# Valproic acid treatment for brain tumors

Tumors arising in the brain represent only 2% of all cancers diagnosed in the United States with 23,000 new cases and 14,000 deaths annually. The World Health Organisation (WHO) classifies brain tumors from grade 1 to grade 4, with 1 being the least aggressive and 4 being the most aggressive. Glioblastoma is a grade 4 tumor and is also the most common brain tumor. Glioblastoma are neurologically devastating and rapidly progressing tumors. The treatment of this tumor consists of surgical removal of the tumor to the greatest extent possible followed by radiation therapy and the chemotherapy drug temozolomide. Radiation therapy and the chemotherapy drug are being given at the same time daily for 6 weeks. This is followed by a one month break and then by further chemotherapy using the same drug at a higher dose for 6 to 12 months. The outcome of this treatment remains poor with only a quarter of patients alive at 2 years and less than 10 % alive at 5 years. Many attempts have been made to to increase the effectiveness of this treatment but to date none have been successful.

Valproic Acid is a drug traditionally used to treat seizures, which are a common presentation and symptom of tumors occurring in the brain. Some studies have found that patients with Glioblastoma who also received Valproic Acid to treat their seizures, had a better outcome compared to patients who did not have Valproic Acid as part of their treatment. This, in addition to studies showing that Valproic Acid can turn off a special DNA repair enzyme in so doing can enhance the effect of radiation in the lab, prompted testing of Valproic Acid together with radiation and chemotherapy in an effort to improve the outcome of patients with Glioblastoma. Our study evaluated the addition of Valproic Acid to standard radiation therapy and temozolomide chemotherapy in patients with Glioblastoma who have just been diagnosed and have not received any treatment for their tumor other than the initial surgical removal.

Thirty-seven patients took part in this trial between July 2006 and April 2013. They were given Valproic Acid together with radiation and temozolomide chemotherapy. The first dose of Valproic Acid was given 1 week before the first day of radiation and gradually increased over the course of a week to the dose considered to be effective based on data previously obtained in the lab.

Of all the patients who participated in the study 81% took Valproic Acid as intended. The average survival, or the time point beyond which half of patients survived longer and half less, was 29.6 months. The average time it took for a patient’s tumor to come back was 10.5 months. At 1 year 86% of patients were alive and at 2 years 56% were alive. The most common side effects of Valproic Acid given together with radiation and chemotherapy were blood/bone marrow side effects (32%), followed by neurological symptoms (11%). Patients who were 50 years of age or younger and those who had fewer symptoms from their tumors did significantly better both in terms of survival and the tumor stability. The levels of Valproic Acid in the patient`s blood however had no relationship to either survival or the side effects they experienced.

The conclusion of this study was that giving Valproic Acid in addition to the current treatment of

radiation and temozolomide chemotherapy in patients with Glioblastoma that has been newly diagnosed, was well tolerated. Additionally, Valproic Acid may have improved the outcome of these patients as compared with historical data and deserves further studies to determine what patients may best benefit from this drug. Unfortunately the small number of patients and the fact that they could not be directly compared to patients with Glioblastoma who did not receive Valproic Acid, made it difficult to determine if this new combination is truly better than the current standard treatment.

## Publication

A Phase 2 Study of Concurrent Radiation Therapy, Temozolomide, and the Histone Deacetylase Inhibitor Valproic Acid for Patients With Glioblastoma.
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