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# Pediatric Phase I and Pharmacokinetic Study of Erlotinib Followed by the Combination of Erlotinib and Temozolomide: A Children's Oncology Group Phase I Consortium Study

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**Purpose:** We conducted a phase I and pharmacokinetic study of the epidermal growth factor receptor (EGFR) inhibitor erlotinib as a single agent and in combination with temozolomide in children with refractory solid tumors.

**Patients and Methods:** Erlotinib was administered orally once daily to cohorts of three to six children for a single 28-day course. Patients then received the combination of daily erlotinib and temozolomide daily for 5 days for all subsequent 28-day courses. An oral erlotinib solution was administered during the dose-finding phase and a tablet formulation was subsequently studied at the maximum-tolerated dose (MTD). Pharmacokinetic studies and ERBB-receptor expression and signaling studies were performed.

**Results:** Forty-six patients, median age 11.5 years, received erlotinib at doses of 35, 50, 65, 85, or 110 mg/m<sup>2</sup>/d. At 110 mg/m<sup>2</sup>/d, two of four patients had dose-limiting toxicity (DLT) consisting of rash and hyperbilirubinemia, whereas one of six patients developed dose-limiting rash at 85 mg/m<sup>2</sup>/d. The most frequent non-DLTs included diarrhea, rash, and hyperbilirubinemia. The combination of erlotinib and temozolomide was well tolerated. The median apparent erlotinib clearance was 3.1 L/h/m<sup>2</sup> and the median terminal half-life was 8.7 hours. One patient with a neurocytoma had stable disease for 19 months, two patients with neuroblastoma remained on study for 23 and 24 months, and one patient with myoepithelioma had a mixed response.

**Conclusion:** The recommended phase II dose of erlotinib in recurrent pediatric solid tumors is 85 mg/m<sup>2</sup>/d, either alone or in combination with temozolomide.

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