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Dramatic response to regorafenib in early glioblastoma progression: case report and review of the literature

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Abstract. – BACKGROUND: Glioblastoma (GBM) is a highly lethal disease despite integrated treatment comprising radiotherapy plus concomitant and adjuvant temozolomide, with a median overall survival of less than 15 months. For recurrent glioblastoma, there is yet no standard therapy, considering that Bevacizumab have failed to improve overall survival (OS) while regorafenib had a little benefit over standard chemotherapy. In addition, the disease control rate is almost exclusively stability, with a poor objective response rate.

CASE REPORT: Here we present a case of rapid response to regorafenib in early glioblastoma progression at the end of adjuvant radiotherapy: after a single cycle of regorafenib the patient observed an impressive improvement in clinical condition, disappearance of headaches and a clear reduction of neoplastic tissue in MRI. A brief review about new radiological patterns in Magnetic Resonance Imaging (MRI) related to the introduction in clinical practice of antiangiogenic drugs and tyrosine kinase inhibitors has also been carried out.

CONCLUSIONS: Regorafenib was certainly a first turning point in the second-line treatment of GBM, showing longer response rates and mostly disease stability than bevacizumab. A switch-maintenance strategy with tyrosine kinase inhibitors may represent a valid second-line therapeutic option.

Key Words:
Glioblastoma, Regorafenib, Radiotherapy, Magnetic resonance imaging, Surgery.

Introduction

The biology of glioblastoma (GBM) is extremely complex and certainly with few therapeutic implications in current clinical practice. As highlighted by The Cancer Genome Atlas (TCGA) Program three cell-signalling pathways are more frequently altered in GBM: the p53 pathway, the retinoblastoma pathway and the receptor tyrosine kinase signalling pathway (RTK)[1]. Further analyses by TCGA identified four molecular GBM subtypes: the mesenchymal subtype, expressing mutation or deletion of Neurofibromin 1 (NF1) and Phosphatase and Tensin Homolog (PTEN) tumor suppressor genes; the classical, linked to amplification and mutation of Epidermal Growth Factor Receptor (EGFR) or deletion of cyclin-dependent kinase inhibitors (CDKN2A and 2B); the neural, exhibiting EGFR amplification and PTEN deletions too; the proneural, displaying mutations or deletions of Platelet-Derived Growth Factor Receptor alpha (PDGFRA), p53 and Isocitrate Dehydrogenase 1 (IDH1)[2]. The complexity of GBM derives from coexistence of different subtypes in same areas of the tumor, coevolving during treatment and radiological progression, leading to unique cancer heterogeneity[3,4]: specifically, disease progression and therapy resistance seems to be predominantly related to mesenchymal phenotype[5].

Patient stratification based on target RTK expression is controversial in recurrent disease[6]. Indeed, it is nowadays clear that this setting is clinically, radiologically and molecularly distinct from front-line one. First of all, blood-brain barrier (BBB) integrity has previously been disrupted by surgery, radiotherapy and chemotherapy[7]. Furthermore, DNA alkylating radiation may have induced double-strand breaks, and then, changed mutational profile of primary gliomas, as highli-

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ghted by analysis of post-radiation occurring high-grade astrocytoma showing an increased frequency of PDGFRA, MET Proto-Oncogene Receptor Tyrosine Kinase (MET), V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) amplifications and genomic aneuploidy compared to spontaneous high-grade gliomas[8,9]. Finally, as main hallmark of GBM, tumor-induced neoangiogenesis may be leakier and more disorganized than first-line setting[10].

The introduction into clinical practice of angiogenesis inhibitors has changed second-line therapy, however, revealing a critical point in the assessment of disease progression[11]. Since neo-vasculature is inhibited, magnetic resonance imaging (MRI) could detect a rapid decrease in tumor enhancement; nevertheless, a large proportion of patients may exhibit a diffuse infiltrating non-enhancing tumor progression at second or even first radiological evaluation, known as atypical pseudoresponse, suggesting that antiangiogenic therapy may select an aggressive phenotype in GBM heterogeneity[11].

Nowosielski et al[11] firstly performed a retrospective analysis about MRI follow-up in patients treated with bevacizumab, classifying four progression patterns: primary non-responders, with no decrease in contrast enhancement (CE) or development of new lesions at first follow-up imaging; T1 flare-up progression, an initial decrease at first evaluation, and then, subsequent flare-up of CE at progression; T2 circumscribed progression without new CE; T2-diffuse progression without new or only speckled CE. Due to this phenomenon, traditional dimensional assessment of target enhanced lesions, the Macdonald criteria, were found to be inadequate, and then, integrated by the international working party Response Assessment in Neuro-Oncology (RANO), including T2/fluid attenuated inversion recovery (FLAIR) abnormalities as an additional marker for tumor progression in MRI. RANO criteria did not establish a cut-off for the definition of progressive disease of non-enhancing lesions in T2/FLAIR sequences, however, a ≥25% increase may be likely considered a putative cut-off of progressive disease (PD)[12].

Regorafenib, an orally multi-kinases inhibitor, has preclinically demonstrated an inhibition of glioblastoma growth in tumor xenografts[13], targeting tumor angiogenesis (Vascular Endothelial Growth Factor Receptor, VEGFR 1-3), oncogenesis (MET, RET and BRAF genes), tumor microenvironment (PDGFR and Fibroblast Growth Factor Receptor, FGFR), and immunity (Colony-Stimulating Factor 1 Receptor, CSF-1R), nevertheless, the role of RTK inhibitors is controversial in GBM treatment[14]. Firstly, they usually affect the activity of more than eight different kinases and this lack of specificity may lead to the activation of compensation mechanisms, a dilution of driver kinases and an increased systemic toxicity that limit treatment duration and efficacy[15]. Secondly, the BBB may filter the entry of drugs through active transport regulated by ATP-binding cassette efflux pumps located within vessel walls, whose most common transporters are P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)[16]. Thirdly, pharmacological interference with metabolic inducers and inhibitors may compromise the effectiveness of treatment[17].

Here we describe an extremely particular case highlighting a rapid and dramatic radiological and clinical response after two months of regorafenib in a patient affected by glioblastoma, with an early PD occurring at the end of adjuvant radiotherapy plus concomitant temozolomide.

Case Report

A 61-year-old woman was admitted to our emergency department at the end of June 2021 due to seizures, with a history of headache lasting for 15 days. Brain MRI scans described an expansive lesion of about 61 mm of maximum diameter in the right temporo-insular lobe, with diffuse perilesional digitiform edema, concomitant contralateral shift of the midline and compression of the right lateral ventricle (Figure 1A). Urgent surgical resection of the lesion was performed, and histopathological examination revealed a wild-type IDH1 GBM. Tumor cells were negative for O-6-methylguanine-DNAmethyltransferase (MGMT) status by methylation-specific Polymerase Chain Reaction (PCR). A 48-h postoperative MRI confirmed no residual disease. Adjuvant radiotherapy for a total of 60 Gy in 30 fractions over 6 weeks with concurrent temozolomide (75 mg/m^2 daily) followed by 6 adjuvant cycles of temozolomide (200 mg/m^2, days 1-5, every 28 days) was administered. Nevertheless, at the end of radiotherapy the patient had a progressive worsening of headache, poorly controlled with steroids, and performance status so an urgent follow-up MRI was performed highlighting volumetric increase of neoplastic tissue with clear peripheral vascularization in right temporal lobe and internal capsule. A significant increase of perilesional edema and shift of the right lateral ventricle was

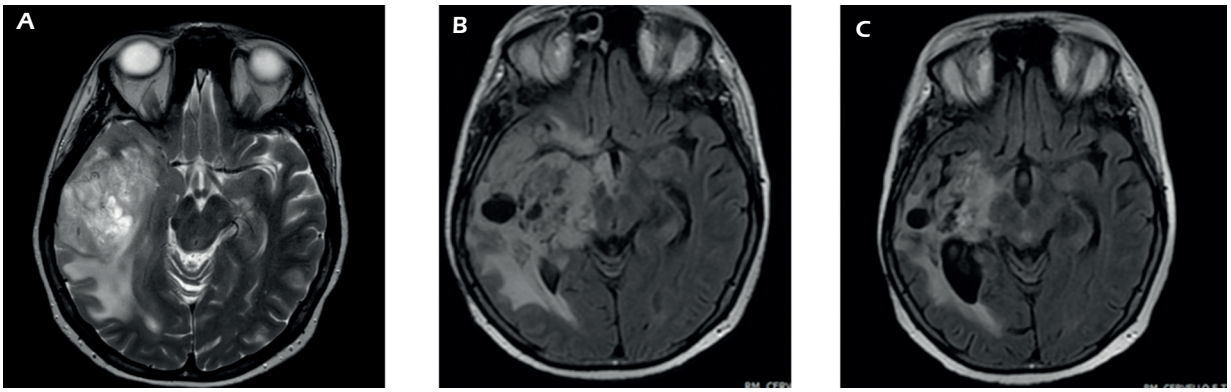

Figure 1. MRI before surgery, describing an expansive lesion in the right temporo-insular lobe, with diffuse perilesional digitiform edema, concomitant contralateral shift of the midline and compression of the right lateral ventricle **(A)**; MRI at the end of radiotherapy, highlighting volumetric increase of neoplastic tissue with clear peripheral vascularization and a significant increase of perilesional edema **(B)**; MRI after two months of regorafenib, reporting a clear reduction of neoplastic tissue in the right temporal site, no edema, and median line in axis **(C)**.

reported (Figure 1B). A second-line treatment with regorafenib 120 mg/day for three of every four weeks was immediately undertaken, increased after 2 weeks to 160 mg/day due to good tolerability. After a single cycle, the patient revealed an impressive improvement in clinical condition, with the disappearance of headaches. At 2 months MRI was repeated, describing a clear reduction of neoplastic tissue in the right temporal site, with no evidence of previously reported edema, and median line in axis (Figure 1C). Treatment is still ongoing.

Discussion

First clinical evidence regarding efficacy of regorafenib in recurrent glioblastoma date back to the recent REGOMA multicenter Italian phase II trial, assigning 59 patients to receive regorafenib and 60 patients to lomustine, showing an encouraging overall survival benefit of 7.4 months with regorafenib *vs.* 5.6 months of lomustine and a Disease Control Rate (DCR) of 44 % (*vs.* 20%) according to RANO criteria, most of all stable disease (39%) and partial response (3%)[18]. A subsequent health-related quality of life evaluation assessed no significant changes during regorafenib treatment rather than chemotherapy[19]. Surely, this study has numerous biases, including a not perfect balance between two arms regarding steroid use, MGMT methylation status and time to relapse. In addition, Lomustine arm performs worse than historical pivotal trials. Finally, another potential limitation is the absence of an independent and central neuroradiology and histopathology review[18]. On the same wavelength, Tzaridis et al[20] conducted a bi-centre retrospective analysis on 24 patients, showing a partial response in 3 patients (13%) and stable disease in 3 patients (13%) according to RANO criteria, with a median OS of 4.1 months in whole cohort. These results, overall, were lower than REGOMA trial, probably having selected a more heavily pre-treated population at a more advanced stage of the disease[20]. Patients who have experienced hand-foot reaction appear to have better OS, 6.7 months *vs.* 2.6 months, implying a greater biological activity of the drug[20]. Analogously, Zeiner et al[21] evaluated efficacy of regorafenib in 21 patients affected by GBM in second-line setting obtaining a DCR of 10%, poorer than Tzaridis experience. Nevertheless, a more recent and wide monocentric real-life study carried out by Lombardi et al[20], analyzing the efficacy of second line regorafenib in 54 patients, demonstrated a median overall survival of 10.2 months, a median progression-free survival (PFS) of 2.3 months, a partial response rate of 7.4% and DCR of 38.9%, similar to REGOMA trial. Interestingly, patients with response or stable disease achieved a median overall survival of 24.8 months, much better than Zeiner and Tzaridis analyses[22] (Table I). Certainly, selection of patients greatly affects these conflicting results, considering that performance status, use of corticosteroids, symptomaticity, and molecular biology of the disease are not perfectly comparable in all previous experiences[22]. In addition, patients recruited were few; therefore, a phase III trial (NCT03970447*)* or a real word-life experience (IOV-GB-1-2020 RE-

Table I. Overview of clinical experience of regorafenib in second-line setting.

Authors	Number of patients	Results
Lombardi et al[18] (REGOMA PHASE II TRIAL), 2019	59	mOS: 7.4 months; DCR: 44%; SD: 39%; PR: 3%
Tzaridis et al[20], 2019	24	PR: 13%; SD: 13%; mOS: 4.1 months
Zeiner et al[21], 2019	21	DCR: 10%
Lombardi et al[19], 2021	54	mOS: 10.2 months; PR: 7.4 %; DCR: 38,9 %

Abbreviations: mOS, median Overall Survival; DCR: Disease Control Rate; PR: Partial Response; SD: Stable Disease.

GOMA-OSS) may afterwards direct the right therapeutic choice, even integrating molecular profiling. In fact, a subgroup genomic classification of REGOMA trial reported that elevated expression levels of Hypoxia-Inducible Factor 1 alpha (HIF1A) mRNA and CDKN1A mRNA, as well as reduced expression of miRNAs miR-93-5p, miR-3607-3p, and miR-301a-3p in tumor tissue at first surgery are capable of identifying a subgroup of patients treated with regorafenib with favorable benefit (mOS ranging from 10.6 to 20.8 months)[23]. Likewise, further analyses of REGOMA trial[24] have revealed that AMPK pathway activation is linked to clinical benefit in relapsed GBM, with a median OS of 9.3 months.

Targeted therapies, as well as antiangiogenic treatments are biologically active, inducing a decrease in CE and T2 hyperintense edema in 88% of patients[25]. As pointed out, specific MRI patterns have requested a revision of response assessment in RANO criteria, including non-enhancing T2/FLAIR lesions as a new criterion for glioma progression[12]. Moving beyond Nowosielsky classification, controversially discussed imaging features on antiangiogenic therapy are the "stroke-like" diffusion-weighted imaging (DWI) restrictions within glioblastomas, with dubious prognostic value[26,27]. Analogously to bevacizumab, distinct MRI alterations were observed in half of patients treated with regorafenib too, as described by Zeiner et al[21]. A reduction of CE despite a progression of non-enhancing tumor lesions was reported in 11 patients with a T2-dominant growth pattern, partially resembled MRI features highlighted during Bevacizumab treatment, showing a significantly better median Overall Survival than primary non-responders (27 weeks *vs.* 10 weeks). No "stroke-like" DWI restrictions were observed while a reduction of peritumoral edema was clinically evaluated in 28% of patients, with a worse steroid sparing effect than Bevacizumab[21]. In the same way Gatto et al[28] described a distinct "T2-FLAIR dominant" MRI pattern of pseudoresponse in a case of recurrent GBM treated with regorafenib, partially resembling the typical MRI feature largely described for bevacizumab treatment, which preceded of about three months the detection of radiological disease progression established with classic Macdonald assessment.

However, also RANO criteria have weaknesses: main critical issue is differential diagnosis between non-enhancing progressive tumor and other causes of hyperintensity in T2-FLAIR sequences, such as vasogenic edema, leukoencephalopathies and microvascular ischemic spots. Functional assessment with Advanced MRI sequences like DWI, MR spectroscopy for the analysis of variations in N-acetylaspartate or choline peaks, and perfusion-weighted imaging as functional evaluation of tumors may overcome the problem[25]. Also, Positron Emission Tomography (PET) using O-(2-[18F]-fluoroethyl)-L-tyrosine (FET) may represent a valuable tool for response assessment in GBM during antiangiogenic treatment, able to discriminate response, pseudoresponse or even pseudoprogression, as shown in small case series[29,30]. Radiologically, our case presents marked reduction of perilesional edema, CE and simultaneous dimensional reduction of neoplastic tissue with appearance of necrosis, showing the classic signs of response in MRI according to RANO. Clinically, the patient had a marked improvement in headache, rapidly tapering steroids and quickly regaining her daily autonomy.

Prognostically the progression at the end of radiotherapy is extremely unfavorable, however, a rapid shift of systemic treatment has quickly determined a clinical and radiological response, rarely described in literature; in fact, although the DCR in REGOMA trial and retrospective analyses ranges between 10% and 40%, the ORR is still less than 3% and clinical benefit low. Pro-

bably, considering tardive biological effects of RT, Regorafenib has enhanced radiosensitivity of GBM by inhibiting the expression of multiple receptor tyrosine kinases, VEGF-mediated angiogenesis and DNA damage response. Surely, the GBM AGILE trial (NCT03970447) evaluating a switch-maintenance strategy with regorafenib after induction with RT plus temozolomide, could provide us a first response.

Conclusions

Despite current research on antiangiogenic treatment and tyrosine kinase inhibitors, short-term benefits are unfortunately observed. Regorafenib was certainly a first turning point in the second-line treatment of GBM, showing longer response rates than bevacizumab albeit with slower symptomatic control, lower objective response rate and mostly disease stability. Acquiring clinical, radiological and molecular predictive markers of response are definitely the future, in such a way as to establish the correct therapeutic sequence among currently available drugs, maybe anticipating regorafenib in up-front setting with definitive or adjuvant radiotherapy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

We declare that written informed consent was obtained from the patient for the publication of this case report.

Authors' Contribution

All the authors equally contribute to writing this work.

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