



Targeted therapy with anlotinib for a H3K27M mutation diffuse midline glioma patient with PDGFR- α mutation: a case report

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Abstract

H3K27M-mutant diffuse midline glioma (H3K27M-mt DMG) was a novel entity, which was defined by K27M mutations in H3F3A or HIST1H3B/C in the 2016 WHO updated fourth edition of the central nervous system (CNS) tumor classification. There is an urgent need for effective therapeutic strategies. Anlotinib is a multitarget tyrosine kinase inhibitor, which has not been reported for H3K27M-mt DMG treatment. Here, we firstly reported an adult multifocal H3K27M-mt DMG patient benefiting from anlotinib. This report provides a promising treatment option for H3K27M-mt DMG patients.

Keywords H3K27M mutation · Diffuse midline gliomas · Multitarget tyrosine kinase inhibitor · Anlotinib

Introduction

H3K27M-mutant diffuse midline glioma (H3K27M-mt, DMG) is a novel entity in the 2016 revised World Health Organization (WHO) classification of tumors of the central nervous system, which was described as “an infiltrative midline high-grade glioma with predominantly astrocytic differentiation and a K27M mutation in either H3F3A or HIST1H3B/C,” typically affecting children and young adults [6, 7]. These tumors mainly arise within thalamic, pontine, and spinal localization, which were challenging sites for surgical treatment. Because of its overall particularly dismal prognosis, H3K27M-mt DMGs were defined as WHO grade IV, no matter tumor histopathological features. Michael et al. reported 24 thalamus H3K27M-mt DMGs, whose median overall survival (OS) was 1.11 ± 0.14 years [4]. Despite ongoing clinical trials, chemotherapeutic options for DMG beyond standard radio-/chemotherapy with TMZ are sparse; hence, the prognosis remains dismal.

Anlotinib is a multitarget tyrosine kinase inhibitor that was originally designed to inhibit PDGFR- α/β , FGFR1–4,

VEGFR2/3, c-Kit, and Ret [9]. Anlotinib can inhibit both tumor angiogenesis and tumor cell growth. It has been used to treat advanced lung cancer [3]. Anlotinib is approved by the National Medical Products Administration for non-small cell lung cancer, small cell lung cancer, medullary thyroid cancer, and soft tissue sarcoma. Preclinical results showed that anlotinib significantly inhibited phosphorylated-PDGFR in U87MG cells [12].

H3K27M gliomas contain a majority of oligodendrocyte precursor cells (OPC) which remain in a state of rapid proliferation, fueling tumor growth, and sustained by PDGFR- α signaling [2].

However, the clinical application of anlotinib monotherapy or combination therapy in H3K27M-mt DMGs has not yet been reported. Herein, we firstly reported that an adult multifocal H3K27M-mt DMG patient with PDGFR- α mutation benefited from anlotinib adjuvant chemotherapy. Symptoms of the patient were stable for at least 21 months and the patient got good Karnofsky performance scale (KPS) scores during follow-up.

Case report

A 49-year-old woman was first admitted to our hospital as a new patient on January 3, 2020, complaining of repeated dizziness for 20 days. Magnetic resonance imaging (MRI) (December 23, 2019) revealed multiple space-occupying lesions in the bilateral thalamus and right cerebellum

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(Fig. 1). The patient underwent tumor gross total resection in the right cerebellum under general anesthesia on January 8, 2020. The immunohistochemical results showed that glial fibrillary acidic protein, Olig-2, ATRX, and S-100 were expressed; Neu-N and IDH-1 were negative; and the Ki-67 proliferation index was about 20%. Although the histological diagnosis was diffuse astrocytoma, IDH wild type, WHO grade II. The H3-K27M immunohistochemistry was strongly positive, which revealed the diagnosis of diffuse middle glioma with H3K27M mutation, WHO grade IV. Next-generation sequencing (NGS) for clinical whole-exome sequencing (CWES) profiling was performed using postoperative fresh tissue and H3F3A p.K28M (allele frequency, AF 56.52%), PDGFR- α p.D400H (AF, 89.80%), PDGFR- α amplification (9.90-fold) TP53 p.A347T (AF, 71.70%), and MET amplification (3.13-fold) were identified. O6-Methylguanine-DNA methyl-transferase promoter (MGMTp) methylation status was negative (0.51%).

The patient underwent three-dimensional conformal radiotherapy on March 3, 2020, because of the COVID-19 outbreak. Radiotherapy was 50 Gy/27fx (CTV) and 54 Gy/27fx (GTV) for bilateral thalamus and right cerebellum postoperative lesions and concurrent temozolomide (TMZ) chemotherapy (75 mg/m² per day). Six adjuvant TMZ cycles (200 mg/m² per day, every day, days 1–5, every 28 days for one cycle) (as Stupp protocol) were given to this patient, because of unmethylation MGMTp.

After three cycles of 200 mg/m² adjuvant TMZ chemotherapy, a brain MRI showed progress (progressive disease, PD) as the lesion in the left thalamus increased and the appearance of one new lesion in the right cerebellum

in T2-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) image. Contrary to imaging progress, the patient did not experience any new discomfort. Three months later, the brain MRI showed that the lesions in the left thalamus and right cerebellum continued to progress with gadolinium-enhancing T1 weighted (October 13, 2020). Anlotinib 10 mg p.o. every day (days 1–14, 21-day cycle) was added as adjuvant chemotherapy by our multidisciplinary team. After 2 months, brain MRI showed a partial response (PR) according to response assessment in neuro-oncology (RANO) standard, as bilateral thalamus and cerebellum lesions all decreased both in T2/T2-FLAIR and contrast-enhanced T1-weighted images. Then, on March 15, 2021, brain MRI images, the lesions were stable disease (SD). Three months later (June 28, 2021), the latest brain MRI images showed PD as a new abnormal increased T2 and T2-FLAIR signal in the right lateral side of the pons, while without symptom progression. The KPS scores were 90 during the whole treatment process. The timeline of treatment and radiographic responses was shown in Fig. 2.

No serious adverse reactions occurred during anlotinib treatment in this patient. The adverse reaction was grade 2 hand and foot syndrome.

Discussion

H3K27M-mt DMGs are WHO grade IV gliomas with a poor prognosis of a mean survival time of less than 1 year [8]. Despite the dismal prognosis of DMGs, there remains no evidence-based standard treatment protocol for H3K27M-mt

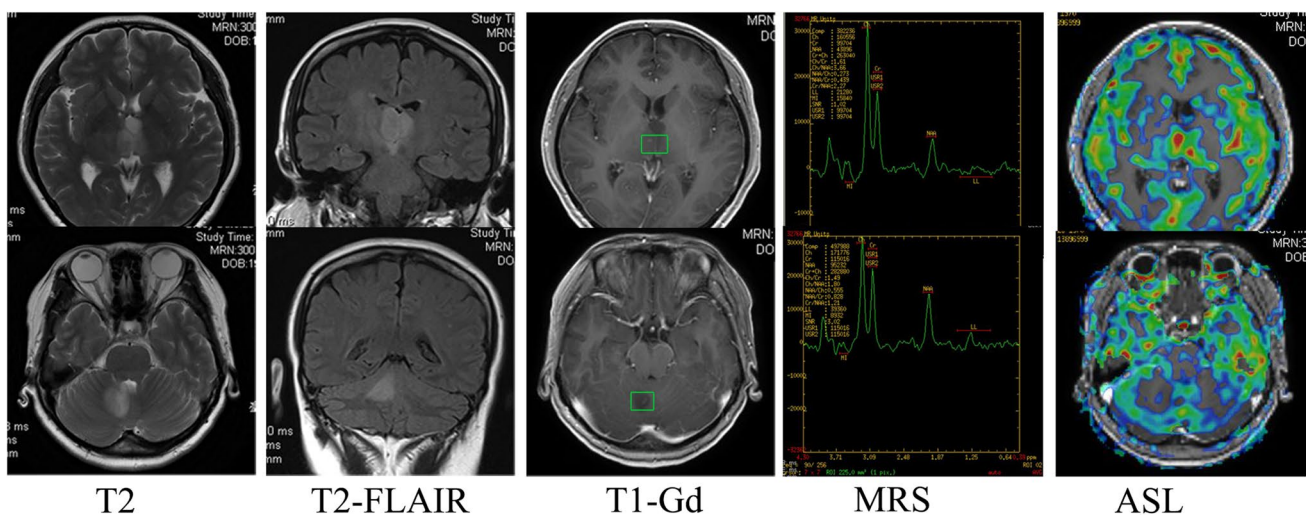


Fig. 1 Magnetic resonance imaging revealed multiple space-occupying lesions in the bilateral thalamus and right cerebellum. High signal intensity was on T2 and T2 FLAIR weighted images. Lesions showed slight punctate enhancement on contrast-enhanced T1-weighted images. MRS showed typical glioma features with decreased N-acetyl

aspartate (NAA) and increased choline (Cho) (Cho/NAA = 3.66, 1.80, respectively for bilateral thalamus and right cerebellum) (green box as region-of-interest (ROI)). Lesions did not present hyperperfusion using arterial spin-labeling (ASL)

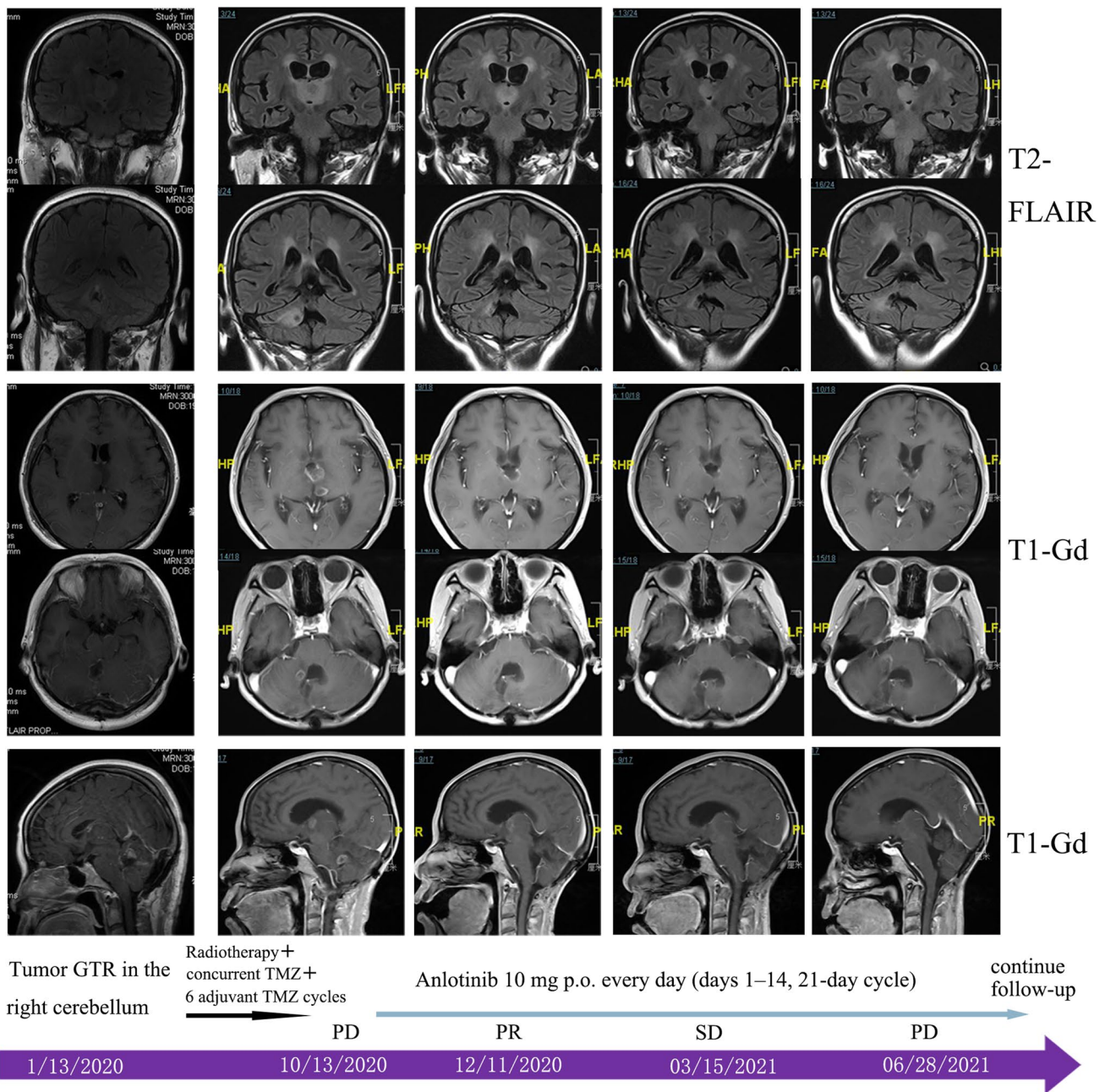


Fig. 2 Timeline of treatment and radiographic responses observed in the brain magnetic resonance imaging during treatments. Abbreviations: SD, stable disease; PD, progressive disease; PR, partial response; TMZ, temozolomide; GTR, gross total resection; Gd, gadolinium

DMGs. In general, surgery, radiotherapy, and chemotherapy can be considered as treatment options for DMGs. No superior effective chemotherapy treatment has been recommended alone or in combination with radiotherapy and surgery.

ONC201 is a dopamine receptor D2 (DRD2) inhibitor, which is currently being investigated in clinical trials (ClinicalTrials: NCT04617002; NCT02525692; NCT03295396) for adult and pediatric H3K27M glioma, including one expanded access protocol [11]. ONC201 clinical efficacy in

adult H3K27M-mutant glioma was first demonstrated in a 22-year-old patient who experienced a durable 96% objective response [1]. Nevertheless, there are still no anticancer drugs for H3K27M-mt DMGs.

Research showed that the H3K27M mutations contributed to RAS pathway signaling, which was augmented by additional RAS activators including PDGFRA. H3K27M mutation led to increased expression of receptor tyrosine kinases (RTK) [5]. Anlotinib (1-[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy] methyl]

cyclopropanamine dihydrochloride) is a multitarget tyrosine kinase inhibitor and an oral small molecule inhibitor, targeted to PDGFR- α/β , VEGFR2/3, FGFR1–4, and c-Kit. Wang et al. reported a patient with recurrent GBM with an FGFR3-TACC3 fusion treated with anlotinib, and the patient achieved a partial response that had been maintained for > 17 months [10].

Given the H3K27M-mt DMG treatment therapy is limited at present, there is an urgent need to explore effective therapeutic strategies. In conclusion, we first reported a H3K28M-mt DMG patient with PDGFR- α mutation responding to anlotinib, who achieved a response with an OS lasting for 21 months.

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Declarations

Conflict of interest The authors declare no competing interests.

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