LB100, a Novel Protein Phosphatase 2A Inhibitor Is Highly Effective Against Atypical Teratoid Rhabdoid Tumor (ATRT) with Marked Sensitivity to PP2A Inhibition Compared to Other Intracranial Tumors

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Introduction

Atypical Teratoid Rhabdoid Tumor in the central nervous system is among the most aggressive tumor in the pediatric population. Despite multimodal therapy, median event-free survival is less than one year. LB100, a novel small molecule Protein Phosphatase 2A (PP2A) inhibitor currently in Phase I trial for adult solid tumor, has demonstrated efficacy in a number of non-intracranial tumors. The objective of this study is to assess LB100 effectiveness for treatment of ATRT.

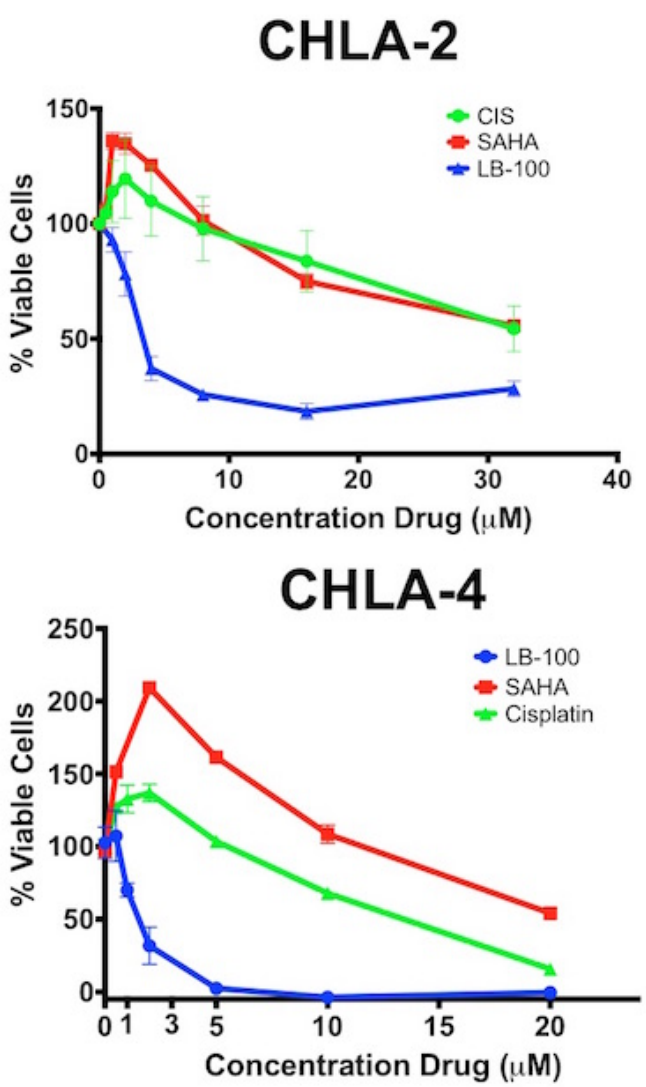
Methods

Experiments were performed using CHLA-4 and CHLA-2 ATRT cell line: XTT assay (Invitrogen) was performed to assess for cell viability. PP2A activity was measured using PP2A immunoprecipitation phosphatase assay kit (Millepore). LB100 effective toxicity to ATRT was compared to cisplatin and SAHA, a HDAC inhibitor. Sensitivity of ATRT to LB100 was compared to ATT-20 (pituitary adenoma), glioblastoma cell line (U251) and nomal human fibroblast. Response of ATRT to PP2A inhibition was also compared to those same cell lines.

Results

LB100 is more cytotoxic compared to cisplatin or SAHA at equal concentration. Cell viability assays showed that IC50s are 1uM, 15uM, and 10uM in CHLA-4 cells and 3uM, >30 uM, >30 uM in CHLA-2 cells for LB100, SAHA and cisplatin respectively at 48 hours after drug administration. ATRT is more sensitive to LB100 compared to glioblastoma (U251), pituitary adenoma (ATT-20) and fibroblast cell lines. PP2A activity measured 3 hours after drug administration showed that ATRT is most sensitive to LB100 inhibition between the cell lines tested. PP2A activity is inhibited to 50% of control at concentration of 0.5uM in CHLA4 and 3 uM in CHLA2 compared to ~10uM, >22uM and 35 uM in ATT-20, U251 and fibroblast resepectively.

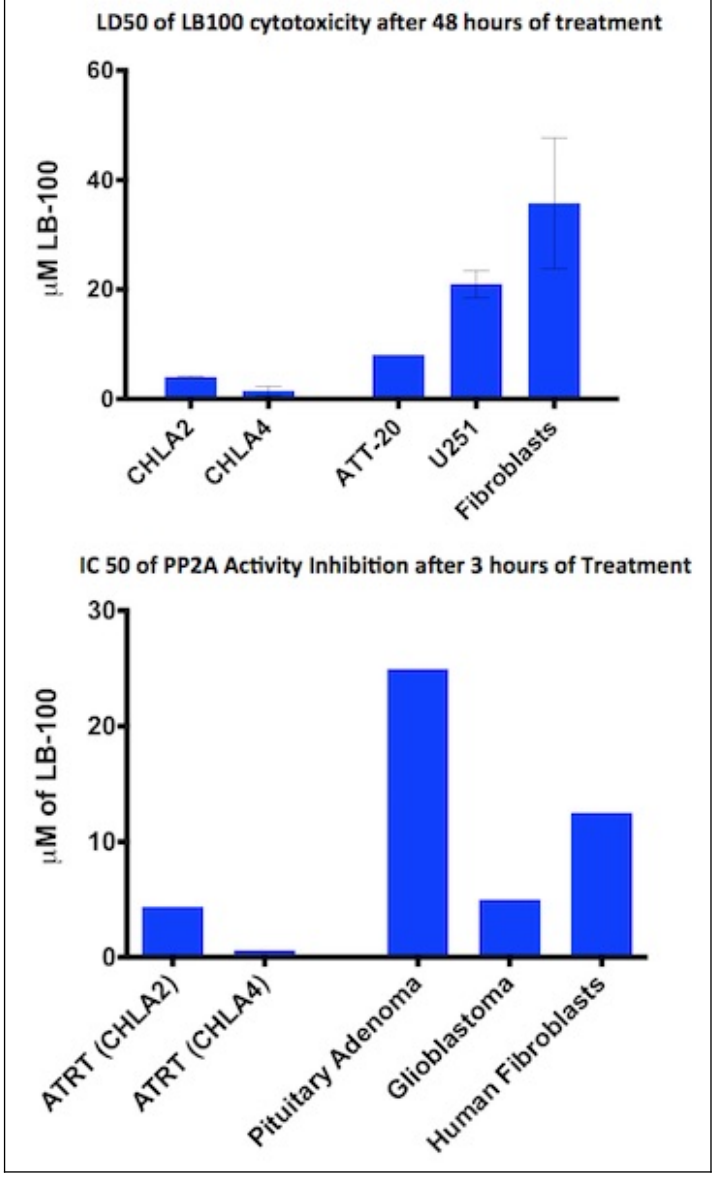
ATRT cells showed high sensitivity to cytotoxic effect of LB100



Conclusions

LB100 showed marked cytotoxic effect on ATRT. This sensitivity is likely attributed to greater PP2A inhibition by LB100 at lower concentration compared to other cell lines.

ATRT cells showed high sensitivity to PP2A inhibition and LB100 mediated cytotoxicity



Learning Objectives

LB100 hold promise as a novel treatment to ATRT.