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Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors.

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Abstract

This multicenter phase I study aimed to establish the recommended dose (RD) of the epidermal growth factor receptor (EGFR) inhibitor erlotinib, given as monotherapy or with radiotherapy to children with malignant brain tumors. Group 1 included patients with refractory or relapsing brain tumors receiving erlotinib alone, and group 2 included newly diagnosed patients with brainstem gliomas receiving radiotherapy and erlotinib. A conventional 3 + 3 dose escalation and a continual reassessment method, respectively, were utilized in 4 dose levels: 75, 100, 125, and 150 mg/m(2) per day. Fifty-one children were enrolled (30 and 21, respectively); 50 received treatment. The RD of erlotinib was 125 mg/m(2) per day as monotherapy or in combination with radiotherapy. Overall, 230 adverse events in 44 patients were possibly treatment related (216, grades 1 and 2; 9, grade 3; 1, grade 4; 4, grade 5). Dermatologic and neurologic symptoms were common; intratumoral hemorrhage was confirmed in 3 patients. In group 1, 8 of 29 patients (28%) had stable disease with tumor regression approaching 50% in a malignant glioma and an anaplastic oligoastrocytoma. In group 2, overall survival was 12.0 months. EGFR overexpression by immunohistochemistry was found in 17 of 38 (45%) tumor samples analyzed, with a partial gain of 7p11.2 in 1 glioblastoma; phosphate and tensin homolog loss was frequent in brainstem glioma (15 of 19). Mean (95% CI) apparent clearance and volume of distribution for erlotinib were 4.0 L/h (3.4-4.5 L/h) and 98.6 L (69.8-127.0 L), respectively, and were independent of the dose level; mean half-life was 16.6 hours. Thus, erlotinib 125 mg/m(2) per day has an acceptable tolerability profile in pediatric patients with brain tumors and can be combined with radiotherapy.

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