A phase I study of perifosine with temsirolimus for recurrent pediatric solid tumors.


Abstract

BACKGROUND: The PI3K/AKT/mTOR pathway is aberrantly activated in many pediatric solid tumors including gliomas and medulloblastomas. Preclinical data in a pediatric glioma model demonstrated that the combination of perifosine (AKT inhibitor) and temsirolimus (mTOR inhibitor) is more potent at inhibiting the axis than either agent alone. We conducted this study to assess pharmacokinetics and identify the maximum tolerated dose for the combination.

PROCEDURE: We performed a standard 3+3 phase I, open-label, dose-escalation study in patients with recurrent/refractory pediatric solid tumors. Four dose levels of perifosine (25-75 mg/m²/day) and temsirolimus (25-75 mg/m² IV weekly) were investigated.

RESULTS: Twenty-three patients (median age 8.5 years) with brain tumors (diffuse intrinsic pontine glioma [DIPG] n = 8, high-grade glioma n = 6, medulloblastoma n = 2, ependymoma n = 1), neuroblastoma (n = 4), or rhabdomyosarcoma (n = 2) were treated. The combination was generally well tolerated and no dose-limiting toxicity was encountered. The most common grade 3 or 4 toxicities (at least possibly related) were thrombocytopenia (38.1%), neutropenia (23.8%), lymphopenia (23.8%), and hypercholesterolemia (19.0%). Pharmacokinetic findings for temsirolimus were similar to those observed in the temsirolimus single-agent phase II pediatric study and pharmacokinetic findings for perifosine were similar to those in adults. Stable disease was seen in 9 of 11 subjects with DIPG or high-grade glioma; no partial or complete responses were achieved.

CONCLUSIONS: The combination of these AKT and mTOR inhibitors was safe and feasible in patients with recurrent/refractory pediatric solid tumors.

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KEYWORDS: AKT; mTOR; perifosine; phase I clinical trials; temsirolimus

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