EFFICACY OF DINACICLIB IN HEPATOBLASTOMA AND MECHANISM OF ACTION.

Srivastava, Rohit K[1], Andres F Espinoza[2], Roma H Patel[2], Yang Yu[3], Richard S Whitlock[2], Samuel R Larson[2], Andrew Badachhape[4], Aayushi P Shah[5], Saiabhiroop R Govindu[5], Jianhua Yang[3], Sarah E Woodfield[2], Sanjeev A Vasudevan[2]

[1] Baylor College of Medicine, Department of Surgery, Pediatric General Surgery
[2] Baylor College Of Medicine, Surgery, Pediatric General surgery
[3] Baylor College Of Medicine, Pediatrics, Texas Children's Cancer Center
[4] Baylor College Of Medicine, Pediatric Radiology, Radiology
[5] Pre-medicine , Undergraduate, Pediatric General surgery

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Background: Hepatoblastoma (HB) is the most frequent liver malignancy of childhood with an annual incidence of 1.5 per million and a survival rate less than 50%. Due to significant side effects of standard chemotherapy the treatment options are now shifting towards targeted therapies. The goal of this study is to assess the therapeutic efficacy and mechanism of dinaciclib with HB in preclinical in vitro and in vivo models.

Materials/Methods: Dinaciclib was tested in HB cell lines to assay cytotoxicity (MTT assay) and proliferation (CCK-8 assay). Differential expression of CDKs between normal liver and HB patients was checked by microarray analysis. Immunoblotting assays were used to assess the induction of apoptosis and to check the expression of CDKs in vitro. Different inhibitors (Z-VAD, ferrostatin-1, necrostatin-1, and 3-MA) were used to find the underlying cell death mechanism. The lentiviral construct (CDK9-pLX307) was used to overexpress CDK9 in HB cell lines, empty vector was used as a control. Dinaciclib was also tested in our orthotopic PDX models of high-risk HB. MRI and Alpha-fetoprotein ELISA were done to evaluate tumor growth.

Results: Dinaciclib suppressed cell proliferation and viability in a dose-dependent manner in all HB cell lines tested with IC50 in the low micromolar range (HepG2- 3.75; HepT1- 0.007; Huh6- 1.42; HB17- 0.72). Microarray analysis showed significant upregulation of CDKs in HB patients' samples, whereas, dinaciclib treatment showed reduction in CDKs 1/2/5/9 expression in vitro. Z-VAD was found effective in reversing cell death in dinaciclib treated cells. Dinaciclib also showed in vivo inhibition of tumor growth in both PDX models (HB47: relative tumor volume $p = 0.03$, T/C ratio= 0.36, tumor weight $p = 0.02$; HB52: relative tumor volume $p = 0.06$, T/C ratio= 0.16, tumor weight $p = 0.07$).

Conclusions: Dinaciclib induced apoptosis and suppressed CDK9 expression and is an effective therapeutic agent for HB treatment.

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