Retrospective analysis of the impact of antidepressants with anti-acid sphingomyelinase activity on survival of patients with glioblastoma

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Aims and scope

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Abstract

Purpose

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults and remains difficult to treat. Though still under investigation, acid sphingomyelinase (ASM) has been implicated in GBM lipid raft formation, which facilitates cancer signaling. We sought to verify if, and if so what kinds of ASM inhibitors (ASMis) improve outcomes in GBM.

Methods

We conducted a retrospective study of GBM patients treated between 2015 and 2024 at one academic center. ASMi impact on overall survival (OS) was assessed using Kaplan-Meier analysis and Cox proportional hazards models adjusting for age, sex, tumor location, use of tumor-treating fields (TTFs), and MGMT promoter methylation status. Propensity score matching was performed to

account for baseline imbalances.

Results

ASMi use alone was not associated with a statistically significant OS benefit (HR = 0.81, 95% CI 0.55–1.2, $p = 0.26$). Stratifying by ASMi revealed fluoxetine as the only medication that significantly improved OS (HR = 0.36, 95% CI 0.15–0.9, $p = 0.03$). In a fluoxetine-only multivariate analysis ($n = 17$ vs. 186 controls), the survival benefit remained significant (HR = 0.38, 95% CI 0.15–0.94, $p = 0.04$). This effect persisted in the adjusted propensity-matched cohort (HR = 0.20, 95% CI 0.05–0.78, $p = 0.02$). Age and unmethylated MGMT promoter status were independently associated with decreased survival.

Conclusion

Fluoxetine was associated with increased survival in GBM patients whereas other ASMis and ASMi use overall was not. These findings suggest that fluoxetine may have unique anti-tumor effects beyond ASM inhibition and justify further investigation.