Subconjunctival topotecan in fibrin sealant in the treatment of transgenic murine retinoblastoma.

Authors: Tsui JY, Dalgard C, Van Quill KR, Lee L, Grossniklaus HE, Edelhauser HF, O'Brien JM

Publication Date: 2008

Abstract:

PURPOSE: To test the effects of subconjunctival topotecan (TPT) in fibrin sealant (FS) in transgenic murine retinoblastoma (RB).

METHODS: Growth inhibitory, apoptotic, and cell cycle effects of TPT were assayed in human RB cell lines. In a dose-escalation study, eight groups of three 10- to 14-week-old wild-type mice were treated bilaterally with a single 30-microL injection of subconjunctival TPT in FS (0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, or 3.2 mg/mL). Two groups of twenty 10-week-old LHbeta-Tag transgenic mice were then treated in the right eye only with TPT in FS (3.2 mg/mL in 30 microL; 0.1-mg total dose) or with FS only. The contralateral eye in each group was left untreated to serve as an internal control. After 3 weeks, ocular tumor burden was determined by histologic examination.

RESULTS: At 48 hours, IC(50) values of TPT in Y79 and Weri-Rb1 RB cell lines were 35 nM and 50 nM, respectively. Growth inhibitory effects were correlated with increased apoptosis and accumulation of cells in G2. Cytotoxicity of TPT was comparable in aqueous media and in FS. In the dose-escalation study, no histopathologic evidence of ocular toxicity was observed at any dose. Clinical toxicities (mild enophthalmos and eyelid alopecia) were observed only at the highest dose tested (3.2 mg/mL). In the treatment study, both eyes of TPT-treated mice demonstrated significant reduction in tumor burden compared with both eyes of mice treated with FS only (59% reduction; P = 0.04). In mice treated with TPT, tumor burden in TPT-treated eyes and in untreated contralateral

eyes did not differ significantly.

CONCLUSIONS: Subconjunctival administration of TPT in FS to one eye allows the formation of a TPT depot sufficient for an effect to occur 3 weeks after treatment. This effect -- bilateral reduction in tumor burden without a significant difference in treated versus untreated eyes -- suggests that the major route of drug delivery in this system is hematogenous rather than transscleral.