Valproic acid for glioma

Several in vivo and in vitro studies have indicated that Valproic acid (VPA) promotes radiosensitivity effects for gliomas and radioprotective influence on normal brain tissue or hippocampal neurons. The results of several retrospective studies have also indicated potential benefit to improve survival of patients with glioblastoma (GBM) [1].

Elahi et al. showed that valproic acid (VPA), a brain penetrant anti-seizure medication and histone deacetylase inhibitor, inhibits the growth of IDH1 mutant tumors in vivo and in vitro, with at least some selectivity over IDH1 wild-type tumors. Surprisingly, genes upregulated by VPA showed no enhanced chromatin accessibility at the promoter, but there was a correlation between VPA-downregulated genes and diminished promoter chromatin accessibility. VPA inhibited the transcription of lipogenic genes and these lipogenic genes showed significant decreases in promoter chromatin accessibility only in the IDH1 MT glioma cell lines tested. VPA inhibited the mTOR pathway and a key lipogenic gene, fatty acid synthase (FASN). Both VPA and a selective FASN inhibitor TVB-2640 rewired the lipidome and promoted apoptosis in an IDH1 MT but not in an IDH1 WT glioma cell line. They further find that HDACs are involved in the regulation of lipogenic genes and HDAC6 is particularly important for the regulation of FASN in IDH1 MT glioma. Finally, they showed that FASN knockdown alone and VPA in combination with FASN knockdown significantly improved the survival of mice in an IDH1 MT primary orthotopic xenograft model in vivo. They conclude that targeting fatty acid metabolism through HDAC inhibition and/or FASN inhibition may be a novel therapeutic opportunity in IDH1 mutant gliomas [2]

Systematic review and meta-analysis

Searches of 7 electronic databases by Lu et al. from Cure Brain Cancer Neuro-oncology Laboratory, Prince of Wales Clinical School, Lowy Cancer Research Centre, University of New South Wales, Sydney, Department of Neurosurgery, Emory University, Atlanta, GA, United States. Computational Neuroscience Outcomes Center, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; School of Pharmacy, MCPHS University, Boston, MA, United States from inception to April 2018 were conducted following the appropriate guidelines.Hazard ratios (HRs) derived from Cox proportional hazard models, and mean differences (MDs), were analyzed using the random effects model. Meta-regression was used to identify potential trend-modifying covariates. Seven retrospective cohort studies satisfied selection criteria describing 2181 primary GBM diagnoses, with 534 (24%) receiving VPA in their treatment. Overall, VPA was shown to confer a statistically significant OS advantage (HR, 0.71; 95% CI, 0.56-0.91; $p < 0.01$) compared to the control group by up to 2.4 months (95% CI, 1.51-3.21; $p < 0.01$). However, upon meta-regression, this survival advantage as inferred by HRs trended towards the null in newer studies (slope, 1.15; $p = 0.02$) or in studies with older participants (slope, 1.13; $p = 0.02$). A similar result was seen with MDs. Based on the literature to date, VPA was significantly associated with better OS in GBM patients by 2.4 months when managed by current standard of care. However, this effect was particularly emphasized among older studies or studies conducted in younger participants indicating the need to exercise caution in assuming generalizability of the pooled effect. Overall, there is considerable bias risks in the current interpretation of the literature, and larger, prospective studies are required for validating this findings.

2016

VPA also promotes hair growth, and thus has the potential to reduce the radiotherapy side effect of hair loss while improving the survival of patients with glioblastoma. The purpose of a study was to determine whether VPA use during radiotherapy for high grade glioma is associated with decreased side effects of radiotherapy and an improvement in overall survival (OS) and progression-free survival (PFS).

Medical records of 112 patients with high-grade glioma were retrospectively reviewed. Watanabe et al., grouped patients by VPA use or non-use during radiotherapy, and evaluated hair loss, OS, and PFS.

The radiation dose and fractionation at the onset of hair loss were 4 Gy and two fractions higher, respectively, in the VPA group compared with the VPA non-use group ($P < 0.01$). Median OS was 42.2 and 20.3 months in the VPA use and non-use groups, respectively ($P < 0.01$; hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.18-0.74). Median PFS was 22.7 and 11.0 months in the VPA use and non-use groups, respectively ($P = 0.099$; HR, 0.62; 95% CI, 0.36-1.09).

VPA use during radiotherapy for glioma is associated with delayed hair loss and improvement in survival. Hair loss prevention benefits patients suffering from the deleterious effects of radiation [3].

Results of a analysis do not justify the use of VPA or levetiracetam (LEV) for reasons other than seizure control in patients with newly diagnosed glioblastoma outside clinical trials [4].

2015

Addition of VPA to concurrent RT/TMZ in patients with newly diagnosed GBM was well tolerated. Additionally, VPA may result in improved outcomes compared to historical data and merits further study [5].

2014

The results of a study suggest that glioblastoma patients may experience prolonged survival due to VPA administration. Sub-analysis confirmed the benefit of VPA use compared to a non-AEDs group and an other-AEDs group. Further RCTs of this subject should be performed [6].

2013

VA use during RT for GB was associated with improved OS, independently of RTOG RPA, seizure history, and concurrent TMZ use [7].

Polytherapy with VPA and LEV more strongly contributes to seizure control than does either as

monotherapy. Use of VPA together with chemoradiation with temozolomide results in a 2-months' longer survival of patients with GBM [8].

2012

The combination of VPA treatment with chemotherapy and radiotherapy in glioblastoma appears a rational option that deserves well-designed prospective clinical trials that assess the efficacy and the molecular characteristics of the responding tumors in these patients [9].

2011

Patients receiving valproic acid (VPA) only had more grade 3/4 thrombopenia and leukopenia than patients without an AED or patients taking an enzyme-inducing AED (EIAED) only. The overall survival (OS) of patients who were receiving an AED at baseline vs not receiving any AED was similar. Patients receiving VPA alone (97 [16.9%]) appeared to derive more survival benefit from TMZ/RT (hazard ratio [HR] 0.39, 95% confidence interval [CI] 0.24-0.63) than patients receiving an EIAED only (252 [44%]) (HR 0.69, 95% CI 0.53-0.90) or patients not receiving any AED (HR 0.67, 95% CI 0.49-0.93).

VPA may be preferred over an EIAED in patients with glioblastoma who require an AED during TMZ-based chemoradiotherapy. Future studies are needed to determine whether VPA increases TMZ bioavailability or acts as an inhibitor of histone deacetylases and thereby sensitizes for radiochemotherapy in vivo [10].

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