

Does valproic acid affect tumor growth and improve survival in glioblastomas?



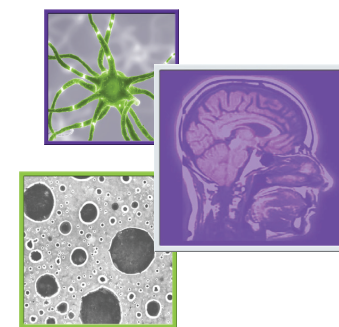
Roberta Rudà¹, Alessia Pellerino¹ & Riccardo Soffietti^{*1}

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Valproic acid (VPA) is an anticonvulsant drug with established activity in controlling seizures in glioma patients [1–2]. The mechanisms of the antiepileptic activity of VPA are well known [3]: enhancement of the inhibitory effects of the neurotransmitter GABA, blockage of the voltage-gated sodium channels and T-type calcium channels, attenuation of NMDA-mediated excitation and alteration of firing frequency of neurons. VPA is extensively bound to plasma proteins (>90%), mainly to plasma albumin, and the extent of binding decreases with increasing drug concentrations. VPA easily penetrates the blood–brain barrier: mechanisms involve both passive diffusion and bidirectional carrier-mediated transport via an anion exchanger at the brain capillary endothelium. Cerebrospinal fluid (CSF) concentrations vary between 1 and 10% of total plasma concentrations. Active transport mediates the uptake of VPA into neuronal and glial cells, which results in intracellular concentrations that are higher than interstitial fluid concentrations. This transport

notably depends on monocarboxylate transporter 1, a membrane protein that is overexpressed in gliomas in correlation with histological grade. VPA is categorized as a nonenzyme-inducing antiepileptic drug (non-EI AED), and slightly inhibits CYP450 (CYP) isoenzymes. Through CYP inhibition, it can decrease the rate of metabolism of nitrosoureas and increase hematological toxicity. Moreover, VPA has been shown to decrease the clearance of temozolomide.

Approximately 30–50% of glioblastoma patients experience seizures, and patients with seizures could have a better prognosis than those without seizures: this has raised questions about whether the AEDs play some antitumor activity [4–5]. In this regard, VPA exhibits some pharmacodynamic properties, that are unrelated to the antiepileptic activity, and preclinical studies have reported that the drug could affect tumor cells in many respects (inhibition of proliferation and angiogenesis, promotion of apoptosis and autophagy) [6]; however, the mode of action of VPA is enigmatic,



KEYWORDS

- clinical studies • glioblastomas
- gliomas • preclinical studies
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¹Department of Neuro-Oncology, University & City of Health and Science Hospital, Via Cherasco 15, 10126, Turin, Italy
^{*}Author for correspondence: riccardo.soffietti@unito.it

and the effects on glioma cells are somewhat contradictory [7–8].

VPA could exert an antineoplastic action mainly as a histone deacetylase (HDAC) inhibitor, resulting in a chromatin decondensation and a better access of transcription factors and the translation machinery to DNA. VPA has been shown to inhibit HDAC 1 and 2 within clinically relevant concentrations. However, compared with other HDAC inhibitors (vorinostat, sodium butyrate, benzamides, depsipeptide), VPA is a relatively weak HDAC inhibitor.

VPA has DNA-demethylation properties, with either potentially positive antitumor effects, such as upregulation of several tumor suppressor genes and apoptosis inducer transcripts (p21, p27, Bax, PTEN) or negative effects, such as an increased expression of MGMT RNA. Other mechanisms, potentially involved in an antitumor effects of VPA in preclinical models of gliomas, such as GABA increase, inhibition of L- and T-type calcium channels and GSK-3 inhibition, remain to be elucidated.

VPA has been shown to inhibit the proliferation of glioma cells through several direct effects (inhibition of HDAC, p21 and NF-κB transcriptional activity); however, the *in vitro* effects of VPA are weak and largely variable depending on cell-line, dose and time of exposure. Paradoxically, submillimolar concentrations of VPA could enhance the proliferation of some glioma cell lines.

The effects of VPA on glioma cell differentiation are also contradictory. Higher concentrations of VPA enhance the expression of glial fibrillary acidic protein (GFAP) and promote the adoption of a glial phenotype in rat C6 glioma cells while reducing their proliferation and migration capacities. Conversely, VPA has been shown to increase the expression of CD133, a stem cell marker, in some glioblastoma cell lines.

More convincing are the preclinical data suggesting a synergistic effect of VPA with radiotherapy and/or chemotherapy. VPA could interfere with the DNA repair, thus enhancing the radiosensitivity of malignant glioma cells while showing some radioprotective properties on normal brain tissue [9–10]. The combination of VPA and temozolomide (TMZ) displayed a significantly enhanced antitumor effect in TMZ-resistant malignant glioma cells, and this potentiation was correlated with a VPA-mediated

reduction of the expression of MGMT [11] which plays an important role in cellular resistance to alkylating agents. The combination of VPA, TMZ and RT has been reported to cause a significant radiation enhancement, without antagonizing the cytotoxic effects of TMZ [12]. Recently, an additive, rather than synergistic, effect when VPA, radiation and TMZ are combined has been reported [13].

Some retrospective clinical studies [4,14–16] and a meta-analysis of individual patient data [17] have suggested that VPA could prolong overall survival in adult patients with GBM. Oberndorfer and colleagues [4] investigated the effects of EI-AEDs or non-EIAEDs on survival in 168 patients with GBM treated with surgery, radiotherapy and chemotherapy (either CCNU or TMZ). A mild statistically significant difference in survival was observed between patients receiving a non-EI AED (13.9 months) and those receiving an EI-AED (10.8 months). Weller and colleagues [14] assessed the association of AED use and survival within the EORTC/NCIC temozolomide trial on 573 patients with GBM. Patients receiving VPA alone (16.9%) appeared to derive more survival benefit from TMZ/RT than patient receiving an EI-AED only (44.6%) or patient not receiving any AED. No significant difference in terms of PFS was observed. In the study performed by Kerkhof *et al.* [16] patients with GBM using VPA in combination with TMZ/RT showed a longer median survival of 69 weeks compared with 61 weeks in the group without VPA after adjusting for age, extent of resection and MGMT methylation status. Another study [15] has reported that VPA use during RT for GBM was associated with improved OS, independently of RTOG, RPA class, seizure history and concurrent TMZ use. Unfortunately, a recent meta-analysis on 1869 patients enrolled in five Phase III trials on newly diagnosed GBM has failed to show any improvement of PFS and OS with the addition of VPA to standard chemoradiation [18].

In summary, some considerations are needed. All the available clinical studies carry important limitations, in particular the retrospective design and the heterogeneity in terms of dose and duration of VPA administration. Moreover, VPA could effectively modify the biologic target in some, but not all, patients [19]. Only a Phase III trial, comparing in newly diagnosed GBM VPA in addition to chemoradiation versus chemoradiation alone, could definitively clarify

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the role of VPA as an antineoplastic agent. In the meantime, we do not encourage the choice of VPA as an antiepileptic drug in patients with seizures based on the potential antitumor activity only.

For the future, recently discovered common pathways of epileptogenesis and tumor growth in gliomas [20] hold promise as potential targets of therapy, and need to be investigated in adequately designed clinical trials.

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