Abstract

Phase 1 dose escalation trial of the safety and pharmacokinetics of cabozantinib concurrent with temozolomide and radiotherapy or temozolomide after radiotherapy in newly diagnosed patients with high-grade gliomas.

Schiff D, Desjardins A, Cloughesy T, Mikkelsen T, Glantz M, Chamberlain MC, Reardon DA, Wen PY.

Abstract

BACKGROUND: Cabozantinib inhibits mesenchymal-epithelial transition factor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2) and has demonstrated activity in patients with recurrent glioblastoma, warranting evaluation of the addition of cabozantinib to radiotherapy (RT) and temozolomide (TMZ) for patients with newly diagnosed high-grade glioma.

METHODS: Cabozantinib doses of 40 mg and 60 mg were explored. Patients on the concurrent treatment arm received cabozantinib daily with standard TMZ and after RT continued cabozantinib daily with adjuvant TMZ. In the maintenance arm, patients who completed RT and ≥1 adjuvant cycle of TMZ continued adjuvant TMZ with added cabozantinib (3 schedules: days 1-28, days 1-14, or days 8-21).

RESULTS: A total of 26 patients (25 with recurrent glioblastoma and 1 patient with anaplastic astrocytoma) aged 30 to 72 years were enrolled (10 to the concurrent arm and 16 to the maintenance arm). The median number of post-RT TMZ cycles was 4.5 (range, 0-14 cycles) in the concurrent arm and 5.5 (range, 1-12 cycles) in the maintenance arm. Cabozantinib at a dose of 60 mg daily was the maximum administered dose and a dose of 40 mg daily was determined to be the maximum tolerated dose for both treatment arms (schedule of days 1-28). The most frequent grade 3/4 adverse events were thrombocytopenia (31% of patients), leukopenia (27% of patients, including 5 patients with neutropenia), and deep vein thrombosis and/or pulmonary embolism (23% of patients) (adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]).

CONCLUSIONS: Cabozantinib at a dose of 40 mg daily with RT plus TMZ and post-RT TMZ for patients with newly diagnosed high-grade glioma was generally well tolerated, and demonstrated no pharmacokinetic interactions with concurrent TMZ. Given the strong theoretical rationale for combining anti-VEGF and anti-MET activity with standard therapy, cabozantinib at a dose of 40 mg daily warrants evaluation in combination with standard therapy for patients with newly diagnosed glioblastoma. Cancer 2015. © 2015 American Cancer Society.

© 2015 American Cancer Society.

KEYWORDS: antiangiogenic therapy; cabozantinib; glioblastoma; high-grade glioma; signal transduction inhibitors
Phase 1 dose escalation trial of the safety and pharmacokinetics of cab...