Phase I and pharmacokinetic study of COL-3 in patients with recurrent high-grade gliomas.


Abstract
COL-3 is a chemically modified tetracycline that targets multiple aspects of matrix metalloproteinase regulation. This phase I clinical trial was conducted to determine the maximum tolerated dose (MTD) of COL-3 in adults with recurrent high-grade glioma, to describe the effects of enzyme-inducing antiseizure drugs (EIADs) on its pharmacokinetics, and to obtain preliminary evidence of activity. Adults with recurrent high-grade glioma were stratified by EIAD use. COL-3 was given orally daily without interruption until disease progression or treatment-related dose-limiting toxicity (DLT). Three patients in each EIAD group were evaluated at each dose level beginning with 25 mg/m²/day and escalated by 25 mg/m²/day. Toxicity, response, and pharmacokinetics were assessed. Thirty-three patients were evaluated. The MTD was 75 mg/m²/day in the -EIAD patients while one was not determined in +EIAD patients. The common toxicities observed were anemia, ataxia, diarrhea, hypokalemia, CNS hemorrhage, and myalgia. One partial response was observed. -EIAD patients tended to have a higher steady-state trough concentration that was apparent only at the 100 mg/m²/day dose level (P = 0.01). This study suggests that: (a) EIAD use does affect the pharmacokinetics of COL-3 at higher doses; and (b) there was not enough suggestion of single-agent activity to warrant further study in recurrent high-grade gliomas.

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