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Cancer Therapy: Clinical

Phase I and Pharmacokinetic Studies of Erlotinib Administered Concurrently with Radiotherapy for Children, Adolescents, and Young Adults with High-Grade Glioma

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Purpose: To estimate the maximum-tolerated dose (MTD) of erlotinib administered during and after radiotherapy, and to describe the pharmacokinetics of erlotinib and its metabolite OSI-420 in patients between 3 and 25 years with newly diagnosed high-grade glioma who did not require enzyme-inducing anticonvulsants.

Experimental Design: Five dosage levels (70, 90, 120, 160, and 200 mg/m² per day) were planned in this phase I study. Dose-limiting toxicities (DLT) were evaluated during first 8 weeks of therapy.

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Local radiotherapy (dose between 54 and 59.4 Gy) and erlotinib started preferentially on the same day. Erlotinib was administered once daily for a maximum of 3 years. Pharmacokinetic studies were obtained after first dose and on day 8 of therapy. Mutational analysis of *EGFR* kinase domain, *PIK3CA*, and *PTEN* was done in tumor tissue.

Results: Median age at diagnosis of 23 patients was 10.7 years (range, 3.7-22.5 years). MTD of erlotinib was 120 mg/m² per day. Skin rash and diarrhea were generally well controlled with supportive care. Dose-limiting toxicities were diarrhea ($n = 1$), increase in serum lipase ($n = 1$), and rash with pruritus ($n = 1$). The pharmacokinetic variables of erlotinib and OSI-420 in children were similar to those described in adults. However, there was no relationship between erlotinib dosage and drug exposure. No *EGFR* kinase domain mutations were observed. Two patients with glioblastoma harbored mutations in *PIK3CA* ($n = 1$) or *PTEN* ($n = 1$).

Conclusions: Although the MTD of erlotinib in children with newly diagnosed high-grade glioma was 120 mg/m² per day, pharmacokinetic studies showed wide interpatient variability in drug exposure.

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