PERSONALIZED TARGETED THERAPY FOR HEPATOBLASTOMA

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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%. The overall goal of this study is to assess the therapeutic efficacies and anti-cancer mechanisms of novel drugs with HB through a drug sensitivity testing pipeline using preclinical patient-derived cell line (PDCL) and patient-derived xenograft (PDX) models.

Materials/Methods: A PDX mouse model was generated with intrahepatic implantation of tumor thrombus from a non-metastatic stage 3 patient. A stable PDCL was grown from the murine tumor, and 60 targeted agents were tested using CellTiter-Glo Luminescent Viability assays. Anti-oncogenic effects of the most efficacious agent, dinaciclib (cyclin-dependent kinase (CDK) inhibitor), were further assayed in vitro with HB cell lines (HepG2, HepT1, Huh6, HB17) for cell toxicity (MTT assay), proliferation (CCK-8 assay), and anchorage independent colony formation (soft agar assay). Immunoblotting assays were used to assess changes in drug targets and induction of apoptosis (PARP cleavage) with cell lines. Dinaciclib was also tested in vivo in our orthotopic PDX models of high-risk HB. The drug was administered 3 times a week by intraperitoneal injection (20 mg/kg, 100 µL) for 3 weeks. Magnetic resonance imaging (MRI) and Alpha-fetoprotein (AFP) ELISA were done to evaluate tumor growth throughout the study. Tumor weights and volumes, as well as immunohistochemistry for H&E, Ki-67, and TUNEL, were also used to assess effects of drug in vivo.

Results: Of the 60 agents tested, dinaciclib showed the lowest IC50 value (0.7 µM). It suppressed cell proliferation and viability in a dose-dependent manner in all HB cell lines tested with IC50 values in the low micromolar range (HepG2 3.75 µM; HepT1 0.007 µM; Huh-6 1.42 µM; HB17 0.72 µM). Immunoblotting with dinaciclib-treated cells showed induction of PARP cleavage, indicating apoptosis, along with decreased protein expression of CDK 1/2/5/9. Dinaciclib also showed significant in vivo inhibition of tumor growth compared to placebo (relative tumor volume p = 0.03, tumor weight p = 0.02).

Conclusions: Drug screening of a novel HB PDCL identified an agent, dinaciclib, that shows significant effects with preclinical HB cell line and animal models. Such a personalized medicine pipeline of development of PDCLs and testing them with targeted agents will lead to the identification of new drugs that can be used with patients that do not respond to standard therapies.

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