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Clinical Investigations

Safety and pharmacokinetics of dose-intensive imatinib mesylate plus temozolomide: Phase 1 trial in adults with malignant glioma

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▶ Abstract

We determined the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of imatinib mesylate, an inhibitor of the receptor tyrosine kinases platelet-derived growth factor

receptor (PDGFR), the proto-oncogene product c-kit, and the fusion protein Bcr-Abl, when administered for 8 days in combination with temozolomide (TMZ) to malignant glioma (MG) patients. MG patients who had not failed prior TMZ were eligible to receive TMZ at a dose of 150-200 mg/m² per day on days 4-8 plus imatinib mesylate administered orally on days 1-8 of each 4-week cycle. Patients were stratified based on concurrent administration of CYP3A4-inducing antiepileptic drugs (EIAEDs). The imatinib dose was escalated in successive cohorts of patients independently for each stratum. Imatinib, at doses ranging from 400 mg to 1,200 mg, was administered with TMZ to 65 patients: 52 (80%) with glioblastoma multiforme (GBM) and 13 (20%) with grade III MG. At enrollment, 34 patients (52%) had stable disease, and 33 (48%) had progressive disease; 30 patients (46%) were on EIAEDs. The MTD of imatinib for patients concurrently receiving or not receiving EIAEDs was 1,000 mg. DLTs were hematologic, gastrointestinal, renal, and hepatic.

Pharmacokinetic analyses revealed lowered exposures and enhanced clearance among patients on EIAEDs. Among GBM patients with stable disease at enrollment ($n = 28$), the median progression-free and overall survival times were 41.7 and 56.1 weeks, respectively. Imatinib doses up to 1,000 mg/day for 8 consecutive days are well tolerated when combined with standard TMZ dosing for MG patients. A subsequent phase 2 study is required to further evaluate the efficacy of this regimen for this patient population.

Key Words: glioblastoma multiforme, imatinib mesylate, malignant glioma, platelet-derived growth factor, temozolomide