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

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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 2016;122:582-7. © 2015 American Cancer Society.

KEYWORDS: antiangiogenic therapy, cabozantinib, glioblastoma, high-grade glioma, signal transduction inhibitors.

INTRODUCTION

Despite improved outcomes in patients with newly diagnosed glioblastoma with the addition of temozolomide (TMZ) to fractionated radiotherapy (RT),1 the median survival remains <18 months, with a 5-year survival rate of approximately 10%. Angiogenesis is a cardinal feature of glioblastoma, and the important role of vascular endothelial growth factor A (VEGFA) has led to studies demonstrating the value of the humanized anti-VEGFA monoclonal antibody bevacizumab in the treatment of recurrent glioblastoma.2,3 Unfortunately, 2 recently reported phase 3 clinical trials failed to demonstrate a survival benefit from the addition of bevacizumab to standard therapy with RT and TMZ in newly diagnosed patients with glioblastoma.4,5 Thus, approaches to prevent the development of resistance to anti-VEGF therapies are of great interest.

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Cabozantinib is an oral, potent inhibitor of mesenchymal-epithelial transition factor (MET), VEGF receptor 2 (VEGFR2), and RET that produces robust antiangiogenic, antiproliferative, and antiinvasive effects in preclinical models.\(^6\)\(^7\) Multiple lines of evidence have suggested a rationale for cabozantinib in the treatment of glioblastoma. MET, VEGFR2, VEGFA, and hepatocyte growth factor (HGF) levels are elevated in glioblastoma.\(^8\)\(^-\)\(^10\) MET is involved in brain tumor growth and vascularization, and increased expression levels correlate with higher tumor grade and a worse prognosis.\(^8\)\(^,\)\(^11\)\(^,\)\(^12\) MET activation appears to be an important mechanism of bevacizumab resistance in human glioblastoma.\(^13\) HGF, the ligand for MET, is often expressed in glioblastoma, implicating an growth factor (HGF) levels are elevated in glioblastoma.\(^8\)\(^-\)\(^10\)

Based on the apparent significance of MET in glioblastoma and its role in mediating resistance to anti-VEGF pathway therapy, a phase 1 dose-finding and pharmacokinetic (PK) study of cabozantinib in newly diagnosed patients with glioblastoma and anaplastic glioma was conducted. In arm 1, cabozantinib was administered concurrently with RT and TMZ whereas in arm 2, cabozantinib was initiated with adjuvant TMZ after patients had completed concurrent RT and TMZ.

**MATERIALS AND METHODS**

Eligible patients had a newly diagnosed glioblastoma or anaplastic glioma, were aged ≥18 years, had a Karnofsky performance score (KPS) ≥70, had adequate bone marrow and normal renal and hepatic function, and were not receiving cytochrome P450 enzyme-inducing antiepileptic drugs. Patients in arm 1 (cabozantinib concomitant with RT/TMZ) initiated RT between 28 and 49 days from surgery and received no other nonsurgical antitumor treatment. Patients in arm 2 were required to have completed a first-line regimen of concurrent TMZ and RT for newly diagnosed glioblastoma or anaplastic glioma followed by a rest phase and to have received at least a single 5-day cycle of TMZ at a dose of 200 mg/m\(^2\)/day without requiring a dose interruption or reduction. The protocol was approved by the local human subjects committees of each participating institution. All patients provided informed consent.

Dose escalation/deescalation of cabozantinib occurred in parallel in arm 1 (concurrent with RT/TMZ and post-RT maintenance). A Cohort Review Committee monitored the study and made decisions regarding dose escalation and the selection of optional concurrent arms. Cohorts enrolled into the study are shown in Figure 1.

Individuals in arm 1 received fractionated focal RT with 1.8 to 2 grays per fraction daily for 5 days per week for 6 to 7 weeks for a total dose of up to 60 grays with daily concomitant TMZ at a dose of 75 mg/m\(^2\). Cabozantinib was given daily for the duration of the concurrent phase. Subjects continued to receive cabozantinib during the 4-week post-RT/TMZ rest phase and during the maintenance phase in combination with TMZ.

Patients in arm 2 (maintenance arm) were enrolled into 1 of 3 maintenance phase arms. In arm 2a, TMZ was given on days 1 to 5 every 28 days, whereas cabozantinib was given daily starting on day 1 of each TMZ cycle. Due to the myelotoxicity observed with continuous daily dosing of cabozantinib in combination with TMZ, the protocol was amended to allow for the exploration of intermittent dosing schedules. In arm 2c, cabozantinib was given daily for 14 days (days 1-14) of each 28-day cycle. In arm 2d, cabozantinib was given daily on days 8 to 21 of each 28-day cycle.

The initial dose of cabozantinib in both the concurrent and maintenance arms was 60 mg (free base equivalent weight) daily. The adverse event (AE) grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The dose-limiting toxicity (DLT) was defined as grade 4 neutropenia with a duration of ≥4 days or grade 4 febrile neutropenia, grade 4 thrombocytopenia or anemia despite optimal treatment, inability to receive ≥75% of the planned dose or a cycle delay ≥2 weeks due to related AE, unmanageable grade ≥3 treatment-related toxicity, grade ≥2 wound infection, or intracranial hemorrhage. The DLT evaluation period was 11 weeks for patients in arm 1 and 4 weeks for patients in arm 2. In the dose escalation/deescalation phase of treatment arms 1 and 2, subjects were accrued following a “3 + 3” design, with dose modification dependent on safety and available PK data from previous dose levels. Only the 60-mg and 40-mg dose levels were used.

Pretreatment safety and tolerability assessments included physical examination, electrocardiography, KPS, complete blood counts and chemistry panels, prothrombin time/international normalized ratio, urinalysis, and urine protein/creatinine ratio. Safety evaluations were repeated at regular time points throughout the study. Magnetic resonance imaging for tumor assessment was performed within 14 days of the initiation of protocol therapy, at the end of the 4-week rest period (arm 1), and after every 4-week cycle of TMZ/cabozantinib (arms 1...
Local investigators used modified Macdonald criteria for response assessments. In arm 1, serial plasma PK assessments for the measurement of TMZ and cabozantinib concentrations were performed on day 1 of cycles 1 and 2 and before the dose on maintenance days 1 and 15 of cycle 1, as well as on day 1 of subsequent maintenance cycles. Patients in arm 2 underwent PK assessments before dose and 4 hours after dose on days 1 and 15 of cycle 1, as well as before dose on day 1 of subsequent cycles.

**Statistical Analysis**

Due to the exploratory nature of the current study and the small number of patients accrued to the trial, no formal statistical testing was planned. Descriptive statistics were used for safety, tumor response, and PK. The safety population consisted of all subjects who received any dose of cabozantinib.

**RESULTS**

The trial accrued subjects at 7 sites between September 2009 and November 2010. Twenty-five patients with glioblastoma and 1 patient with anaplastic astrocytoma were enrolled. Table 1 summarizes patient characteristics. Overall, the population was 38.5% female and had a median age of 56.5 years. The KPS was between 90% and 100% for 61.5% of patients and between 70% and 80% for 38.5% of patients. Six of 19 evaluable patients (32%) exhibited MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation; isocitrate dehydrogenase mutation status was not assessed. Ten patients were
enrolled on arm 1 and 16 patients were enrolled to the 3 cohorts of arm 2 (Table 2).

In arm 1 at the initial cabozantinib dose level of 60 mg, 2 of 3 patients experienced DLTs (pancytopenia and methemoglobinemia); no DLT was observed in the cohort of 7 patients treated at the 40-mg dose (1 subject was replaced for inadequate cabozantinib exposure). In arm 2a at the starting cabozantinib level of 60 mg daily, 2 of the first 3 patients experienced a DLT of thrombocytopenia. No DLT was observed in the cohort of 7 patients in arm 2a who were treated at a dose of 40 mg (1 patient was replaced for inadequate cabozantinib exposure). Thus, the maximum tolerated dose (MTD) of cabozantinib, both in arm 1 and arm 2a, was 40 mg/day. All 26 patients experienced AEs, and the majority (96.2%) experienced treatment-related AEs. Grade 3 or 4 AEs were experienced by 84.6% of patients, and treatment-related grade 3 or 4 AEs occurred in 61.5%. Table 3 summarizes the most frequent treatment-emergent AEs. Fatigue, gastrointestinal side effects, elevated transaminases, and low blood counts were prevalent. Treatment-related serious AEs experienced by >1 patient were thrombocytopenia (4 patients; 15.4%) and pancytopenia (2 patients; 7.7%).

The majority of patients (80.8% overall) had dose modifications due to AEs, chiefly for myelosuppression, including thrombocytopenia (11 patients; 42.3%) and neutropenia (5 patients; 19.2%). Most subjects were able to continue treatment after a dose reduction or resolution of the event. Nine patients (34.6%) discontinued study therapy because of AEs.

In terms of anti-VEGF toxicity, 2 patients experienced grade 1 or 2 proteinuria; both events resolved without treatment, and both patients remained on study without any treatment alterations. One patient experienced a renal infarct that led to treatment discontinuation, and another had a grade 1 intracranial hemorrhage that resolved without treatment. Three patients experienced wound-healing complications; 1 of these events (grade 3 postoperative wound infection) led to treatment discontinuation. Hypertension was observed in 23.1% of patients, and grade ≥3 hypertension was only observed (in 2 subjects; 7.7%) at dose levels greater than the MTD.

PK parameters of cabozantinib with TMZ in the concurrent phase treatment arm (arm 1) demonstrated that the mean maximum concentration (C_{max}) and area under the curve (AUC) values on day 1 were decreased by 35% and 26%, respectively, as the dose reduced from 60 mg to 40 mg (33% decrease). At steady state on day 29, the C_{max} and AUC values for the 40-mg and 60-mg

### TABLE 2. Subject Disposition

<table>
<thead>
<tr>
<th>Cabozantinib Dose</th>
<th>Concurrent Arm 1 (Cabo + RT + TMZ)</th>
<th>Maintenance Arm 2 (Cabo + TMZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 60 mg</td>
<td>Arm 1 40 mg</td>
</tr>
<tr>
<td>Total no. of treated subjects</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Primary reason for study discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Radiologic</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subject request</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rollover to maintenance study</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: Cabo, cabozantinib; RT, radiotherapy; TMZ, temozolomide.

*One patient was replaced due to inadequate cabozantinib exposure.

*Death due to progressive disease 1 day after the last study dose.

### TABLE 3. Most Frequent (>20%) Treatment Emergent AEs Regardless of Cause

<table>
<thead>
<tr>
<th>With AE</th>
<th>≥Grade 3 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (73%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (69%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (39%)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (23%)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

*AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
dose levels were similar. The lack of decrease in the exposure from the 60-mg to 40-mg dose could be due to limited numbers of patients for the 60-mg dose (2 patients) and high intrasubject variability at steady-state concentrations (C\text{max} of 63%; AUC, 67%). The mean accumulation ranged from 6-fold to 9-fold.

The effect of TMZ on the PK of cabozantinib was assessed by comparing the dose-normalized AUC_{0,\text{last}} values of cabozantinib at steady state from arm 1 with the dose-normalized steady state values for the 140-mg dose (175 mg salt weight) in the study by Kurzrock et al., in which cabozantinib was dosed as a single agent. Based on the mean values, no apparent effect of TMZ on the PK of cabozantinib was observed (<2-fold).

The PK profile of TMZ at a dose of 75 mg/m² when given with daily doses of 60 mg and 40 mg of cabozantinib was assessed on day 1 and day 29 during concurrent treatment on arm 1. The mean terminal half-life was 2 hours and was similar to that of previously published data. No TMZ accumulation was observed after repeated doses. Dose-normalized AUC_{0,\text{last}} after a single TMZ dose when given with cabozantinib was compared with the published values when TMZ was given as a single agent. No effect of cabozantinib on the plasma PK of TMZ was apparent (<2-fold). Due to the high number of dose reductions and dose interruptions of cabozantinib and TMZ for the maintenance phase in arms 1 and 2, no further PK data analyses were performed.

**DISCUSSION**

Aberrant activation of multiple molecular signaling pathways drives the malignant behavior of glioblastoma. Glioblastoma manifests intense angiogenesis related to increased expression of proangiogenic factors, notably VEGF. Targeting the VEGF pathway in glioblastoma has been modestly successful, but resistance to anti-VEGF therapy inevitably develops. c-MET and its ligand HGF promote the proliferation, migration, and invasion of cancer cells in general and glioblastoma in particular. MET signaling is key for the survival of glioma stem cells and for acquisition of radioresistance. Moreover, recent studies have suggested critical synergy between the VEGF and MET pathways in glioblastoma. In mouse models of glioblastoma, VEGF blockade induced a proinvasive phenotype and led to MET upregulation and the development of apparent epithelial-to-mesenchymal transition. Lu et al described that MET knockdown blocked this phenomenon and led to prolonged animal survival. Also noted was increased phospho-MET within tumors that progressed despite treatment with bevacizumab compared with pretreatment samples. These data suggest that agents such as cabozantinib that are capable of dual VEGF/MET inhibition may be a useful adjunct to standard therapy in newly diagnosed patients with glioblastoma.

A critical issue in brain tumor therapy is whether the drug penetrates the blood-brain barrier to reach the target. Although to the best of our knowledge no direct human data currently are available, in whole-brain lysates of non-tumor-bearing mice, cabozantinib attained 20% of peak plasma levels, suggesting its ability to penetrate the blood-brain barrier. Moreover, cabozantinib has well-documented single-agent activity in anti-VEGF therapy- naïve patients with recurrent glioblastoma, with an objective response rate of 15.2% confirmed by independent radiology review.

In the current trial, DLTs were consistent with the known toxicities of single-agent cabozantinib and well-established side effects of RT and TMZ. Cabozantinib increases the incidence of thrombocytopenia and leukopenia, similar to what is observed with TMZ alone. Fatigue, gastrointestinal side effects, and hypertension were generally of low grade and not dose-limiting. No unanticipated or new toxicities related to study treatment were identified. The MTD of 40 mg of cabozantinib daily is notably less than the dose of 100 mg daily identified in the single-agent study of recurrent glioblastoma. There were no apparent PK interactions noted between cabozantinib and 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.

**Conclusions**

Cabozantinib can be combined safely with the standard-of-care regimen of RT and TMZ in the concomitant and maintenance phases in the front-line treatment of patients with glioblastoma. The ability to administer the full dose of TMZ and RT was not compromised. The MTD and recommended phase 2 dose of cabozantinib with TMZ and RT was found to be 40 mg/day.

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**CONFLICT OF INTEREST DISCLOSURES**

David Schiff has acted as a paid member of the Advisory Boards for Genentech, Heron, and Midatech Pharma and has received fees for Data Safety Monitoring Committee services from Vascular Biogenics. Payments have been made to his institution from Cavion LLC (for consulting) and Celldex Therapeutics (for Data Safety...
REFERENCES


