Intra-cranial administration of MTL-004, a promising post-resection treatment for glioblastoma.

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Objectives

Gliomas (GBM), are exceptionally hard to treat, aggressive and genetically heterogeneous tumors.

This study reports the control of tumor recurrence and improved survival in male and female rats by combining a single intra-cranial dose of MTL-004 (5-(aziridine-1-yl)-4 hydroxylamino-2-nitrobenzamide), in a bioresorbable paste (a blend of poly DL-lactic acid-co-glycolic acid; (PLGA) and poly ethylene glycol; (PEG)) to surgical resection of primary glioma tumors. Comparison is made with oral temozolomide (TMZ), the current standard of care (SOC), following resection.

Experimental procedures

On day 0, 2 mm³ tumor fragments were implanted into the brains of healthy female and male Fischer rats.

On day 5 rats the growing tumors were removed using microsurgery. Treatments started as follows:

- Group 1 (Placebo) received a single intracranial dose of excipient powder in PGLA/PEG paste,
- Group 2 (SOC) received 5 daily oral doses of TMZ at 50 mg/kg,
- Group 3 (MTL-004) received a single intracranial dose of excipient powder containing 1 mg/kg MTL-004 in PGLA/PEG paste.

Results

Body Weight
Between day 0 and 5, no groups had statistically significant body weight changes.

Between days 5 to 9, mean body weight of rats receiving TMZ was significantly reduced.

Tumor Volumes
Tumor volumes from MRI were evaluated when at least 80% of rats were still alive in each group (day 14 post tumor resection / treatment initiation). Mean tumor volume was significantly higher in the placebo groups compared to MTL-004 and TMZ treatments.

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Survival
Rats were studied for 58-days post tumor resection/treatment. At this time out of twelve rats per group, none or one survived on TMZ, two or no animals were still alive on placebo, and seven or ten rats treated with MTL-004 were still alive (male or female respectively).

Post resection median survival time was between 20.5 to 27.5 days for rats treated with oral placebo or TMZ. Rats treated with MTL-004 had a significantly higher survival compared to both placebo and TMZ groups and remained in apparent good health for the 58 days of the study.

Conclusions
Consistent trends were observed in each group of male and female rats following tumor resection.

- PGLA/PEG paste with MTL-004 or without (placebo) or were both well tolerated.
- Treatment with MTL-004 in PGLA/PEG paste provided good tumor control, was better tolerated and led to significantly greater survival than oral TMZ or placebo.
- Oral TMZ (SOC) provided control of tumor volume but was associated with significant, transient body weight losses and no significant survival gain compared to placebo.

Our data highlight significant survival benefits associated with a single intracranial dose of MTL-004 with PLGA/PEG paste post-surgery. In conclusion, surgery followed by MTL-004 in PGLA/PEG paste is a well-tolerated and promising treatment for glioblastoma, suitable for clinical evaluation.