The survival effect of valproic acid in glioblastoma and its current trend: a systematic review and meta-analysis.

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Glioblastoma (GBM) can often present with seizure. Attempts have been made to associate the use of anti-epileptic medication valproic acid (VPA) in standard of care management with survival benefit in the past; however, results to date have been conflicting, and most likely subjected to historical bias. This study aimed to quantify the overall survival (OS) effect of VPA in patients with GBM based on the current literature, and identify potential trend-modifying covariates. Searches of 7 electronic databases 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 our findings.
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