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Cancer Therapy: Clinical

Phase I Study of Temozolomide and Irinotecan for Recurrent Malignant Gliomas in Patients Receiving Enzyme-Inducing Antiepileptic Drugs: A North American Brain Tumor Consortium Study

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Purpose: To determine the maximum tolerated dose of irinotecan when administered with temozolomide every 28 days, in patients with recurrent malignant glioma who were also receiving CYP450 enzyme-inducing antiepileptic drugs (EIAED), and to characterize the pharmacokinetics of irinotecan and its metabolites. The study was also intended to assess whether temozolomide affects the conversion of irinotecan to SN-38.

Design: Patients with recurrent malignant glioma received a fixed dose of temozolomide (150 mg/m²) daily for 5 days from days 1 to 5 every 28 days, and an i.v. infusion of irinotecan on days 1 and 15 of each cycle. The starting dose of irinotecan was 350 mg/m², which was escalated to 550 mg/m² in 50-mg/m² increments. The plasma pharmacokinetics of irinotecan and its active metabolite, SN-38, were determined during the infusion of irinotecan on cycle 1, day 1.

Results: Thirty-three patients were enrolled into the study and treated. Thirty-one patients were evaluable for both tumor response and toxicity and two patients were evaluable for toxicity only. Common toxicities included neutropenia and thrombocytopenia, nausea, vomiting, and diarrhea. Dose-limiting toxicities were grade 3 diarrhea and nausea/vomiting. The maximum tolerated dose for irinotecan was determined to be 500 mg/m².

<http://clincancerres.aacrjournals.org/cgi/content/abstract/13/23/7133>
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Conclusions: The recommended phase II dose of irinotecan in combination with temozolomide for patients receiving EIAEDs is 500 mg/m², administered every 15 days on a 28-day schedule. This study also confirmed that concomitant administration of EIAEDs increases irinotecan clearance and influences SN-38 disposition. No pharmacokinetic interaction was observed between temozolomide and irinotecan.