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**Phase I pharmacokinetic study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor vatalanib (PTK787) plus imatinib and hydroxyurea for malignant glioma.**

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**BACKGROUND::** This study determined the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of the oral vascular endothelial growth factor receptor (VEGFR) inhibitor, vatalanib, when administered with imatinib and hydroxyurea on a continuous daily schedule among recurrent malignant glioma patients. **METHODS::** All patients received 500 mg of hydroxyurea twice daily. Imatinib was dosed at 400 mg per day for patients not taking enzyme-inducing antiepileptic drugs (EIAEDs; stratum A) and at 500 mg twice-a-day for patients taking EIAEDs (stratum B). Vatalanib was escalated from 500 mg to 1250 mg twice daily in successive cohorts, independently for each stratum. Pharmacokinetics of each drug were assessed. **RESULTS::** A total of 37 recurrent patients, 34 (92%) with glioblastoma and 3 (8%) with grade 3 malignant glioma, were enrolled. Nineteen patients (51%) were taking EIAEDs. The MTD of vatalanib for all patients was 1000 mg twice-a-day. DLTs were hematologic, gastrointestinal, renal, and hepatic. No patients developed intracranial hemorrhage. Concurrent administration of imatinib and hydroxyurea did not affect vatalanib exposure, but EIAEDs decreased vatalanib and imatinib plasma exposures. **CONCLUSIONS::** Vatalanib doses up to 1000 mg twice-a-day combined with imatinib and hydroxyurea were well tolerated. Strategies to target tumor blood vessel endothelial cells and pericytes by inhibiting VEGFR and platelet-derived growth factor, respectively, were safe among recurrent malignant glioma patients and may enhance antiangiogenesis activity. *Cancer* 2009. (c) 2009 American Cancer Society.

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