BRAIN CANCER SUPPORT & SOLUTIONS ALLIANCE (BCSSA)

Supporting Information Sheet

Antidepressants (fluoxetine, vortioxetine, and others)

Over the past decade, several studies have explored the use of antidepressants in glioma patients, yielding conflicting results. For example, a 2011 Mayo clinic study retrospectively reviewed 160 glioblastoma (GBM) patients at their institution between 1999 and 2008; of the 160 patients treated, 35 (21.8%) took a selective serotonin reuptake inhibitor (SSRI) antidepressant during initial treatment for GBM. The 2-year survival rate for the SSRI group was 32% versus 17% for those not taking an SSRI (p= 0.18). After adjusting for age and extent of surgery, absence of an SSRI during treatment was associated with a hazard risk of 1.5 (p= 0.05). However, in a later effort to confirm the Mayo study results, researchers at Northwestern conducted a retrospective analysis of 497 GBM patients using a time-dependent Cox model. Contrary to the Mayo study results, the larger study indicated there was no significant association between SSRI use and overall survival (OS) for GBM patients. Even more recently, a pooled analysis of more than 1,700 patients from 4 different trials found no significant association between use of antidepressants (including SSRIs, tricyclic antidepressants and other types) at baseline or at the start of maintenance therapy and OS. While these studies provide broad insights, they lack detailed analyses of specific antidepressants, dosage levels, and results stratified by tumor molecular characteristics.

With advancements in precision medicine, newer studies are seeking to identify specific antidepressants to target particular tumor molecular markers and/or mechanisms of tumor cell metabolism. Notably, research published in 2021 showed that the SSRI fluoxetine (aka Prozac) can inhibit SMPD1, an enzyme important for GBM cell metabolism and EGFR signaling. The researchers tested Prozac on mice implanted with EGFRvIII-amplified human GBMs and found that the levels of the EFGR oncogene went down significantly and the tumors were suppressed. While the effects of Prozac as a monotherapy were clear, follow-up mice studies showed that combining Prozac with temozolomide treatment improved survival to an even greater extent. Further, they examined real-world evidence from electronic medical records and found that GBM patients treated with Prozac had significantly increased survival compared to controls (median OS: 545 vs 318 days), whereas other SSRI antidepressants (citalopram and escitalopram) did not significantly increase survival. (See here for Stanford blog post)

Building on these initial findings, Duke opened a clinical trial in 2023 to investigate the combination of fluoxetine and temozolomide in treating recurrent high-grade glioma patients who are eligible for biopsy and resection. This Phase 1 window-of-opportunity trial will investigate whether the combination induces tumoral lysosomal stress and, separately, whether it enhances tumor DNA damage. The study will also help determine a safe and effective dose for the combination therapy, and the results will directly support development of larger trials. (See here for Duke blog post and here for detailed trial description)

In addition to fluoxetine, the antidepressant vortioxetine has recently been proposed as a promising drug candidate for GBM. Researchers in Zurich used a novel screening platform to test 130 repurposed neuroactive drugs on fresh GBM tumor samples, and vortioxetine exhibited the strongest anti-glioma activity. Follow-up preclinical mouse testing corroborated this finding, and two clinical trials are now in development to see if vortioxetine, alongside standard of care, can help improve survival for GBM patients. It's worth noting that while vortioxetine outperformed fluoxetine (Prozac) in the screening platform results, there is no published clinical evidence yet on appropriate dosing, safety or efficacy of vortioxetine for GBM patients.

KEY TAKEAWAY: There is some preclinical and real world evidence to support use of fluoxetine as an adjuvant therapy in glioblastoma. Each patient's situation is unique, and treatment decisions should be made in consultation with your neuro-oncology care team. They can provide personalized guidance on whether fluoxetine or other experimental approaches may be appropriate options to consider as part of your comprehensive treatment plan.