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Title: The Therapeutic Potential of Dinaciclib in Hepatoblastoma
Topic:
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Abstract:
Background:
Relapsed and treatment refractory hepatoblastoma (HB) has a survival rate of less than 50% due to limited treatment options. Cyclin-dependent kinases (CDKs) are potential cancer therapeutic targets because of their critical role in promoting cell growth that can result in chemoresistance. This study focused on the pre-clinical therapeutic efficacy of dinaciclib, a cyclin-dependent kinase inhibitor, *in vitro* and *in vivo*.

Methods:
HepT1, HepG2, and Huh-6 HB cells were evaluated with cytotoxic and immunoblotting assays. HB patient-derived xenografts (PDX) mice (n=3 per treatment) were randomized to placebo, vincristine/irinotecan (VI), dinaciclib, or VI/dinaciclib. Mice were started on study when tumor volume reached 0.1-0.5 cm^3 and were euthanized when tumors reached tumor volume > 1cm^3 or at the end of the 6-week study.

Results:
Dinaciclib (IC_{50} of 0.04-2.35mM) showed strong *in vitro* effects for viability, induced PARP cleavage, and decreased CDK9 in all three cell lines. Over-expression of CDK9 in HepT1 and Huh-6 resulted in an increase in dinaciclib IC_{50} of 1.01 and 2.94mM, respectively. After 6 weeks of treatment, the average tumor volume of placebo cohort was 1.185 cm^3 and dinaciclib cohort was 1.63 cm^3 (p=0.87). The VI cohort had an average tumor volume of 0.89 cm^3 while the VI/dinaciclib cohort was 0.15cm^3 (p=0.08)

Conclusions:
Dinaciclib functions through inhibiting CDK9 and RNP-II resulting in apoptotic cell. Combination VI/dinaciclib treatment in our PDX model showed a lower tumor burden compared to placebo, VI, and dinaciclib monotherapy. These results suggest that VI/dinaciclib is a promising targeted therapy for the treatment of HB.