Is non-P450 enzyme inducing antiepileptic drugs the best ADEs choice for glioblastoma patients?

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The seizure prognosis of using P450 enzyme inducing and non-enzyme inducing antiepileptic drugs for seizure prophylaxis after glioma resection surgery has been investigated in several clinical studies. However, the results of these studies are inconsistent. Additional multicenter RCTs are necessary to provide class I evidence on the role of AEDs in the treatment of glioma associated seizure.


Glioma is the most frequent but deadliest one primary malignant brain neoplasm of human beings, accounting for more than 40% of all adult brain tumors, however, glioblastoma multiforme (GBM) is the most deadliest one of gliomas[1]. Normally, extensive surgical resection and radiochemotherapy, followed by adjuvant temozolomide chemotherapy are thought to be standard treatment and could improve 2.6 months on survival. Though the seizure frequency happened among GBM patients are much less than patients with low grade glioma, there are approximately 30% of the GBM patients would experience at least one seizure active during the course of their disease, and the intriguing phenomenon is that patients with seizure history usually get better survival outcome. Whether the tumor different internal molecular mechanism or prophylactic antiepileptic drugs (AEDs) usage conducts the prolonged survival is unclear. Jaeckle KA and his colleagues carried out a cohort study based on 3 North Central Cancer Treatment Group (NCCTG) trials which suggested GBM patients receiving cytochrome P450 enzyme-inducing AED (EIAED) may have a better outcome [2]. And a recently research conducted by DREG.G 2013 published in the Journal of Neurosurgery also support that opinion [3]. Paradoxically, another study support that enzyme-inducing anticonvulsant (EIAC) use correlated with superior outcome of patients with glioblastoma multiforme [4]. At present, there are still no special guidelines for glioma-associated epilepsy (GAS), what helps neurosurgeon to prescribe antiepileptic drugs (ADEs) for post-surgery glioma patients is their personal preference and clinical experience.

Phenytoin, carbamazepine, Sodium valproate, and levetiracetam are most frequently-used AEDs in clinical setting to treat or prevent seizure activity of post-surgery glioma patient, and co-administration of AED and chemotherapy agents often meet by neurosurgeons [5]. The enzyme inducing antiepileptic drugs (EI-AEDs) such as Phenytoin and Carbamazepine are still the first-line AEDs prescribed by neurosurgeons to control seizure of patients with GBM, however, the side-effects of these drugs were reported to meet high incidence. It is
addressed that the Phenytoin and Carbamazepine are potent 6 major human P450 microsomal enzyme (CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4) inducers, which could accelerate the metabolism of chemotherapeutics and molecular targeted agents that may also help to control seizure activity through anti-tumor effect in turn[6]. The non EIAEDs are not metabolized by the P450 system, although there may be other unexpected interactions that do not involve known pathways, hence, from the recent articles it is in favor of valproic acid or newer anticonvulsants like lamotrigine, levetiracetam instead of carbamazepine and phenytoin.

Valproic acid (VPA) is one of the most studied non-EIAEDs for glioblastoma multiforme in vivo and in vitro and in clinical studies, however, the mechanisms for the possible benefit of VPA are not clear. Temozolomide is a prodrug and an imidazotetrazine derivative of the alkylating agent dacarbazine, and the drug to drug interaction between VPA and temozolomide could reduce the clearance of temozolomide, which may increase its biavailability in vivo or induce autophagy in vivo. Another the potential benefit of VPA is the function act as a histone deacetylase (HDAC) inhibitor. As a HDAC-inhibitory agent, valproic acid could enhance the sensitivity of tumor cell for chemotherapy, induce growth arrest, differentiation or apoptosis of glioma cells, and could improve survival for patients combined with one or more chemotherapeutic agents [7]. M. Weller reported 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) [8]. Equally intriguing is the autophagy stimulated by valproic acid, autophagy represents an alternative tumor-suppressing mechanism that overcomes the dramatic resistance of malignant gliomas to radiotherapy and proapoptotic-related chemotherapy. Levetiracetam (UCB Pharma, Inc.) known as the second generation AEDs for glioblastoma to radiotherapy and proapoptotic-related chemotherapy. Levetiracetam (UCB Pharma, Inc.), known as the second generation AEDs, also has been used to control seizures in patients with glioma. The mechanism of anti-epileptic effect of LEV is still unclear, and most of the relevant studies are in clinical setting. On the seizure prophylaxis, Ryan T. and his colleagues found that levetiracetam and phenytoin had similar seizure control when treated patients with glioma[9]. Daniel A. Lim also suggested no statistical significance were found between levetiracetam and phenytoin though a randomized phase II pilot study[10]. Research also shows Both VPA and LEV even appeared to have a beneficial effect on verbal memory in these patients[11]. Other non-EIAEDs like lamotrigine was relatively less used and studied in glioma patients.

Based on above mentioned intriguing results, should non-P450 enzyme inducing antiepileptic drugs need routinely used to control seizure or prolong life of glioblastoma patients, especially LEV or VPA? The answer should be treated with caution and more information is demanded. Most of those results were generated from unplanned retrospective analysis. The prescription and type of AED were depended on investigators’ preference and local practice—though we haven’t found evidence for a bias. However, when meeting high grade glioma patients need seizure prophylaxis or treatment, non-EIAEDs do have its advantages. They not affect anticancer agents with adjuvant treatment, even valproic acid might elevate plasma concentrations and bone marrow toxic effects of concomitant chemotherapeutic drugs, and non-EIAEDs were reported to induce less side-effect. Also, corticosteroids which usually used to control brain edema would not be increased metabolism by non-EIAEDs. Fortunately, additional data concerning this problem may be around the corner from analysis of the recently completed Radiation Therapy Oncology Group phase III trial (RTOG 0525) comparing standard adjuvant temozolomide vs. a dose-dense regimen, as well as phase II trials of VPA (NCT00302159) and the HDAC inhibitor vorinostat (NCT00731731) with radiation therapy and temozolomide for newly diagnosed glioblastoma. We anxiously await the results of this international RCT and hope that they will enhance the evidence to guide the treatment of glioblastoma associated seizure, and more research of LEV need to be conduct.

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