Sunitinib Malate plus Lomustine for Patients with Temozolomide-refractory Recurrent Anaplastic or Low-grade Glioma

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Abstract. Tyrosine kinase signaling through the vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor-α (PDGFR-α) and KIT cell surface receptors mediates neo-angiogenesis and contributes to cancer cell survival in recurrent anaplastic and low-grade glioma. Thirteen patients with temozolomide-refractory recurrent anaplastic or low-grade glioma were treated with sunitinib malate, a small-molecule tyrosine kinase inhibitor of the VEGFR, PDGFR, and KIT receptors, in combination with lomustine. The most frequent grade 3 and 4 adverse events were fatigue, thrombocytopenia, neutropenia and lymphopenia. The best objective tumor response by Response Assessment in Neuro-Oncology (RANO) criteria was one complete response, one unconfirmed partial response and three cases of stable disease. The median progression-free survival was 1.8 months (95% confidence interval=1.0-2.7 months) with 6-month progression-free survival of 15% (95% confidence interval=0-35%). The median overall survival was 6.7 months (95% confidence interval=0.7-12 months). The investigated combination regimen of sunitinib and lomustine is well-tolerated but insufficiently active to warrant further investigation in an unselected population of patients with temozolomide-refractory recurrent anaplastic and low-grade glioma.

Low-grade (WHO grade II) and anaplastic (WHO grade III) gliomas are incurable in the vast majority of cases. The prognosis from the time of initial diagnosis is heterogeneous and correlated with the WHO tumor differentiation grade (II vs. III), morphology (oligodendrogial vs. mixed oligoastrocytic vs. astrocytic differentiation) and molecular genetic characteristics (including the isocitrate dehydrogenase 1 and-2 gene mutation status, loss of heterozygosity for chromosomes 1p and 19q, mutation of the p53 tumor-suppressor gene and methylation status of the O6-alkylguanine DNA alkyltransferase (MGMT) gene promoter) (1-3). Disease control is obtained in the majority of patients following surgery and radiation therapy. Long-term survival of patients affected by anaplastic oligoastrocytoma with chromosome 1p/19q deletion is improved with adjuvant procarbazine, lomustine, vincristine (PCV) chemotherapy (1, 2). Inevitably, these malignancies will recur in the majority of patients after a median of 2 to 3 years in anaplastic cases and 5 to 10 years in low-grade cases (3, 4). Commonly these gliomas transform into a more aggressive phenotype at the time of recurrence and median overall survival (OS) from the time of recurrence for anaplastic glioma is in the order of 39 weeks (6, 7). The highest sensitivity to alkylating chemotherapy (PCV, temozolomide) at the time recurrence is observed for patients with oligodendroglioma gliomas with 1p/19q deletion (1, 5-9). At present, no treatment option has demonstrated improvement of OS of patients with recurrent low-grade and anaplastic gliomas in a phase III randomized clinical trial.

A sub-group of patients with low-grade and anaplastic glioma are characterized by a co-amplification of the KIT, platelet-derived growth factor receptor-α (PDGFRα) or VEGFR2 genes (10, 11). In a recent report on 342 low-grade diffuse gliomas, a gain in PDGFRα copy number was detected in 16.3% of patients with diffuse astrocytoma, significantly more frequent as compared to those with oligodendrogliomas (2.6%) (12, 13). Additionally, up-regulation of the PDGFRα gene on endothelial cells has been documented in human glial tumors (14).

Sunitinib malate is an oral small-molecule tyrosine kinase inhibitor of the VEGFRs; PDGFRα and -β; c-KIT; FLT3;
and RET kinases. Sunitinib has shown substantial clinical activity against hypoxia-inducible factor (HIF)/VEGF-dependent, PDGFR-dependent and KIT-dependent cancer and is approved for the treatment of renal cell carcinoma and gastro-intestinal stromal tumor (15-18). In a previously reported clinical trial conducted at our Institution, sunitinib failed to demonstrate meaningful anti-tumor activity as a monotherapy for recurrent glioblastoma when given at a daily dose of 37.5 mg (19). More recently published clinical trials confirmed the lack of improvement of response rate, progression-free survival (PFS) or OS compared to historical controls (20, 21). Moreover, in all published trials on patients with glioma using sunitinib at a daily dose level of 37.5 mg, considerable toxicity was observed (20, 21).

Despite the lack of significant benefit from sunitinib monotherapy, three patients with a secondary glioblastoma and an age below 40 years treated in our previous trial obtained durable partial tumor responses when treated with lomustine at the time of progression on sunitinib (unpublished data). The hypothesis that exposure to sunitinib might have conditioned the recurrent secondary glioblastoma to the subsequent treatment with lomustine inspired us to set up a sequential clinical trial exploring the activity of a combination therapy of sunitinib and lomustine in patients with temozolomide-refractory recurrent low-grade or anaplastic glioma.

Patients and Methods

Eligibility criteria. In order to be eligible for trial participation, patients had to have a prior history of histologically-diagnosed WHO grade II or III glioma with documented recurrence or progressive disease following treatment with surgery, radiation therapy and at least one line of alkylator chemotherapy. Patients with a histopathological diagnosis of glioblastoma were eligible under the condition that there was confirmation of a lower WHO differentiation grade at a previous time point (secondary glioblastoma). Diagnosis of recurrence or progression needed to be demonstrated on gadolinium (Gd)-enhanced T1-Magnetic Resonance Imaging (MRI) revealing an increasing Gd-enhancing tumor mass with a minimal diameter of 1 cm. An interval of at least 12 weeks after the end of radiation therapy was required in order to minimize the risk of recruiting patients with pseudoprogression.

Patients had to be older than 18 years, with a baseline Karnofsky performance score of ≥60, an absolute neutrophil count of ≥1,500 cells/mm³, a platelet count of ≥100,000 cells/mm³, a White Blood Cell (WBC) count ≥3,500 cells/mm³, a hemoglobin level of ≥9 g/dl, a total serum bilirubin level of <2x the upper limit of normal (ULN), alkaline phosphatase and Aspartate transaminase/Alanine Transaminase (AST/ALT) levels of <1.5×ULN, and a serum creatinine level of <1.5×ULN.

Patients with a history of spontaneous intratumoral hemorrhage, congestive heart failure, myocardial infarction or coronary artery bypass graft in the previous 6 months, or ongoing severe or unstable angina or any unstable arrhythmia requiring medication were excluded. Patients were required to have recovered from toxicities of prior surgery, radiation therapy and chemotherapy, and were not permitted to have had either radiation therapy or a systemic drug therapy within 4 weeks of initiating sunitinib. No prior treatment with a nitrosourea-containing chemotherapy regimen was allowed at the exception of adjuvant treatment and an interval of more than 6 months between the end of adjuvant treatment and recruitment to this study. Corticosteroid dosing had to be stable for at least 7 days before initiating sunitinib. Concurrent treatment with potent Cytchrome P450 3A4 (CYP 3A4) inhibitors and inducers was not allowed from 14 days before dosing (including enzyme inducing anti-epileptic drugs or drugs having pro-arrhythmic potential). This clinical trial protocol (Eudract No. 2007-001561-15) and its amendment were reviewed and approved by the Institutional Review Board of the Universitair Ziekenhuis Brussel and the Belgian competent health authorities; written informed consent was obtained from all patients before participation.

Study treatment, safety and tumor response assessments. Sunitinib malate (Sutent, Pfizer) was administered at a daily dose of 25 mg for 28 consecutive days followed by a 14-day treatment-free interval. Lomustine (CCNU) was administered as a single dose (80 mg/m²) on day 14 of the six week treatment cycle. In case of any grade 3 or 4 related adverse event (excluding alopecia and lymphopenia), the administration of sunitinib and lomustine would be withheld until recovery to grade 1 or lower. If considered sunitinib-related, one dose reduction of sunitinib to 12.5 mg/day was allowed for subsequent cycles. Lomustine-related hematological toxicity required a delay of subsequent dosing until blood values had recovered to acceptable levels (platelet count >100,000/mm³; absolute neutrophil count >1500/mm³). Dose adjustment at the subsequent administration was dependent on the nadir blood counts. Patients who experienced lomustine-related treatment limiting toxicity could continue on-study treatment with sunitinib as a monotherapy in the absence of disease progression.

Clinical visits were planned every two weeks. Assessments included medical history, physical and neurological examination and hematology and chemistry blood analyses. Treatment-related adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) (22). MRI (including T1-Gd enhanced and T2/Fluid-Attenuated Inversion Recovery (FLAIR)-weighted images was performed at baseline and at the end of week six of the first and all subsequent cycles. Tumor response assessments were based on RANO criteria (23).

Study design and statistical analysis. This study was designed as a single-arm, single-center, two-stage phase II, open-label study according to a Simon two-stage optimal design with an alpha error of 0.05 and beta error of 0.20. The primary objective was to determine the best objective response rate (BORR), according to RANO criteria. With a p0 hypothesis of 20% and a p1 of 40%, three objective responses were needed among the first 13 patients treated on this trial in order to justify recruitment in the second stage of the trial. Secondary objectives included safety of the investigated combination regimen, an estimation of the PFS and OS according to Kaplan–Meier method (including six-month survival percentages and medians with two-sided 95% confidence intervals (CI)). Tumor response rates, adverse events, demographic and baseline patient characteristics are reported using descriptive statistics.
Results

Patients' characteristics. Thirteen patients with recurrent gliomas were enrolled between May 2009 and November 2011. Eleven patients had an initial diagnosis of either low-grade (5 cases) or anaplastic glioma (6 cases). An eligibility waiver was attributed to one patient diagnosed with WHO grade IV glioma at an age of 35 years. All patients had evidence of a Gd-enhancing progressive tumor mass following prior surgery and radiation therapy. All patients had been exposed to treatment with temozolomide for recurrent disease and had progressed during or shortly after this therapy.

Baseline patient characteristics are summarized in Table I. Study treatment was offered as a third-line of therapy in seven patients, as a fourth-line in four and as a fifth-line in two.

Treatment. All patients initiated sunitinib at a starting dose of 25 mg/day for 4 weeks followed by a 2-week treatment-free interval. Lomustine (at a dose of 80 mg/m²) was administered on day 14 of the first treatment cycle in all patients. A total of 443 treatment weeks were completed. Median duration of therapy was 6 weeks (range=2-155 weeks). In five patients, lomustine had to be discontinued because of treatment related adverse events in the absence of tumor progression. Treatment with sunitinib was continued in these cases without reoccurrence of the lomustine related AEs. In one patient, sunitinib dosing was lowered to 12.5 mg/day because of sunitinib-related grade 3 myelosuppression observed before the administration of lomustine. In three patients, the dosing regimen of sunitinib was adapted to a daily dose of 25 mg 5 out of 7 days because of treatment limiting fatigue in the context of extended (>6 months) treatment duration.

Adverse events. Sunitinib at a daily dose of 25 mg for 28 consecutive days every 42 days was generally well tolerated (Table II). Grade 2 or 3 fatigue was the single most frequent adverse event, necessitating treatment interruptions for three patients. Hematological adverse events were documented in eight out of 13 patients. Because of recurrent grade 3 or 4 hematological toxicity at a reduced dose of lomustine, lomustine treatment was permanently stopped in four patients.

Tumor response. According to RANO criteria, one patient obtained a complete response (CR) (BORR of 8%) (Figures 1 and 2). An additional three patients experienced a
stabilization of their disease (disease control rate of 31%). Duration of the CR and SDs was 32, 16, 21 and 22 weeks, respectively. All other patients were diagnosed with progressive disease (PD) on Gd-enhanced T1 MRI at first evaluation. For one patient with a stable clinical status, treatment was stopped following the documentation of progression on MRI imaging (Figure 3). The patient was then offered best supportive care at another Center. At follow-up one year later, MRI revealed a significant regression of the tumor compared to baseline MRI and first evaluation at six weeks, indicating a late but durable response to one cycle of the study treatment. For two additional patients meeting the criteria for progression on Gd-enhanced MRI (>25% increase in tumor surface) at first evaluation, it was decided to continue sunitinib treatment despite radiological progression because the clinical status of both patients had stabilized or improved. At subsequent radiological evaluations the tumor dimensions stabilized and the clinical status (including use of corticosteroids) remained stable. Treatment with sunitinib was continued for 42 and 138 weeks, respectively, before progression with neurological deterioration occurred.

Survival. At the time of analysis, all patients had experienced progression of disease. Ten patients had died, all as a result of progressive disease. Three patients are alive and followed-up respectively 22, 36 and 52 months following the initiation of study treatment. The median PFS is 1.8 months (95%CI 1.0-2.7), 6-month PFS is 15%. The median OS is 6.7 months (95%CI 0.7-12.8), with a 6-month OS of 20% (95%CI 1-39%) (Figure 4).

Discussion

The investigated combination of sunitinib malate and lomustine failed to demonstrate the predefined desired level of antitumor activity for study continuation and patient
recruitment was stopped after the first stage of this single-Center phase II trial. Of interest is the observation that durable disease control (>6 months) was achieved in four out of 13 patients (30%) treated in this trial. Sunitinib is suspected to have contributed substantially to this outcome as three out of four patients only received one administration of lomustine and direct evidence for sunitinib sensitivity was found when a fourth patient who stopped study treatment in the absence of progression responded to sunitinib monotherapy at the time of progression. In addition to the objective tumor responses observed among three of the first 13 patients treated on this protocol, indications were that the investigated regimen may offer clinical benefit in the absence of a tumor response according to RANO criteria. Three patients, including one patient with a late response, had prolonged clinical PFS. In these cases, the patients had a progression-free period that was documented either without continuing therapy (one patient) or when sunitinib treatment was continued as a monotherapy beyond radiological progression (two patients). Further studies evaluating sunitinib in patients with low-grade and anaplastic glioma should, therefore, consider using alternative efficacy end-points (e.g. 6-month PFS) and allow for treatment beyond radiological progression when the neurological condition is preserved or improved during study treatment. None of the conventional biomarkers assessed on archival tumor tissues in this study were correlated with outcome. Further investigation of sunitinib in patients with recurrent low-grade or anaplastic glioma should, therefore, integrate a more extensive search for predictive biomarkers, preferably on tumor tissue samples obtained at the time of recurrence.

In contrast to our previously reported study on patients with recurrent glioblastoma treated with a 37.5 mg daily dosing regimen, the current regimen was associated with

Figure 3. Case illustration of a late but durable response to study treatment with sunitinib and lomustine following progression at the first tumor assessment. A: Baseline sagittal image of T1 Gd-enhanced MRI indicating an enhancing tumor mass adjacent to the frontal resection cavity; B: progression of disease on T1 gadolinium enhanced MRI following one cycle of study treatment with sunitinib and lomustine; C: image obtained on T1 Gd-enhanced MRI one year later, indicating a partial response in the absence of any antitumor treatment within this interval.

Figure 4. Kaplan–Meier progression-free (A) and overall survival (B) probability curves.
acceptable toxicity (19-21). In this clinical trial, sunitinib was administered at a daily dose of 25 mg for 28 consecutive days followed by a 14-day treatment-free interval and lomustine was administered at a single dose (80 mg/m²) on day 14 of the 6-week treatment cycle. These dose levels are considerably lower compared to the approved dosing regimen of sunitinib for patients with kidney cancer and the conventional dose level for lomustine (110 mg/m² every 6 weeks). Our results indicate that a higher dosing level would likely not be tolerable given the observed incidence of hematological toxicity (38% of patients experienced grade 3 or 4 hematological toxicity, an incidence that is comparable to the incidence with the 37.5 mg/m² daily treatment regimen) (19). Treatment, limiting hematological toxicity is thought to be driven mainly by lomustine but a contribution from sunitinib is likely since we recorded one patient with grade 3 myelosuppression solely related to sunitinib. Chronic fatigue (grade 2) was the main toxicity associated with sunitinib and of concern in patients who benefited from therapy and were treated for protracted periods of time. As opposed to our experience with the 37.5 mg/m² daily regimen for recurrent glioblastoma, no serious skin or gastrointestinal toxicity were observed in this trial.

Conclusion

The investigated combination therapy of sunitinib at a daily dose of 25 mg for 28 consecutive days followed by a 14-day treatment-free interval and lomustine was administered as a single dose (80 mg/m²) on day 14 of the 6-week treatment cycle was associated with acceptable toxicity. The observed antitumor activity was found to be insufficient to justify further investigation of this regimen in an unselected target population of patients with recurrent low-grade or anaplastic glioma. A sub-group of patients may derive benefit from sunitinib but further study is needed to identify predictive biomarkers for sunitinib sensitivity.

References


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