A novel valproic acid prodrug as an anticancer agent that enhances doxorubicin anticancer activity and protects normal cells against its toxicity in vitro and in vivo.


Abstract

The poor survival of patients with malignant gliomas, underscores the need to develop effective treatment modalities for this devastating disease. Epigenetic agents used in combination with chemotherapy provide a promising approach to evoke synergistic cytotoxicity in glioblastomas. Previously we have described the cytotoxic synergy between a butyric acid prodrug and radiation in glioblastoma cell lines and the potentiation of radiation efficacy in glioma xenografts. Herein, we describe and compare the activities of AN446 (valproyl ester-valpramide of acyclovir) a novel histone deacetylase inhibitor (HDACI) to the previously described AN7 a HDACI prodrug of butyric acid. In various cancer cell lines, AN446 was a ~2-5-fold more potent anticancer agent HDACI than AN7. While AN446 augmented the anticancer efficacy of doxorubicin (Dox) it also reduced the Dox toxicity in non-cancerous cells. The interaction between AN446 and Dox in U251 and in 4T1 cell lines was synergistic in inducing cytotoxicity. We examined the concomitant physical and molecular changes in the tumor and heart of glioblastoma xenografts treated with AN446, AN7, Dox and the combination of the prodrugs with Dox. A weekly dose of 4 mg/kg Dox, caused toxicity in mice whereas AN446 (25mg/kg) or AN7 (50mg/kg) administered thrice weekly, did not. When Dox was administered with AN446 or AN7, the prodrugs ameliorated the decline in body weight, prolonged the time to failure and increased anticancer efficacy. Thus, the combination of Dox with AN446 or AN7 could add safety and efficacy to future treatment protocols for treating glioblastoma and other cancers.

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