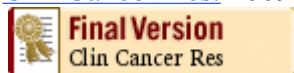




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A phase I trial of enzastaurin in patients with recurrent gliomas.

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PURPOSE: Enzastaurin is a selective inhibitor of protein kinase C beta. Prior phase I studies did not show increased drug exposures with escalating once daily administration. Limits from gastrointestinal absorption may be overcome by twice daily dosing, potentially improving antitumor effects. **EXPERIMENTAL DESIGN:** We conducted a phase I dose escalation study in 26 patients with recurrent malignant glioma, stratified by use of enzyme-inducing antiepileptic drugs, to investigate whether divided twice daily dosing results in higher exposures compared with once daily dosing. Phosphorylated glycogen synthase 3 beta was analyzed as a potential biomarker of enzastaurin activity. **RESULTS:** Enzastaurin was poorly tolerated at all dose levels evaluated (500, 800, and 1,000 mg total daily), with thrombocytopenia and prolonged QTc as dose-limiting toxicities. The average drug concentration of enzastaurin under steady-state conditions was doubled by twice daily dosing compared with daily dosing [1.990; 90% confidence interval (CI), 1.450-2.730]. Additionally, geometric mean ratios doubled with 800 versus 500 mg dosing for both daily (2.687; 90% CI, 1.232-5.860) and twice daily regimens (1.852; 90% CI, 0.799-4.292). Two patients achieved long-term benefit (over 150 weeks progression free). **CONCLUSIONS:** Higher and more frequent dosing of enzastaurin resulted in improved drug exposure but with unacceptable toxicity at the doses tested. Phosphorylated glycogen synthase 3 beta may be a useful biomarker of the biological activity of enzastaurin. Enzastaurin has activity in a subset of malignant glioma patients and warrants continued study in combination with other agents using a maximal once daily dose of 500 mg.

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