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Imaging biomarkers guided anti-angiogenic therapy for malignant gliomas

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ABSTRACT

Antiangiogenic therapy is a universal approach to the treatment of malignant gliomas but fails to prolong the overall survival of newly diagnosed or recurrent glioblastoma patients. Imaging biomarkers are quantitative imaging parameters capable of objectively describing biological processes, pathological changes and treatment responses in some situations and have been utilized for outcome predictions of malignant gliomas in anti-angiogenic therapy. Advanced magnetic resonance imaging techniques (including perfusion-weighted imaging and diffusion-weighted imaging), positron emission computed tomography and magnetic resonance spectroscopy are imaging techniques that can be used to acquire imaging biomarkers, including the relative cerebral blood volume (rCBV), K^{trans}, and the apparent diffusion coefficient (ADC). Imaging indicators for a better prognosis when treating malignant gliomas with antiangiogenic therapy include the following: a lower pre- or post-treatment rCBV, less change in rCBV during treatment, a lower pre-treatment K^{trans}, a higher vascular normalization index during treatment, less change in arterio-venous overlap during treatment, lower pre-treatment ADC values for the lower peak, smaller ADC volume changes during treatment, and metabolic changes in glucose and phenylalanine. The investigation and utilization of these imaging markers may confront challenges, but may also promote further development of anti-angiogenic therapy. Despite considerable evidence, future prospective studies are critically needed to consolidate the current data and identify novel biomarkers.

1. Introduction

Glioma is the most common malignant primary central nervous system (CNS) tumor, with an annual incidence of 5.26 per 100,000 individuals (Omuro and DeAngelis, 2013). The management of glioma requires a combination of surgical excision, chemotherapy, radiotherapy and targeted therapy based on the histological and molecular features of the tumor (Jiang et al., 2016); however, the survival outcome remains poor. The median overall survival (OS) rates for low-grade gliomas (WHO grade II), anaplastic gliomas (WHO grade III) and glioblastomas (GBM, WHO IV) are 159, 96 and 16 months, respectively (Buckner et al., 2016; Wick et al., 2016; Gilbert et al., 2014; Chinot et al., 2014).

Angiogenesis, a hallmark of cancer (Hanahan and Weinberg, 2000),

Abbreviations: ^{18}F-FDOPA, 3,4-dihydroxy-6-[^{18}F]-fluoro-*l*-phenylalanine; ^{18}F-FLT, [^{18}F]-fluoro-3-deoxy-3-L-fluorothymidine; ADC, apparent diffusion coefficient; AVOL, arterio-venous overlap; BBB, blood brain barrier; CBF, cerebral blood flow; CBV, cerebral blood volume; CNS, central nervous system; CT, computed tomography; D-2HG, D-2-hydroxypentanedioic acid; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DSC-MRI, dynamic susceptibility contrast magnetic resonance imaging; DWI, diffusion-weighted imaging; FDG, fluorodeoxyglucose; fDMs, functional diffusion maps; FLAIR, fluid-attenuated inversion recovery; FSE pcASL, fast spin echo pseudocontinuous artery spin labeling; GBM, glioblastoma; K^{trans}, volume transfer constant between blood plasma and extravascular extracellular space; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; nGBM, newly diagnosed glioblastoma; OS, overall survival; PET, positron emission computed tomography; PFS, progression-free survival; PWI, perfusion-weighted imaging; RANO, Response Assessment in Neuro-Oncology; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rGBM, recurrent glioblastoma; ROI, region of interest; RSI, restriction spectrum imaging; SUV, standardized uptake value; TMZ, temozolomide; VAI, vessel architectural imaging; VEGF-A, vascular endothelial growth factor A; VNI, vascular normalization index.

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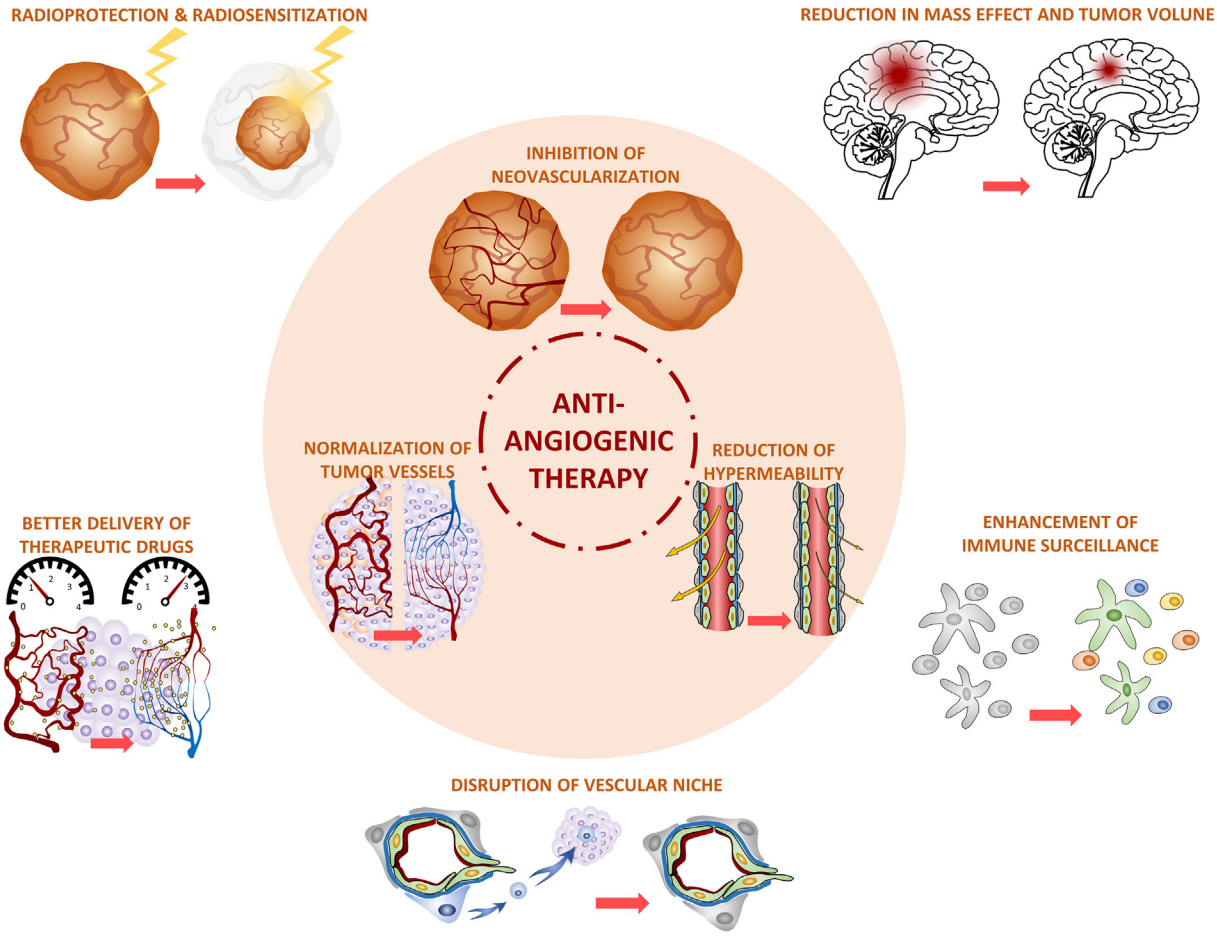

Fig. 1. Anti-tumor effects of anti-angiogenic therapy in gliomas.
The application of anti-angiogenic therapy in gliomas results in the inhibition of neovascularization, the normalization of tumor vessels, and a reduction in hyperpermeability, which bring about multiple clinical effects, including reduction in mass effect and tumor volume; the improved delivery of therapeutic drugs; radioprotection and radiosensitization; the disruption of the vascular niche; and the enhancement of immune surveillance.

occurs by sprouting angiogenesis, vasculogenesis, intussusception, co-opting preexisting vessels, vascular mimicry, or endothelial cells derived from cancer stem cells (Carmeliet and Jain, 2011). As a result of the universality of angiogenesis in most malignant gliomas (referring to WHO grade III and grade IV gliomas), anti-angiogenic therapy has become a critical approach in glioma therapy (anti-tumor effects of anti-angiogenic therapy in gliomas are displayed in Fig. 1). Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), was approved in 2009 for the treatment of recurrent GBM. Bevacizumab treatment has resulted in pharmacological debulking and volumetric reductions in 55% of patients with recurrent malignant gliomas, thereby leading to neurological palliation and increased progression-free survival (PFS) (Wong et al., 2011). Thus, bevacizumab is regarded as the first-line therapy for recurrent malignant gliomas in some institutes. However, bevacizumab combined with temozolomide (TMZ) and radiotherapy failed to demonstrate a significant improvement in the OS of patients with newly diagnosed glioblastoma (nGBM) in two large, multicenter, randomized, phase III clinical trials (RTOG0825 and AVAglio) (Gilbert et al., 2014; Chinot et al., 2014), and bevacizumab combined with lomustine did not provide an OS benefit over lomustine alone in recurrent glioblastoma (rGBM) patients (EORTC 26101 trial) (Wick et al., 2017). These findings suggest that the drug may not benefit all patient subsets (critical clinical trials investigating anti-angiogenic therapy in GBM are listed in Table 1). Thus, biomarkers for predicting the treatment effects and monitoring the treatment responses to anti-angiogenic therapy are urgently required. Several molecular biomarkers, such as the proneural subtype of GBM and the serum levels of MMP2 and MMP9, are correlated with the OS of patients undergone bevacizumab therapy (Sandmann et al., 2015; Tamura et al., 2017); however, use of these biomarkers has the following limitations: (1) continuous monitoring using tumor molecular markers is difficult because repeated sampling is impossible in solid tumors; (2) tumor molecular markers can hardly be obtained from patients without indications for surgery/biopsy, particularly when the detection method of circulating tumor cells and circulating DNA of glioma is not sophisticated; (3) molecular markers may not fully represent the whole tumor considering tumor heterogeneity; and (4) molecular markers of all types require distinct sampling, storage and testing techniques, which may be obstacles to implementation.

Imaging biomarkers are quantitative parameters that are mainly derived from computed tomography (CT), magnetic resonance imaging (MRI) or positron emission computed tomography (PET) and may be employed to objectively describe biological processes, pathological changes and treatment responses in different situations (White paper on imaging biomarkers, 2010). Imaging biomarkers have substantial clinical value in cancer management, namely, for detection, prediction, staging and treatment response assessment (White paper on imaging biomarkers, 2010). As a parallel type of marker, imaging biomarkers may compensate for the deficiencies in molecular biomarkers, thus providing a clinical basis for patient selection and therapeutic monitoring: (1) imaging can be acquired continuously to monitor therapeutic responses; (2) imaging biomarkers can be evaluated in patients without indications for surgery/biopsy given the noninvasiveness of imaging modalities; and (3) imaging can capture heterogeneity within

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