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Effect of Levetiracetam Use Duration on Overall Survival of Isocitrate Dehydrogenase Wild-Type Glioblastoma in Adults: An Observational Study

Pallud J, Huberfeld G, Dezamis E, et al. *Neurology*. 2022;98(2):e125-e140. doi:10.1212/WNL.00000000000013005.

Background and Objectives: The association between levetiracetam and survival with isocitrate dehydrogenase (IDH) wild type glioblastomas is controversial. We investigated whether the duration of levetiracetam use during the standard chemoradiation protocol affects overall survival (OS) of patients with IDH wild-type glioblastoma. **Methods:** In this observational single-institution cohort study (2010-2018), inclusion criteria were (1) age ≥ 18 years; (2) newly diagnosed supratentorial tumor; (3) histomolecular diagnosis of IDH wild-type glioblastoma; and (4) standard chemoradiation protocol. To assess the survival benefit of levetiracetam use during the standard chemoradiation protocol (whole duration, part time, and never subgroups), a Cox proportional hazard model was constructed. We performed a case-matched analysis (1:1) between patients with levetiracetam use during the whole duration of the standard chemoradiation protocol and patients with levetiracetam use part time or never according to the following criteria: sex, age, epileptic seizures at diagnosis, Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) class, tumor location, preoperative volume, extent of resection, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. Patients with unavailable O6-methylguanine-DNA methyltransferase promoter methylation status (48.5%) were excluded. **Results:** A total of 460 patients were included. The median OS was longer in the 116 patients with levetiracetam use during the whole duration of the standard chemoradiation protocol (21.0 months; 95% confidence interval [CI] 17.2-24.0) than in the 126 patients with part-time levetiracetam use (16.8 months; 95% CI 12.4-19.0) and in the 218 patients who never received levetiracetam (16.0 months; 95% CI 15.5-19.4; $P = .027$). Levetiracetam use during the whole duration of the standard chemoradiation protocol (adjusted hazard ratio [aHR] .69; 95% CI .52-.93; $P = .014$), MGMT promoter methylation (aHR .53; 95% CI .39-.71; $P < .001$), and gross total tumor resection (aHR .57; 95% CI .44-.74; $P < .001$) were independent predictors of longer OS. After case matching ($n = 54$ per group), a longer OS was found for levetiracetam use during the whole duration of the standard chemoradiation protocol (hazard ratio .63; 95% CI .42-.94; $P = .023$). **Discussion:** Levetiracetam use during the whole standard chemoradiation protocol possibly improves OS of patients with IDH wild-type glioblastoma. It should be considered in the antitumor strategy of future multicentric trials. **Classification of evidence:** This study provides Class III evidence that in individuals with IDH wild-type glioblastoma, levetiracetam use throughout the duration of standard chemotherapy is associated with longer median OS.

Commentary

Antiseizure medications (ASMs) are commonly used in patients with glioblastoma (GBM) as their lifetime seizure risk ranges between 30-50%.¹ Due to its favorable pharmacokinetic profile, absence of interactions with chemotherapeutic agents and high tolerability, levetiracetam (LEV) is the most prescribed ASM along with the standard postoperative treatment of concomitant

chemotherapy and adjuvant chemotherapy with temozolomide (TMZ).² TMZ is the preferred chemotherapeutic agent for tumors with methylated O6-methylguanine DNA methyltransferase (MGMT) promoters.³ LEV has the additional benefit of inhibiting MGMT and sensitizing GBM cells to TMZ.⁴ Could

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it be that LEV, by acting perhaps as a chemosensitizer to TMZ, improves overall survival (OS) in patients with GBM independent of its antiseizure effects?

Initial studies failed to demonstrate an association between the use of ASMs and improvement in OS. For example, Huppold et al⁵ performed a retrospective analysis in a pooled patient cohort of four randomized clinical trials of GBM treated with chemoradiotherapy, TMZ and various ASMs including LEV. OS of patients taking LEV both at the start of and after chemotherapy was no different from those without LEV use at both time points. Limitations of the analysis included few exposures to LEV and lack of systematic control for duration of LEV use and IDH mutation/MGMT promoter methylation status.

Subsequently, Kim et al⁶ performed a retrospective analysis of 103 patients treated with concomitant chemoradiotherapy with adjuvant TMZ and different duration of treatment with ASMs including LEV. In 56%, LEV was used alone or in combination for 3 months during the postoperative TMZ therapy period. ASMs were discontinued at the treating physician's discretion if there were no seizures after the adjuvant chemotherapy period. Patients treated with LEV had a significantly longer OS compared to patients not receiving LEV ($P = .027$). In multivariate analysis, variables identified as significant prognostic factors for longer OS were MGMT promoter methylation and treatment with LEV ($P < .001$). However, there was a significant difference in the number of complete cycles of adjuvant TMZ chemotherapy between the 2 groups and the study lacked information about isocitrate dehydrogenase (IDH) mutation status.

More recently, Roh et al⁷ performed a retrospective analysis of treatment with LEV or valproate (VPA) in 322 patients with IDH-wildtype GBM who received TMZ-based chemoradiotherapy. After tumor resection, ASM's were administered as prophylaxis regardless of seizure history. The initial dose of LEV was 1000 mg/day with a dose adjustment of 500 mg in case of seizure recurrence. Patients were divided into 2 groups based on whether LEV was used at both baseline and the first visit after the concomitant phase of chemoradiotherapy (LEV+) vs patients who were not taking LEV on both occasions (LEV-), comparing their median OS rate. Preoperative history of seizure and MGMT promoter methylation status were not significantly different between the 2 groups but the LEV+ group had higher pre- and postoperative Karnofsky Performance Status Scores and were more likely to undergo complete tumor resection. The OS was 21.1 months for the LEV+ group vs 17.5 months for the LEV- group ($P = .003$). When compared to patients treated with VPA, median OS was higher for LEV treated patients. In multivariate analysis, the use of LEV was a significant prognostic factor for OS.

In the current study, Pallud et al⁸ report the results of a single-center, observational retrospective study of 460 adult patients (35% of whom experienced seizures at the time of diagnosis) with supratentorial IDH wild-type glioblastoma treated with standard chemoradiation with TMZ and LEV. Treatment

duration with LEV was defined as "whole duration" if started at the time of surgery to the end of 6th cycle of TMZ, "part-time" or "never". OS was measured from the date of surgery to the date of death from any cause with surviving patients censored at the date of last follow-up. To assess the survival benefit of LEV, a case-matched analysis was performed comparing patients with whole duration of treatment with LEV (25.2%) to control patients with part-time (31.5%) or no use (43.3%) of LEV, controlling for tumor location, preoperative volume, extent of resection, seizures at diagnosis and MGMT promoter methylation status. The mean duration of follow-up was 16.5 months with a median OS of 17.4 months.


In univariate analysis, treatment with LEV was associated with longer OS (21 months vs 16 months with partial or no treatment). In a Cox proportional-hazards model, LEV use was also an independent predictor of longer OS. LEV's survival advantage was independent of the presence of seizures, the extent of resection or MGMT promoter methylation status. Surprisingly, total daily dose (<500 mg vs higher) did not significantly influence the OS. Few patients treated with LEV experienced adverse-events (AE) and none reported severe AEs.

Strengths of the study include a well-designed protocol with inclusion of a large group of homogeneous patients from a single center treated with a rigorously standardized protocol. Weaknesses include the retrospective design, lack of EEG to rule-out subclinical seizures, lack of data regarding absence or presence of seizure activity during and post chemoradiation treatment and its correlation with OS, absence of plasma LEV levels and of the exact duration of LEV use when "part time".

Assuming that LEV does act as a chemosensitizer to TMZ and improves OS, these data raise the following questions: is there a benefit of maintaining treatment (assuming the absence of side effects), for extended periods of time or indefinitely even in the absence of a history of seizures; does decreasing the absolute risk of seizures increase OS; is EEG monitoring necessary in all GBM patients to rule-out subclinical seizures; what is the optimal dose of LEV in asymptomatic patients; is there a dose response relationship for LEV and should serum levels be monitored; do these benefits apply to ASMs with similar mechanism of action to LEV (i.e. brivaracetam); can these results be extrapolated to recurrent GBM, tumors with lower rates of MGMT methylation and/or other types of gliomas, including pediatric tumors?

While Pallud's et al⁸ study provides class III evidence that LEV use is associated with longer median OS in patients with GBM, only a prospective, randomized controlled trial can determine the survival benefit of LEV. In the absence of such a study, how should clinicians interpret these data? Given the above-mentioned benefits of LEV, plus low-cost and antiemetic effects,⁹ I would argue for its use in all patients with IDH wild-type GBM, independent of the presence of seizure activity. The potential for extended OS outweighs the potential risks associated with LEV as prophylactic treatment. The definitive answer though, is yet to come.

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