ABSTRACT

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Association of plasma levetiracetam concentration, MGMT methylation and sex with survival of chemoradiotherapy-treated glioblastoma patients.

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Glioblastoma multiforme (GBM) is an aggressive brain tumor, often occurring with seizures managed with antiepileptic drugs, such as levetiracetam (LEV). This study is aimed at associating progression-free survival (PFS) and overall survival (OS) of GBM patients with LEV plasma concentration, MGMT promoter methylation, and sex. In this retrospective, non-interventional, and explorative clinical study, GBM patients underwent surgery and/or radiotherapy and received LEV during adjuvant temozolomide (TMZ) treatment. A high-performance liquid chromatography with UV-detection was used for therapeutic drug monitoring of LEV plasma concentrations. Follow-up average drug concentration was related to patients' clinical characteristics and outcomes. Forty patients (42.5 % female; mean age=54.73 ± 11.70 years) were included, and GBM MGMT methylation status was assessed. All were treated with adjuvant TMZ, and LEV for seizure control. Patients harboring methylated MGMT promoter showed a longer median PFS (460 vs. 275 days, log-rank $p < 0.001$). The beneficial effect of MGMT promoter methylation was more evident for females ($p < 0.001$) and in patients with LEV concentration ≤ 20.6 μg/mL (562 days vs. 274.5 days, $p = 0.032$). Female patients also showed longer OS (1220 vs. 574 days, $p = 0.03$). Also, higher LEV concentration (>20.6 μg/mL) synergized with MGMT promoter methylation by extending the OS (1014 vs. 406 days of patients with no methylation and low LEV average concentration, $p = 0.021$). Beneficial effect of higher LEV plasma levels was more evident in males ($p = 0.024$). Plasma concentrations of LEV may support better outcomes for chemoradiotherapy when other positive prognostic factors are lacking and may promote overall survival by synergizing with MGMT promoter methylation and male sex.

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