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Valproic Acid in Patients with Glioma: A Small Review

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Abstract

Seizures are a well-known and feared manifestation of brain tumors. To some extent, the association between gliomas and the prevalence of seizures correlates inversely with histologic tumor grade. The standard therapy for glioma patients is based on maximal safe resection, followed by temozolomide and radiotherapy. Preclinical studies have proposed a modulatory role of the antiepileptic drug Valproic Acid (VPA) on the efficacy of this treatment increasing overall survival. VPA has shown to: 1) inhibit histone deacetylase increasing the sensitivity of tumor cells to radiation; and 2) have a cytotoxic and proapoptotic role on glioma cells inducing autophagy. We will address the information from studies concerning the use of VPA in patients with glioma.

Introduction

Seizures are one of the most common and dreaded manifestations in patients with primary brain tumors. Glioneuronal tumors and Dysembryoplastic Neuroepitheliomas [DNETs] have a seizure frequency of 90-100% [1], low-grade gliomas (LGGs) of 60-88% [2], and Glioblastoma Multiforme (GBM) of 30-40% [3]. In these tumors, the occurrence of seizures is usually the presenting clinical symptom, and in patients with neuroglial tumors, it may often be the only clinical sign [4]. Recurrence or worsening of seizures is often associated with tumor progression.

Temozolomide (TMZ) is an oral, imidazotetriazine derivative of the alkylating agent dacarbazine, widely used for the treatment of gliomas, considered to be a modestly effective chemotherapeutic drug [5]. Valproic Acid (VPA) is an anticonvulsant and mood stabilizer drug widely used for the treatment of epilepsy, bipolar disorder, migraine and less commonly, major depression; recently, it has been proposed to have hypothetical value treating glioma patients with seizures [6].

Gliomas and seizures

Epileptic seizures are the first symptom of intracranial tumors in 30 to 90%. Patients with supratentorial LGGs have higher incidence of epileptic seizures than high-grade gliomas (HGG) [7].The lower incidence of epilepsy in GBM is probably due to constant tumor growth that might prevent the development or the stability of the "epileptogenic focus", and the usually short Overall Survival (OS) of these patients, who ordinarily don't live enough to develop seizures [8]. Multiple mechanisms are involved in the pathogenesis of tumor-related seizures and have not been fully understood. These mechanisms include tumor features, peritumoral tissue, microenvironment and genetic factors[9]. Brain tumors associated with seizures, frequently show different epileptogenic properties, like cortical dysplasia. Glioma cells and peritumoral tissue can overexpress altered levels of neurotransmitter receptors and neuropeptides, altering the balance between excitation and inhibition. Glutamate concentrations are increased in glioma patients with refractory epilepsy [10]; there is also an aberrant neuronal migration and presence of hypoxic brain regions related to the inflammatory reaction and tumor extension [11]. Glia cells are involved in different ways, leading to local irritation and accumulation of microglial cells. Other hypothesis involved in epileptic genesis is a disturbed intercellular communication through overexpression of gap-junction membrane proteins, connexin (CX) 43 and 32, which, in glial and glioneouronal tumors, are associated with intractable epilepsy [12].There are synaptic vesicle proteins aberrations not present in normal glia cells; dysfunction in synaptic vesicle protein 2A (SV2A) expression may promote seizure generation through calcium accumulation [13]. High impact molecular-genetic pathways findings have been described in gliomas, the immune and inflammatory responses of gangliogliomas are involved through the activation of the complement cascade and the sustaining of an inflammatory state observed in chronic epilepsy [14]; there is evidence of a lower expression of sodium, potassium and calcium channel genes involved in homeostasis that could lead to increased excitability [15].

The leucine-rich glioma inactivated gene 1 (LGI1), on chromosome 10q24 is a feasible tumor suppressor gene and is known to trigger epilepsy [16]. Loss of Heterozygosity (LOH) in chromosomes

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1p and 19q is associated with better response to treatment and better prognosis in patients with oligodendroglial tumors, it has been discovered that patients without this molecular genetic profile are more likely to have seizures [17]. Another biologic observation is the mutation in the genes encoding isocitrate-dehydrogenase 1 (IDH1) or 2 (IDH2), associated with multiple metabolic changes that are probably epileptogenic [18].

Valproic acid in glioma patients

VPA is a potent anti-epileptic and effective mood stabilizer, since 1997 VPA emerged as a potent anticancer drug too, its usefulness has been demonstrated in the treatment of different neoplasms [19]. The short chain fatty acid VPA can alter biology of tumor cells, through multiple routes [20]; it activates the mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) pathway regulating cell proliferation, and p38 MAPK, inducing apoptosis [21]. This drug also induces autophagy through the modulation of oxidative stress in glioma cells, although it has been observed that these cells may choose between the autophagic or apoptotic pathways [22].

VPA also inhibits various isoforms of the enzyme Histone Deacetylase (HDAC), which is associated with epigenetic modulation of gene transcription [10]. Brain tumors are often resistant to antiepileptic drugs; the main molecules involved in drug resistance include *P-glycoprotein* (Pgp), a MDR1 gene product and *MDR-associated protein family* (MRP) that includes MRP1, MRP3 and MRP5 all of which have been observed in glioma cells [23]. VPA apparently is not a substrate for P-glycoprotein or other MRPs, and it might reduce the expression of MRP1 via its histone deacetylase-inhibiting effects, becoming a laudable therapeutic option for the management of seizures [24]. Histone Deacetylase Inhibitors (HDACIs), have a role as antiangiogenic factors inhibiting both the endothelial cell proliferation and VEGF protein secretion by glioma cells *in vitro* and *in vivo* [25].

The benefit of VPA on hair loss has recently been proposed in patients having radiotherapy (RT), based on its ability to promote hair growth via β-catenin stabilization. In a clinical trial of 112 HGG patients treated with RT, those who used VPA had delayed hair loss [26,27].

Although VPA is generally well tolerated, it should be used with caution because its use in combination with some chemotherapy agents might increase the frequency of hematologic toxicity, liver failure and teratogenesis [28,29].

VPA and TMZ

As described above, VPA induces histone acetylation, resulting in increased DNA accessibility; thereby, VPA could allow demethylases to remove methylation of specific genes. Some gliomas are TMZ resistant due to the DNA repair protein O- methylguanine-DNA-methyltransferase (MGMT) [30], and unexpectedly it has been demonstrated that there is a synergistic effect when combining VPA and TMZ that might be due to VPA loosening up chromatin, thereby enabling TMZ to increase DNA access, leading to more methylation [31]. The histone hyperacetylation, induced by VPA, sensitizes cells obtaining a better response to chemotherapy and has synergistic effect on tumor growth delay, increasing the OS of glioma patients [32]. Another synergistic effect takes place during the induction of autophagic cell death in glioma cells both *in vitro* and *in vivo*; TMZ reduces the intrinsic epileptogenicity of the tumor, possibly through a decrease in glutamate levels released from glioma cells [10].

There are some studies that support the benefit of this concomitant therapy (VPA and TMZ); the combination of these drugs have been associated with significantly increased OS and prolonged Progression Free Survival (PFS) in grade II/III glioma patients with a dose-dependent manner [33]. In a previous trial involving patients with GBM and seizures treatment with VPA showed HDAC inhibition but did not significantly affect OS, in comparison with concomitant therapy with TMZ [34].The European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), in their retrospective analysis suggested using VPA over an enzyme-inducing antiepileptic drug for the management of seizures in GBM patients, and established that GBM patients treated with VPA, TMZ and (RT) had better OS, however, they advise the need for more studies to determine the effectiveness of this antiepileptic drug [35].

VPA and RT

TMZ and VPA are independently known as radiation sensitizers in experimental glioma models [36], since 2004 the concomitant use of temozolomide with radiotherapy has become the standard of care for HGG patients [37].

VPA enhances the sensitivity of radiation of human glioma cells both in vitro and in vivo, the mechanism by which this radiosensitivity is obtained is not fully understood, a relation with alterations in the induction or repair of DNA damage is speculated [38,39], VPA sensitizes glioma cells 24 hours after radiation exposure [40]. A study of 544 GB patients found that patients receiving VPA had a median OS of 16.9 months, and when combined with TMZ during RT, the median OS was 23.9 months, of all antiepileptic drugs with HDAC inhibitory properties, VPA is the most potent and the only one associated with improved OS [41]. In another study, 37 patients with newly diagnosed GBM were added VPA to the standard therapy RT/TMZ and showed a 1 year OS rate of 86%, and 6 month PFS rate of 70% [42].

A recent cohort of 1,869 patients, obtained from several phase III trials, reported that there is no clear association between the use of VPA and a better OS or PFS; clarifying that the previously described studies had small sample sizes and insufficient data about dosage and exposure time of this combined treatment [43].

Conclusion

VPA has the potential of apoptosis, growth arrest, and cell differentiation of cancer cells through inhibition of histone deacetylase and other means. Although promising as a sensitizer for both chemotherapy and radiotherapy in glioma patients, further studies are needed. It is crucial to have larger sample sized studies to confirm this effectiveness.

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