

MINI-REVIEW

Roles of Valproic Acid in Improving Radiation Therapy for Glioblastoma: a Review of Literature Focusing on Clinical Evidence

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Abstract

Glioblastoma (GBM) is the most common and aggressive type of primary brain neoplasm. The current standard therapy for GBM consists of maximal surgical resection within safe limits, followed by radiation therapy (RT) and chemotherapy with temozolomide. Despite advances in treatment, the prognosis of GBM remains poor. Epileptic seizure is one of the most common symptoms in patients with GBM. Valproic acid (VPA), a histone deacetylase inhibitor, is often used as an anti-epileptic drug in patients with brain neoplasms due to its effectiveness and low toxicity profile. Several *in vivo* and *in vitro* studies have indicated that VPA has radiosensitizing effects for gliomas and radioprotective influence on normal brain tissue or hippocampal neurons. The results of several retrospective studies have also indicated potential benefit to improve survival of patients with GBM. Moreover, the promising treatment results of a phase 2 trial of concurrent radiation therapy, temozolomide, and VPA for patients with GBM have been recently reported. The use of VPA in patients with GBM has thus recently receiving more attention. In this article, we review the role of VPA in radiation therapy for GBM, focusing on the clinical evidence.

Keywords: Valproic acid - anti-epileptic drug - glioblastoma - radiation therapy - chemoradiation therapy - temozolomide

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Introduction

Glioblastoma (GBM) is the most common primary brain neoplasm according to the World Health Organization (Louis et al., 2007). It has been reported that it comprises 15% of all intracranial neoplasms and about half of malignant primary brain and central nervous system tumors (Ostrom et al., 2014). The prognosis of GBM is still poor despite advance in treatment. The standard therapy consists of surgical resection to the extent that is safely feasible, followed by radiation therapy (RT) and chemotherapy with temozolomide (TMZ) (Stupp et al., 2005; Stupp et al., 2009). The median overall survival (OS) is approximately 15 months (Stupp et al., 2005; Oike et al., 2013; Szczepanek et al., 2013), and the five-year survival rate is less than 10% (Stupp et al., 2009; Oike et al., 2013).

New-onset seizures often represent the first clinical symptom of patients with GBM. It has been reported that 30 - 40% of GBM patients initially presented with epileptic seizures (Beaumont et al., 2000; Kerkhof et al., 2013; Berendsen et al., 2015). Although it still remains controversial, epilepsy has been reported to be a favorable

factor for survival in GBM (Chaichana et al., 2009; Stark et al., 2012; Rosati et al., 2013; Vecht et al., 2014; Berendsen et al., 2015).

Valproic acid (VPA), a histone deacetylase inhibitor, is a frequently used anti-epileptic drug (AED) in patients with brain neoplasms due to its effectiveness and relatively low toxicity profile (Chateauvieux et al., 2010; Vecht et al., 2014). *In vivo* and *in vitro* data suggest the benefit of use VPA combined with radiation therapy for glioma due to radiosensitizing effect for glioma and radioprotective effect for normal brain tissue or hippocampal neurons (Brown et al., 2008; Fu et al., 2010; Shao et al., 2012; Van Nifterik et al., 2012; Oike et al., 2014; Rubner et al., 2014; Zhou et al., 2014; Hosein et al., 2015; Pont et al., 2015; Thotala et al., 2015; Zhou et al., 2015).

In this article, we review the role of VPA in radiation therapy for GBM, focusing on the clinical evidence.

Effects of AED Use for GBM

Oberndorfer et al. (2005) evaluated the effects of enzyme inducing AED (EI-AED) and non-EI-AED in

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patients with GBM treated with chemotherapeutic agents (Oberndorfer et al., 2005). One hundred and sixty eight GBM patients treated with surgery, RT and chemotherapy were retrospectively analyzed. Patients were separated into three groups: patients without AED (n=88), patients with EI-AED (n=43) and patients with non EI-AED (n=37). A significant difference was detected in survival between non-EI-AED (10.8 months) and EI-AED group (13.9 months). Lomustine (CCNU) was the most frequently used chemotherapeutic agent in the study.

Guthrie et al. evaluated the impact of antiepileptic drugs on survival of patients with GBM (Guthrie et al., 2013). They reviewed a cohort of 236 consecutive patients in whom GBM had been diagnosed in their institution, and 210 patients were included in the analysis. Among them, 138 patients (65.7%) had received no AED and 72 patients (34.3%) had received some AED. The patients who had received AED had longer survival compared with those who had not received AED (Mantel-Cox log-rank test, $p < 0.001$).

Barker et al. reported a retrospective analysis of 544 patients with GBM (Barker et al., 2013). In their cohort, 403 patients (74.1%) were taking an AED during RT. The median OS of their entire cohort was 14 months (range, 0 - 197 months), and that was 13.8 and 13.5 months in patients taking and not taking an AED during RT, respectively ($p = 0.98$). In the Cox regression analysis, OS was not associated with AED use during RT ($p = 0.25$, Hazard ratio [HR] 1.13; 95% confidence interval [CI], 0.92 - 1.33).

Weller et al. reported a post hoc analysis of the European Organization for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada (NCIC) CE.3 clinical trial which is the landmark trial established the current standard management for GBM (Stupp et al., 2005; Stupp et al., 2009; Weller et al., 2011). They assessed whether AED modulated the effectiveness of chemoradiotherapy (CRT) with TMZ in patients with newly diagnosed GBM. In the CRT with TMZ arm, the outcome of patients receiving an AED at baseline was similar to that of the patients not receiving an AED (overall survival [OS]: $p = 0.89$, HR 0.98, 95% CI; 0.76 - 1.27).

Although these findings indicate that the AED use in the treatment of GBM has potential benefit to improve the outcome of GBM, the benefit of AED remains unclear.

Comparison between VPA and Other AED in the Treatment of GBM

In the report of EROTC/NCIC TMZ trial for GBM, patients were divided into 3 groups: patients without AED (n=175), patients with EI-AED only (n=252) and patients with VPA only (n=97) and the OS was compared (Weller et al., 2011). The patients treated with VPA only had a superior survival benefit from CRT (HR 0.39, 95% CI; 0.24 - 0.63) compared with patients treated with an EI-AED only (HR 0.69, 95% CI; 0.53 - 0.90) or patients without any AED (HR 0.68, 95% CI; 0.49 - 0.93). In the CRT with TMZ arm, the median OS was 13.96 months, 14.42 months, 17.35 months for patients without AED, with EI-AED only and with VPA only, respectively.

In the retrospective study by Guthrie et al., of the evaluated 210 patients, 138 patients received no AED, 24 had VPA, 19 had carbamazepine, 20 had phenytoin, and 9 had another AED (Guthrie et al., 2013). Patients treated with VPA had significantly longer survival than those who did not receive an AED (Mantel-Cox log-rank test 17.506, $p < 0.001$), and patients treated with VPA had a significantly longer survival than those who had received other AEDs (Mantel-Cox log-rank test 5.303, $p < 0.02$).

In the retrospective study by Barker et al., of the evaluated 544 patients, 403 (74%) patients were taking an AED during RT, and VPA was used by 29 patients (7%) (Barker et al., 2013). Among the patients who were taking AED during RT, median OS of patients taking VPA was 16.9 months, compared with 13.6 months in patients using another AED. Multivariable Cox regression analysis revealed that OS was associated with VPA use during RT (HR 0.67, 95% CI; 0.27 - 1.07, $p = 0.047$). On the other hand, Cox regression analysis showed no association of OS with any of the other AED (phenytoin, levetiracetam, carbamazepine or phenobarbital).

These findings indicate that VPA may have a more advantage in the treatment for GBM compared with other AED.

VPA in Treatment for GBM

Kerkhof et al. conducted a retrospective study to examine the efficacy of VPA given with or without levetiracetam on seizure control and on survival in patients

Table 1. Summary of the effect of VPA on survival

Study	No of Pts	No of Patients receiving VPA (%)	Median OS with VPA (mo)	Median OS without VPA (mo)	Median OS without AED (mo)	Median OS with other AED (mo)
Weller (2011)	524	97 (18.5)	12.8		12.5	13.2
Weller (2011) ^a	265	49 (18.5)	17.4		14	14.2
Kerkhof (2013) ^b	165	105 (63.6)	15.9	14.2		
Barker (2013)	531	29 (5.4)	16.9		13.5	13.6
Barker (2013) ^c	134	12 (9.0)	23.9	15.1		
Berendsen (2015) ^d	212	55 (25.9)	13.8	12.7		

No: number; Pts: patients; OS: overall survival; mo: months; VPA: valproic acid; AED: anti-epileptic drug; a) cohort of patients treated with concurrent chemoradiation therapy with temozolomide; b) cohort of patients treated with concurrent chemoradiation therapy with temozolomide; c) cohort of patients treated with concurrent chemoradiation therapy with temozolomide; d) cohort of epileptic patients with glioblastoma

with GBM treated with CRT (Kerckhof et al., 2013). In the report, they performed Cox regression survival analysis on 165 patients receiving CRT with TMZ. In the cohort, 108 patients received VPA for at least 3 months. Patients using VPA in combination with TMZ showed a longer median survival of 69 weeks (95% CI; 61.7- 67.3) compared with 61 weeks (95% CI; 52.5 - 69.5) in the group without VPA (HR 0.63, 95% CI; 0.43 - 0.92, $p=0.016$), adjusting for age, extent of resection, and O(6)-DNA methylguanine-methyltransferase promoter methylation status.

In the retrospective study by Barker et al., the benefit of VPA in subgroup of patients who received CRT with TMZ, which is the current standard treatment for GBM, were also evaluated (Barker et al., 2013). Patients receiving VPA during CRT had a median OS of 23.9 months, compared with 15.1 months in patients not receiving VPA ($p=0.25$). Cox regression analysis of patients receiving CRT with TMZ revealed that VPA use during RT was associated with longer OS with borderline significance (HR 0.54, 95%CI; -0.09 - 1.17, $p=0.06$), independently RTOG RPA class (HR 1.39, 95%CI; 1.18 - 1.6, $p=0.02$) and seizure history (HR 1.69, 95% CI; 1.31 - 2.07, $p=0.007$).

Berendsen et al. reported a retrospective analysis to investigate the relationship between survival and epilepsy at presentation in GBM patients (Berendsen et al., 2015). Six hundred and forty seven patients were included in the analysis. Multivariate regression analysis showed that GBM with epilepsy was significantly associated with an increased OS compared with GBM without epilepsy ($p<0.00005$). On the other hand, they reported that the survival of patients who received VPA ($n=55$; median OS 13.8 months, 95%CI; 10.1 - 17.4) did not differ significantly from those with seizures who did not received VPA ($n=157$; median OS 12.7 months, 95%CI; 10.6 - 14.8, log-rank test $p=0.55$, crude HR 0.90, 95%CI; 0.62 - 1.29, $p=0.55$). They concluded that epilepsy is an independent prognostic factor for longer survival in GBM and survival is not associated with VPA treatment.

The effect of VPA in these retrospective studies was summarized in Table 1. Although many retrospective studies have suggested a favorable effect of VPA, there seems to be still controversy in the benefit of VPA on OS of GBM patients. The findings of Berendsen et al. seem to be interesting because none of the patients in their cohort without epilepsy received prophylactic AED treatment (Berendsen et al., 2015). On the other hand, in the retrospective study of Baker et al (Barker et al., 2013), of 544 evaluated patients, seizure was noted before the end of RT in 217 (40%) patients. However, 403 (74%) patients were taking AED during RT, suggesting that many took AED to prevent seizures. Besides, according to the findings of Weller et al. and Barker et al, the absolute benefit of VPA seems to be larger when VPA is used concurrently used in CRT with TMZ compared RT alone. (Weller et al., 2011; Barker et al., 2013) (Table 1). The study cohort of Berendsen et al. consisted of heterogeneous population, including patients treated with adjuvant RT or TMZ monotherapy, and without adjuvant therapy (Berendsen et al., 2015). These findings may indicate that the concurrent use of VPA during RT, regardless of the presence of epilepsy or

seizure as the symptoms of GBM, is essential to improve the outcome of patients of GBM, and the benefit of VPA may be mainly due to radiosensitizing effect for glioma and radioprotective effect for normal tissue as indicated in vivo and in vitro studies (Brown et al., 2008; Fu et al., 2010; Van Nifterik et al., 2012; Shao et al., 2012; Oike et al., 2014; Rubner et al., 2014; Zhou et al., 2014; Hosein et al., 2015; Pont et al., 2015; Thotala et al., 2015; Zhou et al., 2015).

Prospective Trial of VPA in the Treatment of GBM

Recently, Krause et al. reported the results of a single-arm phase 2 study of concurrent radiation therapy, temozolomide and VPA for patients with GBM (Krause et al. 2015). Thirty-seven patients with newly diagnosed GBM were enrolled in the study. Patients received VPA, 25 mg/kg orally, divided into 2 daily doses concurrent with radiation therapy and TMZ. Median overall survival was reported to be 29.6 months (range, 21 - 63.8 months). The most common grade 3/4 toxicities of VPA in conjunction with radiation therapy and TMZ were blood and bone marrow toxicity (32%), neurological toxicity (11%), and metabolic and laboratory toxicity (8%). The survival outcome of the study is promising and the toxicity profile also seems to be well-tolerated.

In summary, we reviewed the role of VPA in RT for GBM, focusing on the current clinical evidence. Although many pre-clinical and retrospective data suggest the benefit of VPA combined with CRT for GBM, there still remains controversy. VPA seems to be one of the most promising agents to improve the outcome of GBM, the prospective data is still limited. Further investigations are warranted to evaluate the efficacy and to provide optimal treatment.

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