-261 tumor bearing animals, while PD-1 blocked resulted in a proportion of long time survivors. As opposed to standard TMZ that abolish survival benefits of PD-1 blockade, metronomic dose TMZ sustained survival effects of PD-1 blockade. Effects of standard and metronomic TMZ on host immunity and tumor microenvironment were studied in details to clarify their different effects on animal's survival in combination with PD-1 blockade. TMZ induced dose dependent lymphopenia while metronomic and standard TMZ increased Treg frequency. Both standard and metronomic TMZ increased PD-1 and PD-L1 expression on peripheral T cells. Peripheral blood myeloid derived suppressor cells (MDSCs) increased with standard TMZ treatment but not with metronomic TMZ. Standard TMZ exhausted peripheral blood T cells by upregulation of Tim 3 and Lag3, which was not elicited by metronomic TMZ. In addition, standard TMZ combined with PD-1 blockade exhaust tumor infiltrating T cells that was not seen in metronomic TMZ and PD-1 blockade combination.

Metronomic TMZ induce more robust immune responses in combination with PD-1 blockade compare to standard TMZ. The results showed that dose modification of TMZ can leverage immunotherapy by changing host immunity and tumor microenvironment.