Journal of Cancer Research and Clinical Oncology (2019) 145:1037–1042
https://doi.org/10.1007/s00432-019-02868-5

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Regorafenib in patients with recurrent high-grade astrocytoma

Sied Kebir[1,2,3,4] · Laurel Rauschenbach[3,4,5] · Alexander Radbruch[6] · Lazaros Lazaridis[1,3,4] · Teresa Schmidt[1,3,4] · Ann-Kathrin Stoppek[1,3,4] · Daniela Pierscianek[3,4,5] · Martin Stuschke[7] · Michael Forsting[6] · Ulrich Sure[3,4,5] · Kathy Keyvani[8] · Christoph Kleinschnitz[9] · Björn Scheffler[2,3,4] · Martin Glas[1,2,3,4]

Received: 26 January 2019 / Accepted: 18 February 2019 / Published online: 28 February 2019

Abstract

Purpose Antiangiogenic treatment approaches have failed to improve outcome in randomized trials of high-grade astrocytoma. One key mechanism of resistance to antiangiogenic treatment may concern the upregulation of alternative pro-angiogenic pathways. Regorafenib is a potent multikinase inhibitor that may alter some of those pathways. In this retrospective study, we investigated efficacy and radiographic tumor growth patterns of regorafenib in recurrent high-grade astrocytoma.

Methods We screened for patients with high-grade astrocytoma in whom regorafenib was administered for at least 4 weeks. We assessed treatment efficacy in terms of progression-free survival (PFS), overall survival, and adverse events defined by Common Toxicity Criteria (CTC). In addition, radiographic tumor growth patterns were determined at baseline and recurrence.

Results A total of 6 patients met eligibility criteria. The number of recurrences prior to regorafenib varied between 2 and 6. Patients were on regorafenib treatment for at least 4 weeks and maximally 14 weeks. Median PFS was 3.5 months and ranged from 2.0 to 4.0 months. Radiographic response was progressive disease in all patients with an objective response rate of 0%. CTC°3 adverse events were observed in all but one patient. The most common radiographic growth pattern was local with no change in growth pattern at recurrence. An infiltrative tumor growth was not induced in any patient.

Conclusions This retrospective study indicates a very poor performance of regorafenib in recurrent high-grade astrocytoma with a fairly high number of CTC°3 adverse events. In addition, regorafenib does not seem to bear a potential for infiltrative tumor growth promotion.

Keywords Regorafenib · Astrocytoma · Glioblastoma · High-grade glioma

✉ Martin Glas
Martin.Glas@uk-essen.de

[1] Division of Clinical Neurooncology, Department of Neurology, University Hospital Essen, University Duisburg-Essen, 45147 Essen, Germany

[2] DKFZ-Division Translational Neurooncology at the West German Cancer Center (WTZ), University Hospital Essen, Essen, Germany

[3] German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany

[4] West German Cancer Center (WTZ), University Hospital Essen, University Duisburg-Essen, Essen, Germany

[5] Department of Neurosurgery, University Hospital Essen, University Duisburg-Essen, Essen, Germany

[6] Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

[7] Department of Radiotherapy, University Hospital Essen, Essen, Germany

[8] Institute of Neuropathology, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany

[9] Department of Neurology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Introduction

Despite state-of-the-art treatment of high-grade astrocytoma consisting of maximum safe resection, radiotherapy, and alkylating chemotherapy, median progression-free survival (PFS) is in the order of 6.2–42.8 months (Chinot et al. 2014; van den Bent et al. 2017) with lower PFS pertaining to the most malignant astrocytoma, i.e., glioblastoma. When tumor has recurred, the standard treatment regime is less clearly defined (Weller et al. 2017) with median PFS being even lower and ranging from 1.5 to 6.3 months (Wick et al. 2017; van den Bent et al. 2018). High-grade astrocytoma are known for their marked vascularization with high expression of VEGF, a growth factor known to promote endothelial proliferation (Das and Marsden 2013). Among treatment options investigated in controlled phase 2 and 3 trials in first-line and second-line settings, bevacizumab, an antibody to VEGF-A ligand, has been shown to increase PFS as compared to standard treatment (Gilbert et al. 2014; Wick et al. 2017). However, the PFS benefit did not translate into an increase of overall survival (OS). In addition, there are conflicting reports as to whether antiangiogenic treatment in glioblastoma might elicit diffuse and infiltrative tumor growth (Schaub et al. 2018).

Acquired resistance by upregulation of alternative pro-angiogenic signaling pathways is one of the discussed explanations for the lack of OS benefit following treatment with antiangiogenic agents (Hundsberger et al. 2017). Regorafenib is a multikinase inhibitor known to direct a multitude of signaling pathways, among which several are associated with angiogenesis (Uschner et al. 2018). Among treatments considered at tumor progression, alkylating nitrosurea compounds, such as carmustine (BCNU) or lomustine (CCNU), are widely established as standard treatment. CCNU tends to yield better results in patients with methylated MGMT promoter with a median overall survival rate of 10.4 months in those methylated and 7.2 in those unmethylated (Wick et al. 2017). In a recently published phase II trial of patients with first glioblastoma recurrence, in fact, one of very few positive trials in glioblastoma recurrence, regorafenib was superior to lomustine with overall survival of 7.4 months in regorafenib-treated patients as compared to 5.6 months in lomustine-treated patients (Lombardi et al. 2019). Notably, the effect size with regorafenib was independent of MGMT promotor status.

In our single-center study, we retrospectively evaluated our experience with regorafenib in patients with high-grade astrocytoma recurrence. Results for efficacy, toxicity, and radiographic tumor growth patterns are reported.

Methods

Study design

In this study, we retrospectively investigated patients' medical records from our neuro-oncology center recorded between January and December 2018 for the following criteria:

1. Patients diagnosed with recurrent high-grade astrocytoma in accordance with 2016 WHO guidelines (Louis et al. 2016).
2. Patients underwent treatment with regorafenib for at least 4 weeks.
3. Baseline prior to and follow-up MRI upon regorafenib treatment is available to assess treatment response.

Treatment response was established in each patient by virtue of Response Assessment in Neuro-oncology Criteria (Wen et al. 2010). MRI scans to evaluate treatment responses were obtained at the investigator's discretion every 2–4 months. Regorafenib was given according to the summary of product characteristics at a dose of 160 mg in a 21 days on/7 days off schedule. Adverse events were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.3. Approval for publication of this report was obtained from the patients involved and the institutional review board.

Definition of tumor growth patterns

At baseline, before onset of regorafenib treatment, and at the time of recurrence, MRI-based tumor growth patterns were determined as previously published (Schaub et al. 2018) based on T1-weighted MRI scans before and after injection of a gadolinium-based contrast agent and T2-weighted-fluid-attenuated inversion recovery scans. In brief, the following growth patterns were considered.

- Local: one contiguous contrast-enhancing (CE) lesion site.
- Multifocal: at least 2 non-contiguous CE lesion sites with intervening areas of normal brain signals.
- Distant (assessment held only at recurrence): one single new CE or non-CE lesion, occurring beyond a 3 cm radius from the primary tumor margin and being non-contiguous to it.
- Diffuse: when the signal on FLAIR images extended diffusely at least 2 cm beyond the CE area. In the event of multiple lesions, any lesion meeting the definition of

diffuse was sufficient for the pattern to be categorized as diffuse.
- Non-diffuse: lesions not meeting the definition of diffuse were classified as non-diffuse.

Statistics

To estimate the survival function from lifetime data, we used the Kaplan–Meier estimator. For PFS, the event of interest was the time from latest MRI-defined recurrence before regorafenib onset until the next MRI, indicating repeat recurrence, while under regorafenib treatment. For OS evaluation, the event of interest was the time from regorafenib treatment onset until death from any cause. If the patient had not died at the time of analysis (December 30, 2018), the patient was considered censored. For data visualization, Stata (release 14.0; StataCorp LP) and R (version 3.3.1; The R Foundation for Statistical Computing) were employed.

Results

Patients' characteristics

A total of 6 patients met the selection criteria. Clinical characteristics are given in Table 1. Two of the six patients had anaplastic astrocytoma, whereas the remainder was diagnosed with glioblastoma. All six patients were in a good clinical performance status with Karnofsky Performance Status Indices ranging from 70 through 90%. Regorafenib treatment was initiated in half of the patients as third-line treatment; in the other half at a much later stage (Table 1). Patients were on regorafenib treatment for at least 4 weeks and maximally 14 weeks. It should be noted that half of the patients had additional tumor-directed treatment modalities during the same line of treatment as regorafenib, including tumor treating fields, D,L-methadone, and resection followed by radiotherapy. Intriguingly, as shown in Table 1, adverse events of CTCAE°3 occurred in all but one patient. The most vexing and debilitating adverse event was a treatment resistant hand–foot syndrome (Palmar-Plantar Erythrodysesthesia Syndrome CTCAE°3) in one patient that accounted for a severe reduction in quality of life until continuous treatment with opioid analgetics relieved the painful symptoms.

Treatment response

Treatment with regorafenib was associated with a particularly poor objective response with progressive disease evident on the first follow-up MRI while under regorafenib treatment in all patients. PFS was in the order of 2.0–4.0 months (Fig. 1a). PFS-6 was 0%. In those patients, in whom death had occurred at the time of analysis, OS (measured from the time of regorafenib treatment onset) was less than 6 months (5.2 and 5.6 months, Table 1). Notably, tumor size increased substantially on follow-up MRI as shown in the waterfall plot (Fig. 1b) with tumor sizes increasing up to fivefold in one patient. Exemplary images of a patient with a substantial tumor growth at recurrence on regorafenib are given in Fig. 2.

Tumor growth patterns

A local tumor growth was observed in almost all patients (5 of 6). In 4 out of 6 patients, there was no change in tumor growth pattern compared to the situation before regorafenib initiation. A diffuse growth pattern was observed in all patients. A change in growth pattern from a local to distant growth was observed in one patient only (Fig. 1c). Another patient changed from a local to multifocal growth pattern.

Discussion

Our retrospective study reveals that regorafenib at late-stage recurrence of high-grade astrocytoma shows a poor treatment response. Objective treatment response was not observed in any patient. In addition, a notable incidence of adverse events of CTCAE°3 was observed. The MRI growth patterns did not differ significantly from baseline to the time-point of tumor progression, indicating that regorafenib does not seem to induce an infiltrative tumor growth.

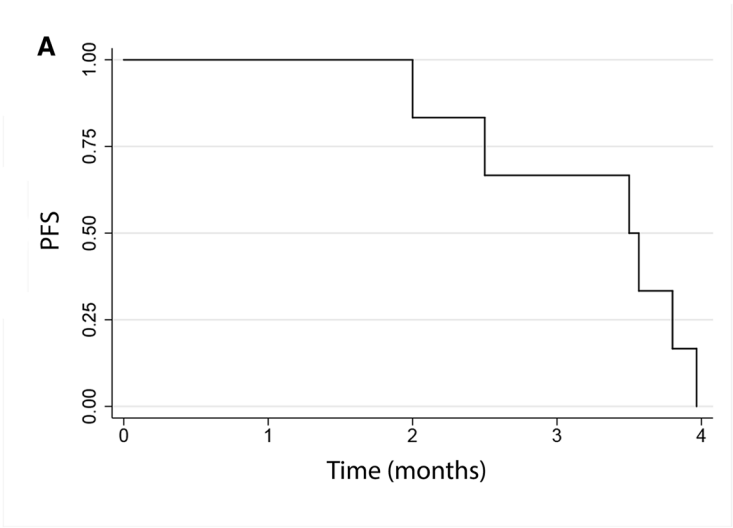
As PFS was defined as the time interval between the MRI immediately prior to regorafenib onset and the next MRI showing tumor progression, the duration of PFS is built on the investigator-selected MRI schedule and thus highly variable even when there is no objective radiographic response among patients. This explains why median PFS in our study (3.5 months) was formally higher—although within 95% confidence interval—compared to 2.0 months in the REGOMA trial (Lombardi et al. 2019). When comparing the objective response rates, however, there is a marked difference in our study as compared to the REGOMA trial, with disease control in 44% as compared to 0% in our study. This provocative finding might well be explained by the patients' heterogeneity in terms of tumor diagnosis (glioblastoma and anaplastic astrocytoma) in our cohort. Moreover, in our retrospective analysis, regorafenib was administered at a much later stage during the course of disease (number of prior recurrences were 2–6 at the time of regorafenib administration) and additional treatment modalities were mixed with regorafenib in some patients. Yet, the marked difference in overall response rate between our study and the REGOMA trial raises more doubts as to whether regorafenib is efficacious in high-grade astrocytoma. This is particularly important, since the rate of

Table 1 Patients' characteristics

Patient-ID	1	2	3	4	5	6
Gender	Male	Male	Female	Male	Female	Female
Age at tumor diagnosis (years)	69	18	38	56	38	63
Tumor diagnosis	Primary GBM IV°	Primary AA III°	Primary AA III°	Primary GBM IV°	Secondary GBM IV°	Primary GBM IV°
MGMT promoter	Not methylated	Methylated	Methylated	Methylated	Methylated	Not methylated
IDH1 status	Wild type	Wild type	Mutated	Wild type	Wild type	Wild type
1p19q codeletion status	Not determined	Wild type	Wild type	Not determined	Not determined	Not determined
Weeks on regorafenib treatment	8	4	14	10	9	8
Number of recurrences at first regorafenib treatment	4	6	3	2	2	2
KPS at onset of regorafenib treatment	70%	90%	70%	70%	80%	90%
Treatment prior to regorafenib	B, S, RTX + TMZ, TTF + TMZ; S, TTF + CCNU; EBL; S, BEV	S, RTX + TMZ, TMZ; S, TMZ; CYX, CCNU + TMZ	S, RTX + TMZ, TMZ; CCNU; S, TRO + ETO	S, RTX + TMZ, TMZ; CCNU; S, RTX	S, RTX + TMZ, TMZ; S, RTX + TMZ + CCNU + TTF	S, RTX + TMZ, TMZ; CCNU
Treatment concomitant to regorafenib	None	D,L-Methadone	None	S, RTX	TTF	None
Number of regorafenib courses	2	1	3	3	2	2
Regorafenib dosing schedule	160 mg, 21/28 days	160 mg, 21/28 days	160 mg, 21/28 days	160 mg, 21/28 days	160 mg, 21/28 days	160 mg, 21/28 days
Response to regorafenib	PD	PD	PD	PD	PD	PD
PFS (months) after regorafenib treatment	2.5	2.0	4.0	3.6	3.5	3.8
Toxicity while under regorafenib (≥ CTCAE°3)	Hypertension CTCAE°3	None	Palmar-plantar erythrodysesthesia syndrome CTCAE°3, hypothyroidism	Hypophosphatemia CTCAE°3	Hyperbilirubinemia CTCAE°3	Lipase increased CTCAE°3, decrease lymphocyte count CTCAE°3, UTI
OS after regorafenib treatment (months)	5.4*	6.7*	5.6	5.2	2.4*	3*

B biopsy, *BEV* bevacizumab, *CCNU* lomustine, *CTCAE* Common Terminology Criteria for Adverse Events, *CYX* Cyber Knife, *EBL* eribulin, *ETO* etoposide, *GTR* gross total resection, *IDH1* isocitrate dehydrogenase 1, *KPS* Karnofsky Performance Scale Index, *MGMT* O6-methylguanin–DNA–methyltransferase, *NTR* near total resection, *OS* overall survival, *PC* procarbazine + CCNU, *PD* progressive disease, *PFS* progression-free survival, *RTX* external beam radiotherapy, *TMZ* temozolomide, *TRO* trofosfamide, *TTF* tumor treating fields

*still alive



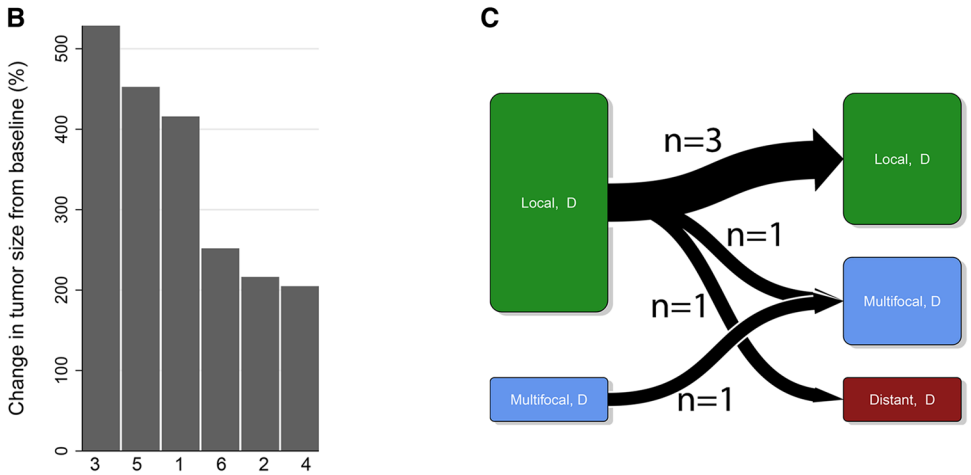


Fig. 1 **a** Progression-free survival. **b** Waterfall plot showing the change in tumor size (as measured according to RANO criteria) at follow-up MRI (contrast-enhanced T1) compared to baseline prior to regorafenib onset. **c** Transition plot visualizing how tumor growth pattern changed from baseline (before regorafenib) to recurrence (while under regorafenib). Distant tumor growth was induced in one patient only. Other than that local growth pattern was the dominant with no change at recurrence. *D* diffuse

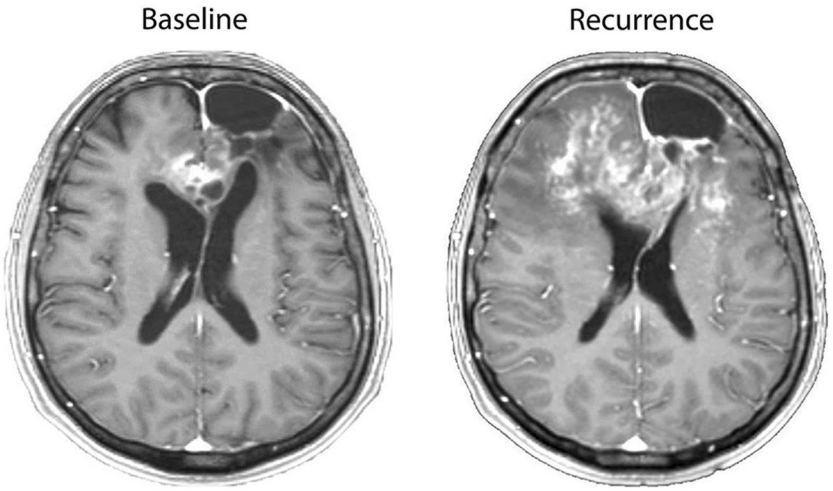


Fig. 2 Exemplary tumor recurrence on regorafenib treatment as evidenced on MRI (contrast-enhanced T1 sequence) is shown for a patient, where tumor size increased 453% as compared to baseline

adverse events was high with adverse events of grade 3 occurring in all but one patient, thereby calling into question of whether the risk of severe adverse events is balanced with the possible benefit in outcome. To answer these remaining questions, more confidently results of the upcoming phase 3 trial are needed.

As reported by some studies, antiangiogenic treatment might enhance diffuse and infiltrative tumor growth patterns (Norden et al. 2008), while other studies suggested otherwise (Wick et al. 2016; Schaub et al. 2018). Here, we could not observe regorafenib to induce altered tumor growth patterns. A distant tumor growth appeared in only 1 out of 6 patients. It is noteworthy to recognize that the criteria based on which tumor growth patterns are usually determined are predominantly based on contrast-enhancing T1 scans. This might make for some amount of imprecision, for example, when defining a local as opposed to multifocal tumor growth pattern in the presence of multifocal non-enhancing tumor sites. This scenario is most certainly rarely encountered, but, nonetheless, should be kept in mind. Certainly, more extensive research on a larger patient cohort is necessary to arrive at definite conclusions.

Shortcomings of this single-center experience are mainly the very small sample size and its retrospective nature that may account for some variability, particularly linked to the assessment of PFS. Due to a high rate of censoring, OS was not held informative enough to evaluate efficacy.

In conclusion, this retrospective study reflects a "real-life" single-center experience with the treatment of regorafenib as relapse chemotherapy in recurrent high-grade astrocytoma with multiple recurrences and reveals a complete lack in objective response to treatment, while adverse events were frequently encountered. In addition, regorafenib does not seem to promote infiltrative or distant tumor growth.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study, formal consent is not required.

References

Chinot OL, Wick W, MasonW et al (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370(8):709–722

Das S, Marsden PA (2013) Angiogenesis in glioblastoma. N Engl J Med 369(16):1561–1563

Gilbert MR, Dignam JJ, Armstrong TS et al (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370(8):699–708

Hundsberger T, Reardon DA, Wen PY (2017) Angiogenesis inhibitors in tackling recurrent glioblastoma. Expert Rev Anticancer Ther 17(6):507–515

Lombardi G, De Salvo GL, Brandes AA et al (2019) Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 20(1):110–119

Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131(6):803–820

Norden AD, Young GS, Setayesh K et al (2008) Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 70(10):779–787

Schaub C, Kebir S, Junold N et al (2018) Tumor growth patterns of MGMT-non-methylated glioblastoma in the randomized GLARIUS trial. J Cancer Res Clin Oncol 144(8):1581–1589

Uschner FE, Schueller F, Nikolova I et al (2018) The multikinase inhibitor regorafenib decreases angiogenesis and improves portal hypertension. Oncotarget 9(90):36220–36237

van den Bent MJ, Baumert B, Erridge SC et al (2017) Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet 390(10103):1645–1653

van den Bent MJ, Klein M, Smits M et al (2018) Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol 19(9):1170–1179

Weller M, van den Bent M, Tonn JC et al (2017) European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 18(6):e315–e329

Wen PY, Macdonald DR, Reardon DA et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28(11):1963–1972

Wick W, Chinot OL, Bendszus M et al (2016) Evaluation of pseudoprogression rates and tumor progression patterns in a phase III trial of bevacizumab plus radiotherapy/temozolomide for newly diagnosed glioblastoma. Neurooncology 18(10):1434–1441

Wick W, Gorlia T, Bendszus M et al (2017) Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 377(20):1954–1963