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Regorafenib in glioblastoma recurrence: A case report

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ABSTRACT

GBM (glioblastoma multiforme) is the most common and aggressive brain tumor. To date, treatment options for glioblastoma recurrence are lacking. Recently, REGOMA trial showed the superiority of regorafenib to lomustine in patients with first glioblastoma recurrence. We report an excellent response to three months treatment with regorafenib, in a patient who presented a rapid progression after the end of post operative radio-chemotherapy and after only one cycle of adjuvant TMZ (Temozolomide).

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary tumor in central nervous system (CNS), associated with poor prognosis despite treatments and with a high risk of progression or recurrence . Surgery, followed by radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ) is the standard of care for newly diagnosed GBM. These multimodal approach is associated with a median overall survival (OS) of less than 24 months [1] and relapse occurs in over 75% of patients, with a median time interval of 8 months . At recurrence, no standard treatment exists; options include re-operation, re-irradiation, systemic therapy, alone or in combination. As currently, there are no guidelines to facilitate decisions in the recurrent setting. Recently a randomised, multicentre, open-label phase 2 trial done in ten italian centres was published (REGOMA trial). Patients with documented disease progression after surgery followed by RT and TMZ were randomly assigned to receive regorafenib (REG) 160 mg once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m2 once every 6 weeks. At the median follow-up of 15·4 months the median OS was significantly improved in the regorafenib group compared with the lomustine group (median OS 7.4 and 5.6, respectively). Overall, REGOMA trial showed an encouraging overall survival benefit of regorafenib in recurrent GBM, with acceptable toxicity; treatment-related adverse events occurred in 56% and 40%, respectively [2].

Regorafenib (Stivarga) is an inhibitor of several kinases involved in the mechanisms that regulate neoangiogenesis processes, through the inhibition vascular endothelial growth factor (VEGF) receptors and the modifications of the tumor microenvironment. In December 2019, Regorafenib has been inserted in the list of medicines that can be paid by the National Health Service for the treatment of the first relapse of glioblastoma, after adjuvant treatment with RT and chemotherapy with TMZ. The progression disease (PD) (according to the RANO criteria) should be at least 12 weeks after the completion of the RT (unless the recurrence has occurred outside of radiation field or has been histologically documented).

In the current manuscript, we report our experience with regorafenib, administered in a patient who developed rapid progression after the end of postoperative radio chemotherapy treatment and after a single cycle of adjuvant TMZ, showing excellent response after three months of therapy.

Case report

A 60-year-old male presented with a 2-month history seizures, invastigated at October 2019 with a Magnetic Resonance Imaging (MRI) showing a 7.1 × 5.1 × 5.1 cm mass in the left frontal lobe (Fig. 1A). He underwent a craniotomy excision of the lesion. The histopathological examination was compatible with the diagnosis of GBM. Molecolar testing was significant fore the presence of methylation of MGMT promoter. The post-operative MRI showed a residual disease and the appearance of a new nodularity of about 7 mm in the ipsilateral basal

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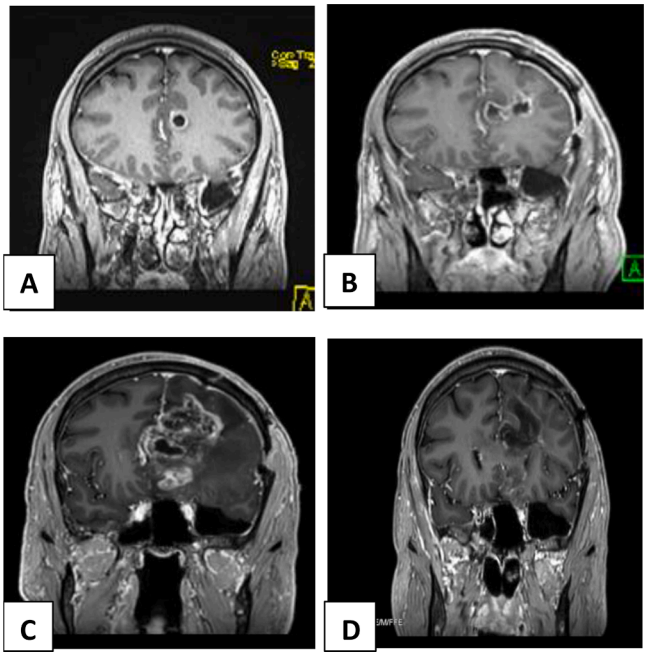

Fig. 1. MRI findings of the tumor. (A) Coronal gadolinium contrast-enhanced T1-weighted MR images obtained at the time of diagnosis, (B) post surgery, (C) after 1 cycle of adjuvant Temozolomide, (D) after 3 months with Regorafenib.

frontal site (Fig. 1B). Based on these results, from December 2019 to January 2020 yhe patient was given postopertive RT the for a total dose of 60 Gy in 30 fractions, with multiple noncoplanar dynamic arc, in combination with TMZ at the dose of 75 mg/mq (140 mg/day), according to the STUPP regimen [1]. At February 2020 he started adjuvant TMZ at the initial dose of 280 mg/day; only one cycle was administered, since a new MRI was required due to progressive clinical deterioration. MRI imaging showed a large signal alteration area in cortico-subcortical left frontal site (55 × 42 × 60 mm) characterized by inhomogeneous contrasting uptake due to the presence of intralesional colliquation areas. Signal alteration is associated, in the T2-weighted sequences, with a mixed edemogenic/infiltrative nature, at left front-insular site extended to the head of the caudate, to the anterior arm of the left internal capsule and to the knee of the corpus callosum with consequent tendency to involvement of the contralateral hemisphere. The findings described determine mass marks on the frontal horns and the middle cells of both lateral ventricles, with a shift of the median line to the right in the frontal seat of about 8 mm (Fig. 1C).

After 8 weeks from completion of RT, treatment with Regorafenib was started at 160 mg/day (three weeks on and one week off). Blood count and chemistry panel were obtained every 2 weeks for the first two cycles, neurological assessment and examination every 4 weeks. No side effect was reported. A new brain MRI after 4 months of therapy, in June 2020, demonstrated an important reduction in the size of the lesion in the frontal subcortical cortical site, a substantial reduction of enhancement in its context and also a reduction of the signal alteration in the T2 sequences (Fig. 1D and Fig. 2). MRI tumor assessments were 2-dimensional and made according to Macdonald criteria. An excellent clinical response is also noted shortly after the beginning of therapy, with resolution of symptoms previously described. Patient is fine and still on regorafenib.

Discussion

GBM is a vascularised tumor, characterised by high level of expression of VEGF and other proangiogenic cytokines and receptors. From this observation the rationale for using antiangiogenic drugs. Bevacizumab, an antibody that blocks VEGF-A ligand binding to VEGFR is approved in the USA for the treatment of recurrent GBM, based on trials showing an improvement in PFS compared with nitrosourea-based treatment; however, Bevacizumab, alone or in combination with chemotherapy did not prolong OS in the setting of GBM recurrence. Recently, in preclinical study, a new target anti-angiogenic therapy was

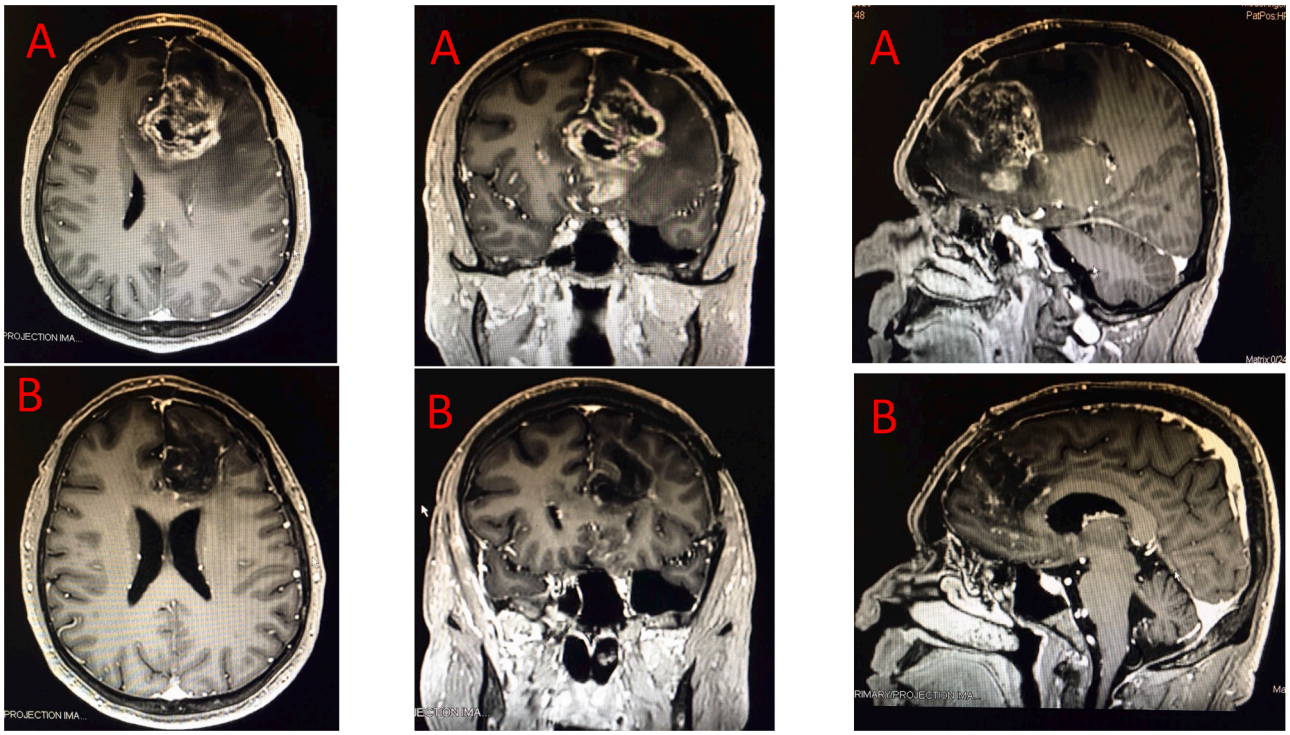

Fig. 2. Comparison of T1- weighted axial, coronal and sagittal MRI before (A) and after treatment (B) with regorafenib.

evaluated, Regorafenib. REG is approved as monotherapy by the US Food and Drug Administration and the European Medical Agency for the treatment of metastatic colorectal cancer, gastrointestinal stromal tumours, and hepatocellular carcinoma. The REGOMA study showed a substantial benefit in both PFS and OS of Regorafenib when compared with lomustine at glioblastoma recurrence.

Kebri et al., in a retrospective analysis of patients with high grade astrocytoma treated with Regorafenib, reported a PFS of only 3.5 months; patients rapidly progressed during the therapy and developed a high rate of grade G3 toxicity. However, the trial enrolled patients with different histology and regorafenib was administered at a much later stage during the course of disease (number of prior recurrences were 2–6), mixed with and additional treatment modalities in some patients [4].

Zainer et al., analyzed, in a retrospective study, the Regorafenib kinetic and the correlation between the radiological characteristics and the type of response. In particular, two different MRI growth patterns under REG treatment were identified: classic PD and a T2-dominant growth pattern. The occurrence of a T2-dominant MRI growth pattern was associated with a significantly better median OS in contrast to patients with a classic PD pattern (27 vs 10 weeks, respectively). Overall, treatment response was poor, with a median OS from initiation of REG of 14 weeks; however, also in this case, patients considered had different histologies and received Regorafenib after other treatment lines. Authors identified a distinct MRI pattern that might be associated with an improved OS in half of the patient cohort [3].

In our case Regorafenib was administered early, two months after the end of RT, for rapid progression desease. We reported an excellent clinical and radiological response after only three cycles of Regorafenib, and without development of side effects.

Conclusion

In conclusion, Regorafenib drug might be a new potential treatment option for recurrent glioblastoma. Phase 3 study should be performed in an adequately powered population to identify predictive response factors and thus select the patients who could find the greatest benefit.

Compliance with ethical standards

The Authors disclouse no potential conflict of interest.

All patients gave informed written consent for using clinical data.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R. Stupp, W.P. Mason, M.J. Van den Bent, et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. (2005). https://doi.org/10.1056/NEJMoa043330.

[2] G. Lombardi, G.L. De Salvo, A.A. Brandes, M. Eoli, R. Ruda, M. Faedi, I. Lolli, A. Pace, B. Daniele, F. Pasqualetti, et al., Regorafenib compared with lomustine in patients with relapsed glioblastoma(REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial, Lancet Oncol (2019), https://doi.org/10.1016/S1470204518)30675-2.

[3] P.S. Zeiner, M. Kinzig, I. Divé, G.D. Maurer, Filipski, P.N. Harter, C. Senft, O. Bähr Elke Hattingen, J.P. Joachim, F.S.M. Martin Voss Eike Steidl, M.W. Ronellenfitsch, Regorafenib CSF Penetration, Efficacy, and MRI Patterns in Recurrent Malignant Glioma Patients, J. Clinical Med. (2019), https://doi.org/10.3390/jcm8122031.

[4] S. Kebir, L. Rauschenbach, A. Radbruch, L. Lazaridis, T. Schmidt, A.K. Stoppek, D. Pierscianek, M. Stuschke, M. Forsting, U. Sure, et al., Regorefenib in patients with recurrent high-grade astrocytoma, J. Cancer Res. Clin. Oncol. (2019), https://doi.org/10.1007/s00432-019-02868-5.