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Valproic acid as a radio-sensitizer in glioma: A systematic review and meta-analysis

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Abstract

Background. Histone deacetylase inhibitors (HDACi) including valproic acid (VPA) have the potential to improve radiotherapy (RT) efficacy and reduce treatment adverse events (AE) via epigenetic modification and radio-sensitization of neoplastic cells. This systematic review and meta-analysis aimed to assess the efficacy and AE associated with HDACi used as radio-sensitizers in adult solid organ malignancy patients.

Methods. A systematic review utilized electronic searches of MEDLINE(Ovid), Embase(Ovid), The Cochrane Library, and the International Clinical Trials Registry Platform to identify studies examining the efficacy and AEs associated with HDACi treatment in solid organ malignancy patients undergoing RT. Meta-analysis was performed with overall survival (OS) reported as hazard ratios (HR) as the primary outcome measure. OS reported as median survival difference, and AEs were secondary outcome measures.

Results. Ten studies reporting on the efficacy and/or AEs of HDACi in RT-treated solid organ malignancy patients met inclusion criteria. All included studies focused on HDACi valproic acid (VPA) in high-grade glioma patients, of which 9 studies ($n = 6138$) evaluated OS and 5 studies ($n = 1055$) examined AEs. The addition of VPA to RT treatment protocols resulted in improved OS (HR = 0.80, 95% CI 0.67–0.96). No studies focusing on non-glioma solid organ malignancy patients, or non-VPA HDACi met the inclusion criteria for this review.

Conclusions. This review suggests that glioma patients undergoing RT may experience prolonged survival due to HDACi VPA administration. Further randomized controlled trials are required to validate these findings. Additionally, more research into the use of HDACi radio-adjuvant treatment in non-glioma solid organ malignancies is warranted.

Keywords

central nervous system neoplasm | glioma | histone deacetylase inhibitor | radiation-sensitizing agents| valproic acid

Cancer is currently the second most prevalent cause of mortality globally, accounting for nearly 10 million deaths worldwide in 2020.[1] Cancers can be divided into hematological and solid organ malignancies, with the latter, the subject of this review, including but not limited to cancers of the central nervous system (CNS), respiratory tract, gastrointestinal tract, male and female reproductive systems, and the skin.[1]

Radiotherapy (RT) is one of the most common cancer treatment modalities worldwide and is used in a variety of solid organ malignancies for either curative purposes, to induce partial or complete remission, or for palliation.[2,3] Ionizing radiation acts on tumor cells primarily by inducing DNA damage, including double-stranded DNA breaks, thereby resulting in the apoptosis of neoplastic cells.[2,4,5] However RT is associated

with both short and long-term side effects, ranging from acute dermatological effects, alopecia, nausea, and lethargy to uncommon RT-induced secondary cancers.[2]

Radio-sensitizing agents, or radio-sensitizers, are drugs that act to increase the susceptibility of neoplastic cells to RT by modulating cellular responses to radiation. These agents aim to improve the efficacy of RT treatment and reduce radiation dosage requirements, thereby decreasing RT-associated side effects.[5] Histone deacetylase inhibitors (HDACi) are one such class of drug that may act as radio-sensitizers for solid organ malignancies,[2,4–6] with preclinical studies demonstrating beneficial radio-sensitization effects against multiple cancers, including glioblastoma (GBM), melanoma and squamous cell carcinoma, as well as esophageal, colorectal, lung, prostate and breast cancers.[2,4,7,8]

The use of radio-sensitization treatment is of particular importance in cancers that are relatively resistant to radiation exposure,[9] including CNS neoplasias.[2,10] Glioma is the most common histological type of CNS cancer and is further divided into high-grade glioma (including GBM, anaplastic astrocytoma, and anaplastic oligodendroglioma) and low-grade glioma.[11] Of these, GBM is the most common primary malignant brain tumor in adults, with an incidence ranging from 0.59 to 5 per 100 000 individuals.[12,13] Despite some improvement in OS over the past 2 decades, the global burden of CNS cancers over the past 25 years has been increasing[11,13–15] and the median survival of high-grade glioma remains at less than 15 months. As such, this cancer represents a significant international health issue, and an area of particular interest in the research of radio-sensitizing agents.[11,12,16,17]

Over 30 different HDACi have been identified, including valproic acid (VPA), phenylbutyric acid, trichostatin A, vorinostat, romidepsin, belinostat, and panobinostat.[18] VPA is of particular importance for investigation given its generally well-tolerated side effect profile, low cost, and easy accessibility, including in resource-constrained developing nations.[19] VPA is a nonenzyme inducing antiepileptic drug with European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) registered indications including treatment of epilepsy and bipolar disorder, as well prevention of migraine headaches.[20–22] In recent years, VPA has also been demonstrated to have class I and IIa selective HDACi properties[23–25] and although not currently EMA or FDA registered for this purpose, this has renewed research interest in their potential application to cancer treatment.

Specifically, within the high-grade glioma population up to 60% of patients present with or develop epileptic seizures during the course of their treatment, with VPA a common first-line therapy in these patients.[26–28] Recent studies have identified that GBM patients treated with VPA appear to have a survival advantage independent of anti-seizure drug effects,[23,24] hypothesized to be attributed to its HDACi properties, as epigenetic modulation of GBM cancer cell DNA improves tumor response to RT.[29–31] Of note, 2 systematic reviews in recent years support the use of VPA in GBM patients,[32,33] though neither focused on the impact of VPA as a radio-sensitizer. From these studies, Yuan et al. (2014) identified prolonged survival in GBM patients treated with VPA when compared to other antiepileptic drugs (HR 0.56; 95% CI 0.44–0.71), while the review by Lu et al. (2018) identified a statistically significant OS advantage (HR 0.71; 95% CI 0.56–0.91) by 2.4 months with VPA treatment in GBM patients, though the latter paper cautioned that this finding may not be generalizable among patient populations of all ages. Whilst VPA is currently not registered by the EMA or FDA for use in CNS malignancy patients without seizures, assessment of this off-label use of VPA may have important repercussions in defining future treatments within this patient population.

Given that there are currently no published systematic reviews focused on the use of HDACi adjuvant treatment in RT programs for solid organ malignancies generally, or glioma specifically, there remains a significant knowledge gap in our understanding of the application of these drugs in RT programs. This review, therefore, aimed to evaluate the efficacy and side effects of HDACi in combination with RT for the treatment of solid organ malignancies, including glioma.

Methods

We conducted this systematic review as per the previously peer-reviewed, published protocol in accordance with the guidelines of JBI methodology for systematic reviews of effectiveness.[18,34]

Search Strategy and Study Selection

In November 2021, an electronic search of MEDLINE(Ovid), Embase(Ovid), Scopus, and The Cochrane Library was undertaken to identify potentially relevant articles reporting on HDACi treatment in patients with solid organ malignancies undergoing RT. The search strategy included the medical subject headings of "neoplasms," "histone deacetylase inhibitors," and "radiotherapy" and free text searches, with the full search strategy found in the published protocol.[18] Limits were applied to studies written in the English language and for a 20-year date range from 2001 to 2021. This 20-year time limit was chosen to capture survival statistics relevant to modern cancer prognoses, an important consideration given the improvements in RT treatment efficacy in recent decades.[35] The references contained in the identified articles were examined to identify other relevant papers and The International Clinical Trials Registry Platform was searched for relevant trials.

Included studies reported on adult patients with a solid organ malignancy diagnosis treated with RT and one or more HDACi, with or without other cancer treatments. Studies were required to include a control group of patients undergoing RT without a HDACi and to report on efficacy outcomes such as overall survival (OS) and/or safety outcomes such as AE. Eligible study designs were experimental and quasi-experimental studies and analytical observational studies including cohort studies. Excluded study types were qualitative studies, text and opinion papers, nonhuman studies, and conference proceedings and abstracts without final results confirmed or sufficient information available. Studies utilizing the HDACi nicotinamide as a radio-sensitizer in carbogen and nicotinamide (CON) protocols were also

excluded from analysis due to the well-established hypoxia modification mechanism of radio-sensitization using CON protocols[36] invalidating comparison with other HDACi, and the difficulty in assessing the effect of nicotinamide separate from carbogen in these papers.

Data Extraction and Endpoints

Studies were screened and quality assessment was performed by two independent reviewers, with differences resolved by discussion and consensus with a third author. Critical appraisal utilized the standardized critical appraisal instruments from JBI.[37]

Data were extracted from eligible studies using a standardized form, including details about the study (author, year of publication, aim, study size, study population, study design, setting, and methodology), patients (age, gender, type, and grade of cancer), treatments (type of HDACi used, details of RT protocol, other therapies used) and relevant outcome data (OS and AE). Emails were sent to corresponding authors requesting missing information as appropriate.

Statistical Methods

Analysis was performed comparing HDACi use in specific solid organ malignancy chemoradiotherapy protocols. OS was the primary outcome measure. The primary meta-analysis pooled hazard ratios (HR) comparing RT and VPA with RT without VPA. In articles where results from more than 2 control groups were reported, we combined groups using the methods described in Borenstein et al..[38] As many studies reported median survival times instead of HRs a secondary analysis of OS using the pooled difference in medians as the measure of the effect was performed. Methods for pooling median survival times are poorly developed. The methods used here essentially treated the medians as means and results should be viewed as indicative rather than definitive. Meta-analyzes were conducted using the metafor() package in R Software[39] and principal results were presented using Forest plots. To assess statistical heterogeneity between studies the I^2 statistic was used. Publication bias was assessed using a funnel plot with the Egger test used to assess for funnel plot asymmetry where appropriate. Subgroup analysis was performed for median OS parameters for patients treated with RT and TMZ, the current standard of care for GBM. The secondary outcome of this meta-analysis was reported AEs, with summative data provided in narrative form.

Results

A flow diagram depicting the literature search process based on PRISMA[40] is shown in Figure 1. The initial search identified 3721 potentially relevant studies. After the exclusion of duplicate publications, 2260 unique references remained for further screening and evaluation. Among these, 85 were assessed as full-text articles for eligibility with 10 meetings all inclusion criteria.

Study and Patient Characteristics

Summary statistics for included trials are presented in Table 1. All 10 included studies examined the use of HDACi VPA in high-grade glioma patients,[41–50] of which 8 included patients only with histologically confirmed GBM. Nine of the papers were retrospective cohort studies, and one was a secondary analysis of pooled data sourced from clinical trials. No randomized controlled trials assessing the OS or AEs associated with VPA treatment in RT-treated glioma patients were identified.

Our meta-analysis included efficacy results from 9 studies involving 6138 patients of which 1695 were treated with VPA and AEs results from 5 studies involving 1055 patients of which 267 were VPA treated. Studies included patients treated between 1998 and 2014. From the 10 papers included, 4 were from Europe, 2 from the United States, 2 from Asia, and 2 were multinational studies. The median sample size in included studies was 347 patients (range: 101–2379 patients) with a median follow-up period of 8 years (range: 2–15 years). Within the population of patients with GBM in our study ($n = 3749$) age (median 57 years) and sex distribution (61% male) correspond well with reported population data for GBM patients.[51]

No studies reporting on non-VPA HDACi treatment in glioma patients undergoing RT met the meta-analysis inclusion criteria, and nor did any papers focusing on HDACi treatment in solid organ malignancies other than glioma meet meta-analysis criteria.

Methodological Quality

Of the relevant quality criteria, 4 were fulfilled by all the studies. That is, exposure to VPA and outcomes were measured in a valid and reliable way, with sufficient follow-up time for outcomes to occur and appropriate statistical analysis performed. An additional 4 of the remaining 7 quality criteria were met by 80% or more of the studies, including ensuring the 2 groups were similar and recruited from the same population, that exposure was measured similarly to assign people to exposed and unexposed groups and that confounding factors were identified. In 70% of studies strategies to deal with confounding factors were utilized. Adequate identification and description of loss to follow-up occurred in only 40% of the studies. Specific details of treatment regimens, including VPA dose and duration of therapy, radiation dose and fractionation, and the use of adjunctive therapies were often poorly reported and poorly standardized within the observational studies included in this review.

Overall Survival of Glioma Patients Undergoing Radiotherapy With Valproic Acid

Six studies reported OS using HR as the primary outcome measure, totaling 5007 patients of whom 1538 were treated with VPA. As shown in Figure 2, patients undergoing RT with VPA treatment have improved OS compared to those patients who were not treated with VPA (HR = 0.80, 95% CI 0.67–0.96). There was statistically significant heterogeneity among the pooled studies ($I^2 = 58.9\%$, $P = .033$). It should

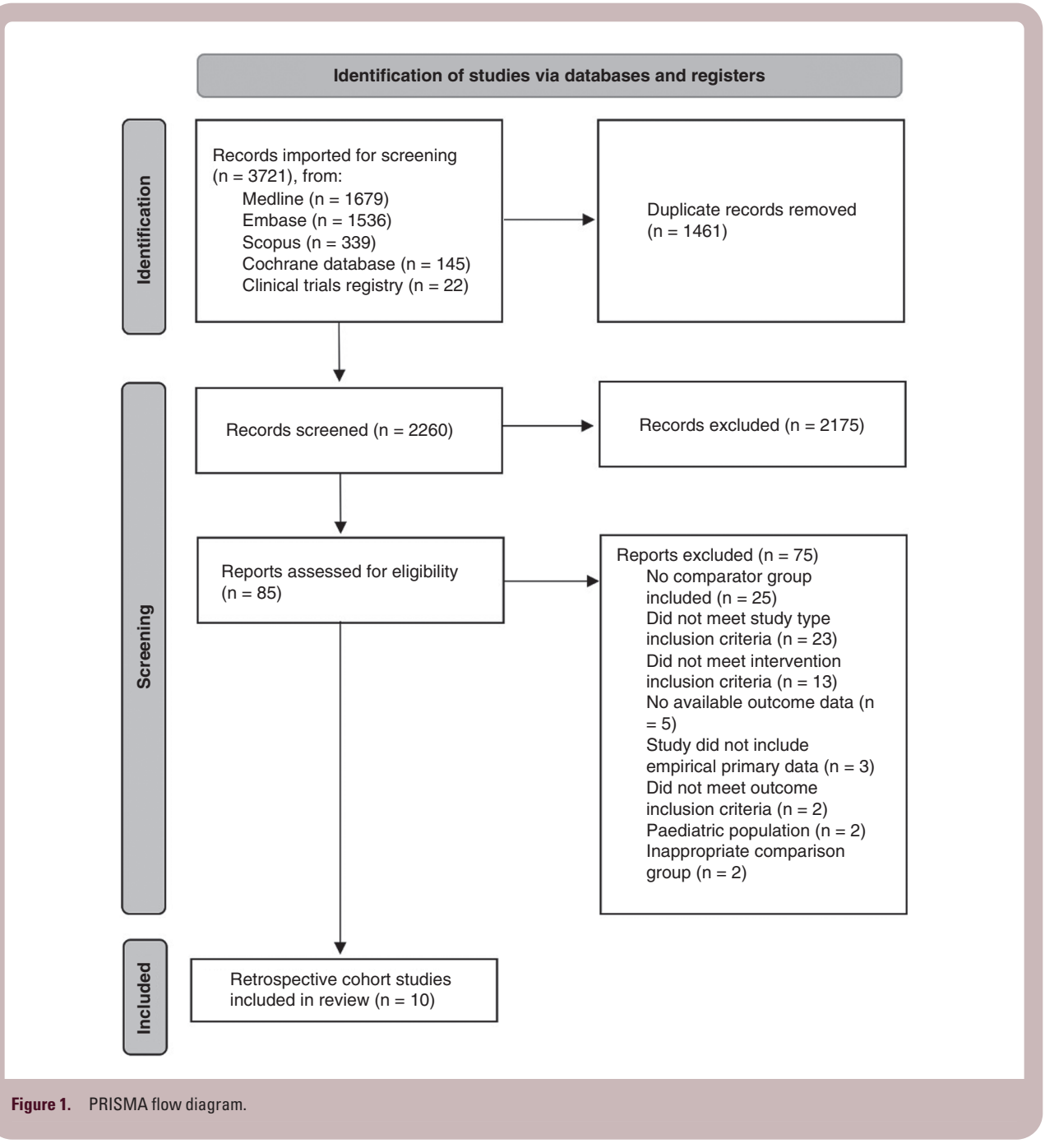

Figure 1. PRISMA flow diagram.

also be noted that there are too few studies to address the issue of publication bias (see Supplementary Material).

Five studies were included in the analysis of median OS performed utilizing the difference in medians, involving 3249 patients of whom 482 were treated with VPA (Figure 3). These data should be interpreted with caution given the nonstandard statistical analysis utilized, however was included as it provides further support for an improved median OS with VPA treatment. The pooled difference in median survival of glioma RT patients treated with VPA, compared to those without VPA, was 4.79 months (95% CI 1.92–7.66), however, there was significant heterogeneity between studies ($I^2 = 99.0\%$, $P < .0001$). Although the direction of results is consistent, providing cumulative evidence of a VPA protective effect, the high degree of heterogeneity between studies resulted in an inability to establish the true magnitude of protection. Of note, 2 of the 5 studies[44,45] ($n = 1747$) were included in both OS calculations as both HR and median difference data were available for analysis.

Overall Survival of Glioma Patients Undergoing Chemoradiotherapy With Valproic Acid and Temozolomide

Subgroup analysis examining the effect of VPA on OS in high-grade glioma patients treated with RT and temozolomide (TMZ) included 4632 patients of whom 1521 were treated with VPA in the HR analysis and 2561

Table 1. Study characteristics

Study	Country	Study Period	Cancer Type, Grade*	Median Age, Years (Range, Years)	Total Number of Patients	Number of Patients Treated With VPA	VPA Dose	VPA Duration	Seizure Frequency in VPA Group	EBRT Total Dose; Dose Fractions	Patients Receiving TMZ; TMZ Protocol
Barker et al. (2013)[43]	USA	1998–2008	GBM	56 (18–70)	531	29	NR	Used for more than half the duration of radiotherapy	75.9%	Variable (>80% patients received > 54.4 Gy); fractions NR	34.8%; NR
Happold et al. (2016)[44]	International (>140 countries)	2000–2011	GBM	56.9 (18–82)	1582	215	NR	NR	NR	60 Gy; 2 Gy	100%; Standard therapy**
Kerkhof et al. (2013)[45]	The Netherlands	1999–2011	GBM	60 (24–85)	165	108	1000–2000 mg/day	>3 months	100%	NR	56.7%; NR
Knudsen-Baas et al. (2016)[46]	Norway	2004–2010	GBM	60–69 (0–85+)	245	84	NR	NR	100%	NR	68.6%; NR
Krauze et al. (2020)[47]	USA	2006–2013	GBM	54–57 (22–84)	448	37	25 mg/kg/day	7 weeks (duration of RT/TMZ therapy)	NR	60 Gy; 2 Gy	100%; Standard therapy**
Kuo et al. (2020)[48]	Taiwan	1998–2013	Glioma, grade III–IV	51.2–54.1 (range NR)	2379	1078	>1500 mg/day	>84 defined daily doses	51%	NR	100%; NR
Simo et al. (2012)[49]	Spain	2001-2009	GBM	56(range NR)	101	25	NR	NR	NR	60 Gy; 2 Gy	100%; Standard therapy**
Tinchon et al. (2015)[50]	Austria	2005–2013	GBM	57 (20–76)	104	13	NR	53–100 days	NR	60 Gy; 2 Gy	100%; Standard therapy**
Weller et al. (2011)[41]	International (15 countries)	2000–2002	GBM	55.8 (18.6–70.8)	573	97	NR	NR	NR	60 Gy; 2 Gy	46.2%; standard therapy**
Watanabe et al. (2017)[42]	Japan	2006–2014	Glioma, grade III–IV	62 (21–84)	112	24	Median dose 800 mg (range 400–1600 mg)	NR	NR	Median 60 Gy (range 36-60 Gy); 2 Gy	100%: Standard initial therapy**; adjunctive TMZ dose and protocol not stated

AED = antiepileptic drug; EBRT = external beam radiotherapy; GBM = glioblastoma multiforme; NR = not reported; RT = radiotherapy; TMZ = temozolomide; VPA = valproic acid.
*Note that glioma tumors of the GBM subtype are always considered Grade IV tumors.
**Standard therapy consists of administration of TMZ at 75mg/m^2 daily during initial RT course, followed by a 4-week break, then a varied number of adjuvant cycles (patient dependent) of 150–200mg/m^2 for 5 days per 28 days.

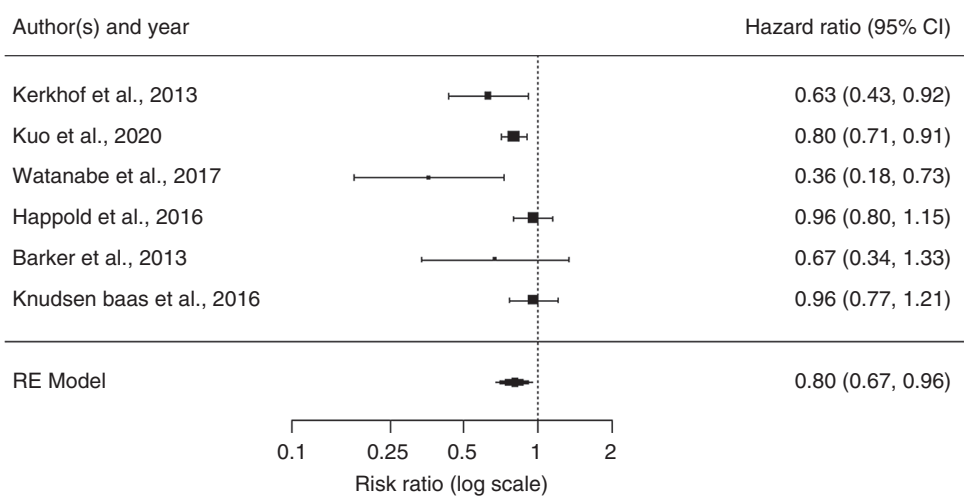

Figure 2. Effect of valproic acid on overall survival in high-grade glioma patients treated with radiotherapy. Hazard ratios were analyzed with the random-effects model.

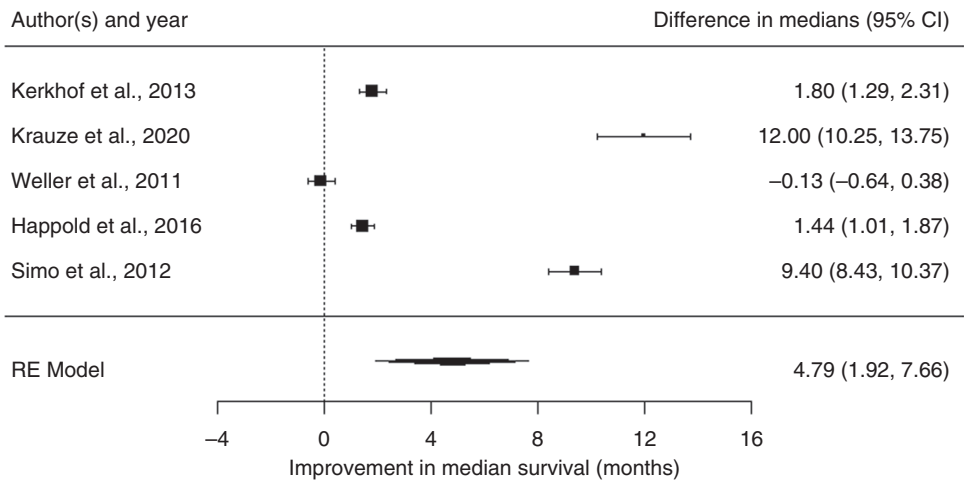

Figure 3. Effect of valproic acid on median overall survival time in high-grade glioma patients treated with radiotherapy. Median survival was measured in months and analyzed with the random-effects model.

patients of whom 434 were treated with VPA in the difference in median OS analysis. Both analyses demonstrated improved OS of patients in the VPA treated group compared to those who did not receive VPA (HR 0.79, 95% CI 0.66–0.95; the difference in median OS 5.47 months, 95% CI 2.71–8.23) (see Supplementary material). Of note, 92.5% and 78.8% of all patients in the initial OS analyses using HR and difference in medians respectively were included in the TMZ subgroup analysis. This accounts for the very small difference in OS parameters found in this subgroup analysis.

Adverse Events in Glioma Patients Undergoing Radiotherapy With Valproic Acid

Five of the included studies reported on AE occurring in glioma patients treated with RT, with and without VPA, of which 4 studies focused on hematological AEs. Three studies ($n = 317$) specifically examining hematological parameters throughout RT treatment found no significant difference in rates of anemia, leukopenia, or thrombocytopaenia between VPA and non-VPA-treated groups. Conversely, 2 studies ($n = 738$) noted increased thrombocytopaenia rates in patients treated with VPA, with 1 study

($n = 573$) also noting increased rates of leukopenia, though no data on these hematological effects were provided in either study. Few studies reported on non-hematological AEs, though 1 paper ($n = 98$) reported that AEs in the VPA-treated group included psychiatric effects (depression, psychosis), weight gain, pancreatitis, and tremor. No data were provided on these AEs however, and no statistical analysis was performed to indicate increased AEs in individuals treated with VPA compared to those without VPA. Additionally, given the lack of reported information on the dose or duration of VPA therapy in many of the included trials, any existing dose dependency of AEs was not able to be addressed.

Discussion

This meta-analysis provides new evidence that the addition of VPA to RT protocols for the treatment of glioma results in improved OS (HR = 0.80, 95% CI 0.67–0.96; the difference in median OS 4.79 months, 95% CI 1.92–7.66). All studies included in this meta-analysis involved patients with high-grade glioma, with 8 focused on GBM specifically. In the studies included in this systematic review, VPA was utilized either to control seizures in patients with brain tumors, or as a prophylactic measure to prevent seizures within this patient cohort. Importantly, in several of the included studies, the improvement in OS occurred in patients irrespective of the presence of seizures or seizure history,[43,45,48] known independent positive prognostic factors for GBM.[52–54] As such, although VPA was not utilized for its purpose as a HDACi in many of the included studies, we postulate that it is the HDACi effects of VPA that are responsible for the improved OS in these patients.

HDACi are epigenetic modifying agents that act on histone proteins, important components of nucleosome packaging of DNA, to regulate gene expression and transcriptional activity of target cells without alteration of the DNA base pairing sequence.[55,56] There is a growing body of evidence that HDACi when given either pre-or post-RT, can provide a synergistic radio-sensitization response.[2,5,57] It has been proposed that these agents act by inducing hyperacetylation of the histone proteins which is thought to concurrently increase RT-induced DNA double-strand breaks, interfere with chromosomal folding and remodeling, and inhibit DNA damage repair mechanisms, resulting in cell cycle arrest and enhanced tumor cell death.[2,7,31,58] Supporting the positive findings of VPA treatment on OS of the current meta-analysis, multiple *in vitro* and *in vivo* studies have demonstrated a radio-sensitization effect of VPA on glioma cells due to HDACi activity.[59–62]

Current standard of care for GBM includes maximum safe tumor resection, followed by external beam RT with concomitant and adjuvant TMZ.[16] Subgroup analysis revealed a protective effect of VPA when examining patients treated with both RT and TMZ, the current GBM standard of care (HR 0.79, 95% CI 0.66–0.95; the difference in median OS 5.47 months, 95% CI 2.71–8.23). Given that the majority of patients included in the current meta-analysis were on TMZ, minimal differences were found in subgroup analysis excluding patients without TMZ therapy, though these findings confirm the potential relevance of VPA in current GBM treatment protocols. Several pre-clinical studies support an additive effect of combined VPA, TMZ, and RT.[24,63,64] This occurs as, in addition to radio-sensitization effects, HDACi affect numerous tumor cell functional pathways also affected by chemotherapy agents, resulting in inhibition of tumor growth, inhibited angiogenesis, increased apoptosis of cancer cells,[30,64–67] and improved antitumor immune-modulatory activity.[29,30,67–69] Previous authors have alternatively suggested that hepatic enzyme inhibition by VPA, and subsequently increased chemotherapy bioavailability, may account for the improved survival of glioma patients taking TMZ and VPA during RT.[23] However, as it has been estimated that VPA decreases TMZ clearance by only 5%,[41] and given that a clinical trial by Gilbert et al. (2013) failed to determine any improvement in OS in patients with dosage intensified TMZ protocols,[70] we believe it is unlikely that this small change in TMZ bioavailability is the cause of improved OS in these patients.

Further studies have demonstrated that VPA has antitumor and radio-sensitization effects in other cancer cell lines and animal models, including osteosarcoma, breast, prostate, and colon cancers,[30,54,67,71–74] potentially indicating a therapeutic use of VPA as a HDACi for non-glioma cancers. Despite there being several promising clinical trials and retrospective analyses of VPA use in other cancer types,[75–78] we failed to find any studies meeting the inclusion criteria for this review and this remains an area where further research is required.

Additionally, no studies of appropriate methodological quality were found examining the effect of newer, potentially more potent, HDACi as radio-sensitizers in solid organ malignancy patients. Despite over 30 HDACi having been identified, currently, there is only one EMA-authorized HDACi, panobinostat,[79] and there are only 4 FDA-approved HDACi, vorinostat, romidepsin, belinostat, and panobinostat, each indicated for use in specific hematological malignancies.[20,80] Numerous phase I and II trials have been published focusing on these agents as radio-sensitizers for solid organ cancers,[81–86] however were excluded from the current meta-analysis due to lacking appropriate control groups for analysis. Thus, although there is currently insufficient evidence to recommend the use of alternate HDACi in glioma or other solid organ malignancies, this is a rapidly evolving area of research.

Few of the included studies in this meta-analysis robustly reported on AEs associated with VPA incorporation into RT protocols. VPA is generally considered to be a well-tolerated antiepileptic drug with a favorable side effect profile. Severe side effects of VPA that have been previously reported include hepatotoxicity, hematological toxicity, idiosyncratic hypersensitivity reactions,[87] and increased cardiovascular risk,[88,89] with concerns raised that the combination of VPA with chemotherapeutics such as TMZ may exacerbate chemotherapy-induced thrombocytopaenia or myelosuppression.[90–92] Three papers in this review specifically examined hematological AEs in VPA-treated patients and found no significant difference from non-VPA-treated patients. Two other included papers noted increased thrombocytopenic risk in VPA patients but did not provide any specific data relating to this. Within the RT-treated

glioma patient population of this meta-analysis, VPA was not demonstrated to worsen hepatic function or increase cardiovascular disease and no idiosyncratic hypersensitivity reactions were reported. Although promising, it should be noted that only a limited number of included papers ($n = 5$) reported on AEs, with those that predominantly focused on hematological AEs, and therefore further larger-scale clinical trials will be needed to confirm these findings.

The use of radio-sensitizers has also gained the interest of late for their potential ability to reduce the side effects of RT.[2] Concomitant use of HDACi with RT has been suggested to provide radioprotective responses to non-neoplastic tissue, protecting normal cells from radiation-induced cell killing.[10,58,93] This protective effect has been demonstrated with VPA using both *in vitro* and *in vivo* studies,[62,94] and has been theorized to occur due to the abnormal chromatin structure and upregulation of HDACs in neoplastic cells compared to healthy cells.[56,95–97] Although not a focus of this meta-analysis, one included paper did report on VPA use during RT being significantly associated with delayed hair loss.[42] With further study, this may provide additional consideration for the inclusion of VPA into RT protocols.

The results of this review are of particular importance to the treatment of high-grade glioma in developing nations. CNS cancer represents a substantial global health challenge, as the capacity to both diagnose and treat patients with these tumors, including high-grade glioma, is complicated by the requirement for highly specialized medical and surgical resources, resulting in poorer mortality to incidence ratios in countries with lower socioeconomic development.[11] Given that VPA is currently included in the World Health Organization List of Essential Medicines,[19] and as RT has been demonstrated to be both affordable and feasible for cancer treatment in low and middle-income countries,[3] research into the effectiveness of low-cost radio-adjuvant therapies such as VPA is of increasing international importance.

Our meta-analysis has several potential limitations. First, to the best of our knowledge, there are no currently published randomized controlled trials on HDACi treatment in solid organ malignancy patients undergoing RT. Nine of the studies included in the paper are retrospective cohort analyses and 1 a retrospective analysis of clinical trial data, and thus, as patients were not randomized to treatment groups, selection at the level of the treating clinician cannot be excluded. Secondly, the majority of studies did not report on VPA dosage and/or duration of therapy. Given that the therapeutic regimen of VPA can vary widely and that there is no established VPA dosage for treatment in this context, we cannot rule out the possibility of a dose-dependency effect that would not be captured in this meta-analysis. In fact, several of the studies utilized VPA at a dose below the defined daily dose (DDD) of 1.5 g/day,[42,45] which may have masked the full extent of the effect of VPA on OS. Additionally, although the total included study participants for the primary outcome of OS reported as HR ($n = 5007$) provides strength to the review results, the numbers of RT/VPA treated patients in many of the studies were relatively small. In contrast to many of the other included studies, the paper with the highest patient number, Happold et al. 2016, found no survival benefit for VPA-exposed patients. Given the pooled study design the reason for this discrepancy is difficult to assess, however as the study did not assess VPA dose a dose dependency effect cannot be excluded. Additionally, this study included in the treatment group only patients who started on VPA use at baseline (commencement of treatment) and did not include any patients who subsequently commenced on VPA in the treatment group. As approximately one-third of GBM patients who develop seizures do so throughout the treatment course and are started on antiepileptic drugs during RT treatment,[45,98] this too may have confounded results. Finally, included studies calculated OS from different initiation points (from diagnosis, date of surgery, the start of RT, or date of randomization), which may account for small differences in OS between studies.

Conclusions

This review aimed to consolidate the evidence surrounding the use of HDACi treatment efficacy and AEs in solid organ malignancy patients undergoing RT, however, found that current evidence is restricted to the use of VPA in RT-treated glioma patients. The results of this systematic review found that the addition of VPA to standard care (external beam RT and TMZ treatment) may result in an improved OS. Given the low cost, ease of use in the clinic environment, favorable side effect profile, and dual utility as an antiepileptic drug and HDACi, valproic acid may make an ideal addition to glioma treatment. However, considering the limitations of this review, namely the lack of randomized controlled trials of this treatment combination and the relatively small total numbers of glioma patients treated with VPA in the available literature, we suggest that further clinical trials are warranted to confirm findings, as well as to refine VPA treatment protocols within this patient population. There is also a need for further research evaluating the role of non-VPA HDACi in the treatment of glioma and other solid organ malignancies in patients undergoing RT.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Authorship

Conception and design: Jessica Sullivan, David Lim, Paul Fahey. Collection and assembly of data: Jessica Sullivan, Simon Hurley, David Lim. Data analysis and interpretation: Jessica Sullivan, Paul Fahey, Kingsley Agho, David Lim, Simon Hurley, Ric Day. Manuscript writing: Jessica Sullivan. Final approval of manuscript: All authors.

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