Multimodal imaging findings in patients with glioblastoma with extensive coagulative necrosis related to regorafenib

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Keywords

FET PET; PWI; DWI; glioma; bevacizumab

The prospective phase 2 REGOMA trial suggested considerable survival benefits of the oral multikinase inhibitor regorafenib for treating patients with recurrent glioblastoma [1]. For response assessment, the criteria of the Response Assessment in Neuro-Oncology (RANO) Working Group for anatomical MRI are used in daily routine and clinical trials [2]. Nevertheless, anatomical MRI may present inconclusive findings related to its limited specificity for neoplastic tissue [3,4]. Accordingly, similar to glioma patients treated with standard chemoradiation using alkylating agents, equivocal MRI findings were also reported in glioma patients treated with regorafenib at recurrence [5-7].

It has been suggested that amino acid PET using *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) or 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) may help to identify treatment-related changes such as pseudoresponse or pseudoprogression, and to assess response to regorafenib [5-7]. In addition, perfusion-weighted MRI (PWI) and diffusion-weighted MRI (DWI), including the apparent diffusion coefficient (ADC), may also be of value in diagnosing treatment-related changes after regorafenib initiation [8].

Here, we report on ill-defining MR imaging findings of three patients with recurrent IDH-wildtype glioblastoma (age range, 43-63 years) treated with regorafenib, which are hitherto not well characterized and challenging to interpret. During treatment, all patients developed imaging correlates of an extensive necrosis with a contrast-enhancing rim on serial MRI. Besides the manifestation of the contrast-enhancing rim as a potential sign of tumor progression, restricted diffusion combined with partially low and decreasing ADC values suggested increased cellularity related to neoplastic tissue rather than necrosis. In contrast, the relative cerebral blood volume on PWI was equal to zero and markedly extensive photopenic defects on FET PET suggested treatment-

related effects such as necrosis. In line with treatment-related effects, all three patients who developed these imaging findings showed a considerably longer post-progression overall survival (range, 7.8-27.3 months) after initiation of regorafenib. Discrepancies in MRI and FET PET prompted a stereotactic biopsy in one patient, revealing reactive changes consistent with coagulative necrosis lacking vital tumor cells (Figure). At last follow-up, this patient was still alive after 13.4 months and 10 cycles of regorafenib, whereas after initiation of regorafenib the other patients died after 7.8 and 27.3 months, respectively.

Several reports have already suggested that the occurrence of coagulative necrosis in tumoral regions with restricted diffusion and hypovascularity on PWI is closely related to the use of bevacizumab [9,10]. Our observations suggest that the use of regorafenib may also induce a coagulative necrosis with restricted diffusion and hypovascularity. It is important to point out that regorafenib not only targets the vascular endothelial growth factor pathway like bevacizumab, but additionally inhibits several other targets such as the angiopoietin-1 receptor, proto-oncogene c-Kit, Ret proto-oncogene, Raf-1 proto-oncogene, fibroblast growth factor receptor, and BRAF [1]. Thus, a quite similar constellation of MRI findings and neuropathology following bevacizumab could not necessarily be expected from regorafenib.

As described for glioma patients treated with bevacizumab [9], multimodal imaging including PWI, DWI, and FET PET may also help to characterize lesions induced by regorafenib, which are not consistent with aggressive tumor. In addition, advanced MRI and amino acid PET may be useful to identify patients undergoing antiangiogenic therapy with decreased overall survival characterized by progressing diffusion restriction on DWI and coagulative necrosis surrounded by viable tumor [10].

In summary, the development of extensive necrosis with a contrast-enhancing rim related to regorafenib appears to be of considerable clinical relevance as it may be misdiagnosed as tumor progression by anatomical MRI alone. Additional imaging using PWI, DWI, and FET PET may provide valuable information for identifying this phenomenon to avoid a premature termination of a potentially effective treatment. The latter is also relevant since clinical trials evaluating regorafenib, such as the REGOMA-2 trial, are currently ongoing.

Our preliminary observations warrant confirmation in further studies with more patients, preferably prospectively and with neuropathological confirmation.

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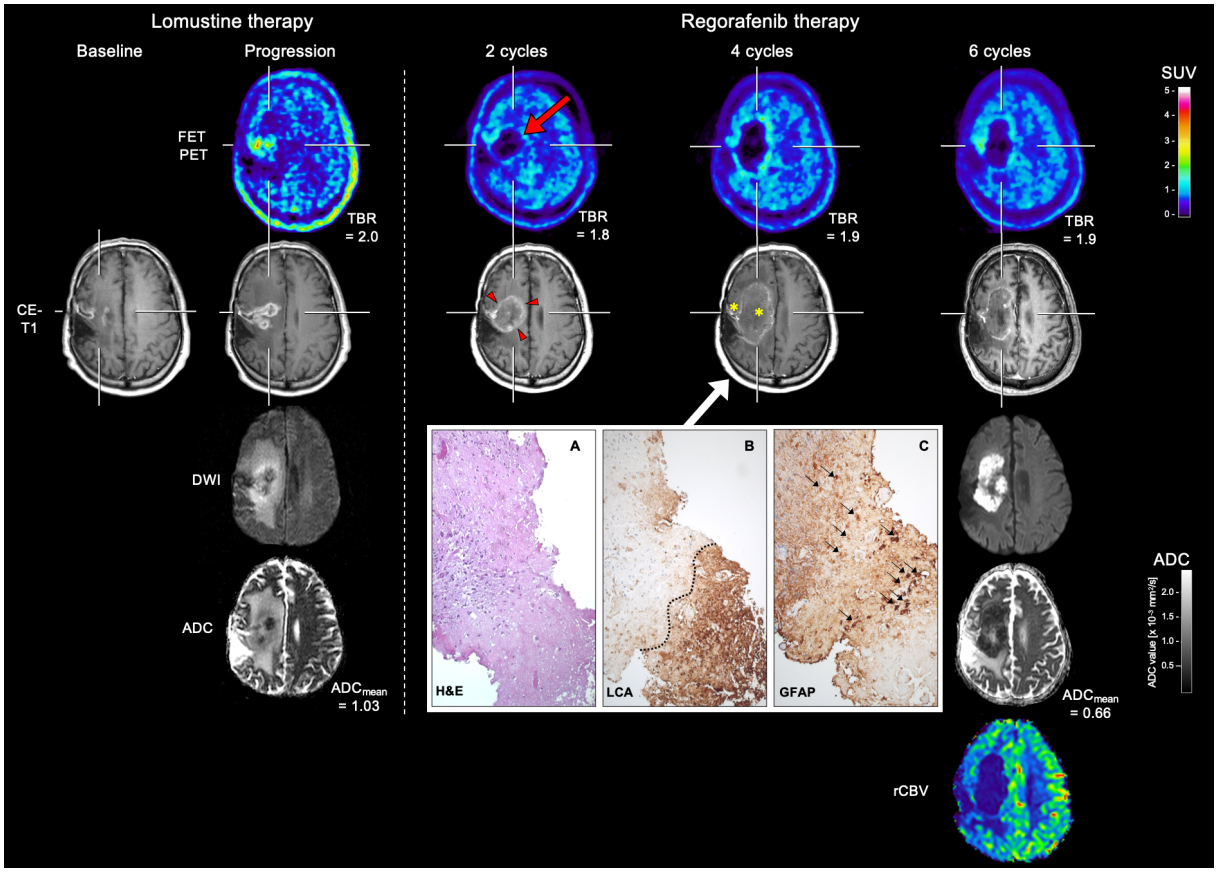
FIGURE LEGEND

Illustrative example of a 44-year-old male patient treated with regorafenib at progression under lomustine chemotherapy. After two cycles of regorafenib, the patient developed imaging signs of extensive necrosis with a contrast-enhancing rim (arrowheads). To further evaluate this finding as a potential sign of tumor progression, additional PWI and DWI were performed. The restricted diffusion combined with partially low and decreasing mean ADC values at follow-up compared to baseline suggested increased cellularity related to neoplastic tissue rather than necrosis. In contrast, the relative cerebral blood volume was equal to zero and the corresponding FET PET scan showed an extensive photopenic defect (red arrow) without pathologically increased metabolic activity (i.e., a mean tumor-to-brain ratio (TBR_{mean}) < 2.0), indicating a treatment-related effect. A stereotactic biopsy was performed after four regorafenib cycles to further evaluate these discrepant multimodal imaging findings (biopsy sites are marked with yellow asterisks). Neuropathological evaluation of the obtained tissue revealed predominantly an acellular coagulative necrosis (A; hematoxylin and eosin (H&E) staining). The necrosis harbors numerous leukocytes, predominantly attributed to foamy macrophages (B; dotted line between necrosis and reactive brain parenchyma; immunohistochemistry with mouse anti-LCA; DCS, Hamburg Germany). Note numerous reactive astrocytes (arrows) in the vital brain parenchyma without tumor cells (C; immunohistochemistry with mouse anti-GFAP; Biogenex, Hamburg, Germany; A-C, original magnification x100). At last follow-up, the patient was still alive after 13.4 months and 10 cycles of regorafenib.


Lomustine therapy
Regorafenib therapy
Baseline
Progression
2 cycles
4 cycles
6 cycles
FET PET
TBR = 2.0
TBR = 1.8
TBR = 1.9
TBR = 1.9
SUV
CE-T1
DWI
ADC
ADC$_{mean}$ = 1.03
A
B
C
H&E
LCA
GFAP
ADC
ADC value [x 10^{-3} mm^2/s]
ADC$_{mean}$ = 0.66
rCBV