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Could valproic acid be an effective anticancer agent? The evidence so far

Seth A Brodie[1,2,3] and **Johann C Brandes**[1,2,3]

[1]Atlanta VAMC

[2]Department of Hematology and Medical Oncology, Emory University

[3]Winship Cancer Institute, Emory University

Abstract

Valproic acid is an inhibitor of class I histone deacetylases. Epigenetic therapies in cancer have been focus of a keen interest and HDAC inhibitors in particular have been approved for certain types of hematologic malignancies. Valproic acid is an attractive candidate for cancer therapy due to its mechanism of action, its low cost and generally good clinical tolerability. In the following editorial we will review its role as monotherapy for cancer, its place in combination epigenetic therapy, and its role as chemosensitizer, immunomodulator and cancer preventative agent.

With the discovery of its function as inhibitor of class I and IIa histone deacetylases, significant interest in establishing a possible role of valproic acid, (VPA) a well-established anti-seizure drug, for cancer therapy arose[1, 2]. Epigenetic changes such as aberrant DNA methylation and histone acetylation are common in cancer, providing a strong rationale for the use of epigenetic therapies. Moreover, the completion of The Cancer Genome Atlas (TCGA) project has demonstrated frequent mutations in critical epigenetic regulators, further strengthening a link between genetic and epigenetic events in cancer. Due to its low cost, favorable side effect profile and its ease in crossing the blood brain barrier, VPA is an attractive drug candidate for a variety of possible indications. In the following paragraphs we will summarize the available evidence for VPA's role in cancer therapy and in cancer prevention.

VPA as monotherapy for cancer

The experience with VPA as monotherapy for cancer is limited. Interesting findings exist in metastatic neuroendocrine carcinomas, where VPA exposure has been shown to increase NOTCH1-expression[3] considered to serve as tumor suppressor gene. In a small phase I study with 8 patients, treated at target concentrations between 50–100 ug/ml, 1 patient achieved a partial response, while 5 patients had stable disease. High level Notch-1

Corresponding author: Johann C Brandes, M.D., PhD, Atlanta VAMC, Winship Cancer Institute, Atlanta, GA, 30322, johann.brandes@emory.edu.

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induction was associated with partial response to VPA. In myeloid malignancies, VPA has been shown *in vitro* to induce both apoptosis and differentiation in leukemic blasts, leading to trials assessing its role as monotherapy or in combination with all-trans-retinoic acid (ATRA) in either acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). Response rates in a phase II study of 58 patients with AML were 5%[4] compared to 44% in a separate study of 18 patients with MDS[5].

VPA as epigenetic combination therapy for cancer

Given the modest benefit for VPA in the monotherapy of cancer, it is not surprising that the majority of evidence for a possible role of VPA as anticancer drug is based on its effects observed in combination with other drugs. For simplicity sake, these can be categorized into combination therapies with other epigenetic modifiers, combinations with cytotoxic chemotherapy agents and combinations with immune-modulators. The discovery in 2006 that treatment with the DNAmethyltransferase (DNMT1) inhibitor azacytidine was associated with dramatically improved overall survival compared with conventional care (HR 0.58; 95% CI 0·43–0·77) in patients with poor risk myelodysplasia was proof of concept for a major role of epigenetic therapies in cancer[6]. Since HDAC inhibition was found to be synergistic with azacytidine *in vitro*, numerous studies have focused on combinations of demethylating agents with HDAC inhibitors including VPA. In a phase II study of VPA with ATRA and azacytine of patients with poor-risk AML and MDS, responses were observed in 23% of patients and median overall survival was 12.4 months. In this study, responses correlated with demethylation of several aberrantly methylated promoter regions. These survival rates were inferior to those observed with azacytidine alone in either high risk MDS or AML(24.5months)[6, 7]. However, this could partly be explained by patient selection and number of previous treatment regimens. It does raise the important question, however, if HDAC inhibition adds clear benefit to that of demethylating agents alone. A randomized phase II study of decitabine plus VPA vs. decitabine alone in 76 patients with AML and MDS found a marginally improved response rate in the VPA arm (53% vs 42%, p=NS) without improvement in survival. These findings are supported by the recent lack of benefit when the HDAC inhibitor entinostat was added to azacytidine in the E1905 trial for the treatment of AML and MDS[8]. Neurotoxicity was also a major dose limiting toxicity in a phase I study of 8 patients with advanced non-small cell lung cancer (NSCLC). No responses were seen in this small cohort and somnolence, lethargy and disorientation was observed at low concentrations[9].

VPA in combination with cytotoxic chemotherapy for cancer

An interesting and unexpected finding of a phase I/II trial of azacytidine in combination with the HDACi entinostat in NSCLC was the observation that epigenetic therapy seemed to restore sensitivity to previously used chemotherapeutics[10]. The precise mechanism for this observation remains unclear. Based on the hypothesis that HDACi mediated changes in chromatin structure favoring a more euchromatic chromatin pattern, VPA has been studied in combination with cytotoxic chemotherapy, particularly with DNA damaging agents: In combination with the topoisomerase II inhibitor epirubicin responses were seen in 22% of 44 patients including those with tumors considered to be refractory to anthracyclines such as

melanoma or in patients with previous anthracycline exposure[11]. In a subsequent phase II extension cohort of 15 patients with metastatic breast cancer, VPA in combination with 5-FU, epirubicin and cyclophosphamide produced objective responses in 64% of patients with acceptable toxicities[12]. Potential synergy between VPA and doxorubicin was also observed in a phase II study of 16 patients with unresectable and platinum-refractory mesothelioma[13], a clinical scenario for which no accepted treatment options exist. VPA and doxorubicin yielded encouraging response rates of 16% and disease control rates of 36%. In combination with a new topoisomerase I inhibitor karenitecin, VPA use led to disease stabilization in 47% of patients treated in a phase I/II study for metastatic melanoma[14]. In a small randomized study of 36 patients with advanced cervical cancer the addition of epigenetic therapy with hydralazine and VPA to cisplatin and topotecan led to a statistically significant improvement of progression free survival (PFS) of 10 vs 6 months ($p=0.034$)[15] compared to chemotherapy alone, suggesting for the first time in a randomized fashion possible superiority of VPA based epigenetic therapy as chemosensitizer. Similar results were observed in other studies in which VPA based epigenetic therapies were combined with platinum based chemotherapies in an attempt to overcome previous platinum resistance[16]. Interestingly, a VPA induced increase in H3 acetylation has also been show to prevent the emergence of resistance to MTOR inhibitors in RCC[17].

VPA in cancer prevention

It is known that HDAC inhibition can lead to reduced levels of DNMT1 expression[18]. A recent report from our laboratory showed that class I HDAC mediated stabilization of DNMT1 protein expression is an early event in smoke carcinogen induced transformation of bronchial epithelial cells[19]. This was associated with uncoupling of DNMT1 expression from the usually tight limitation to the S-phase of the cell cycle, leading to de-novo methylation and epigenetic silencing of tumor suppressor genes. Importantly, treatment with VPA partially reversed aberrant DNA methylation, leading to re-expression of previously silenced genes and suppression of anchorage independent colony formation. We hypothesized based on these data that VPA may play an important role in chemoprevention of smoke-related malignancies such as lung-, head-and neck- and bladder cancer. In a retrospective cohort study of 439,628 US veterans with indications for routine clinical use of VPA (bipolar disorder, seizure d/o, PTSD, migraines) the risk only for squamous cell carcinomas of the head-and neck was significantly reduced in the 26,911 patients with long term VPA use (HR, 0.66; 95% CI, 0.48–0.92)[20]. Risk for lung-, bladder-, prostate- and colon- cancers were not statistically different between VPA users and non-users. Risk reduction was only observed in patients with median VPA levels in the therapeutic range (>40uM) for seizure prevention and HDAC inhibition and only after at least 3years of use, reducing the likelihood that the conclusions were build on spurious results. The lack of effect on lung-, colon- and prostate-cancer risk is confirmed in a study from Denmark, which did not find a significant correlation between VPA use and cancer risk between VPA users and non-users, but did not specifically investigate head-and neck cancer risk[21]. A third study based on the UK General Practice Research database found no impact of VPA on total cancer incidence, but did detect an increase in colorectal cancers (HR: 3.95, 95% CI: 1.97–7.92, P = 0.001) and trends towards increased prostate cancer risks (HR: 2.15, 95% CI:

0.92–5.02, P = 0.08) and decreased breast cancer risks (HR: 0.40, 95% CI: 0.14–1.30, P = 0.08)[22]. The incidence of head and neck cancer was low, preventing conclusions about VPA's role in further reducing its risk in this study. The increased risk for colon cancer was neither seen in our study nor in the Danish study, making an uneven distribution of risk factors the most likely explanation for this phenomenon. The risk reduction for head and neck cancer in our study is interesting and seems to be largely limited to patients with non-oropharyngeal head-and neck cancer making an antiviral effect of VPA against HPV driven cancers less likely as etiology. It will need to be seen in further studies if his effect can be generalized to other smoking-related squamous cell carcinomas of the upper aerodigestive tract such as those of the lung and the esophagus. Despite its large size, our study lacked sufficient number of cases to conclusively answer this question. Likewise, our study does not answer the question if resistance to VPA emerges in the epithelium of the head and neck after long-term exposure and by which mechanism it is mediated.

Summary

While VPA's role in cancer therapy as monotherapy or in combination epigenetic therapy may be only be moderate both due to toxicity and limited efficacy, its use in combination regimens with cytotoxic chemotherapy and in chemoprevention against upper aerodigestive malignancies may hold promise and are deserving of further study.

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