Annals of Medical and Clinical Oncology
Zhang L, et al. Ann med clin Oncol 3: 137.
www.doi.org/10.29011/AMCO-137.000137
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Case Report

Durable Response from Temozolomide Combined with Apatinib in a Pediatric Patient with Recurrent High-Grade Glioma: A Case Report

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Citation: Zhang L, Xie XQ, Xie P, Wang YA, Su L, et al. (2022) Durable Response from Temozolomide Combined with Apatinib in a Pediatric Patient with Recurrent High-Grade Glioma: A Case Report. Ann med clin Oncol 3: 137. DOI: 10.29011/AMCO-137.000137

Received Date: 04 April, 2022; **Accepted Date:** 08 April, 2022; **Published Date:** 12 April, 2022

Abstract

High-Grade Gliomas (HGGs) are the most frequently diagnosed Central Nervous System (CNS) tumors in children. Maximal safe surgical resection is the cornerstone of management of pediatric HGGs. Radiation therapy is the standard of care after surgical resection and significantly improves survival of children older than 3 years-old with HGGs, but the recurrence rate of pediatric HGGs remains very high. Currently, there are no effective treatments for pediatric patients with recurrent HGGs, but inhibition of Vascular Endothelial Growth Factor (VEGF) pathway has shown promising clinical benefit in several clinical studies as it can reduce brain edema, lead to symptomatic relief. Temozolomide (TMZ) is a standard chemotherapeutic modality in treating adult patients with HGGs.

In this case, we described a 3-year-old boy who received repeated surgery and proton beam radiation therapy due to severe clinical symptoms. He experienced recurrence 6 months after first surgical resection. Finally, he received Apatinib combined with temozolomide (TMZ) as salvage therapy and obtained a durable response with manageable adverse events. Though the effect of Apatinib combined with TMZ has been confirmed in adult patients with recurrent HGGs, the clinical benefit in pediatric patients with recurrent HGGs has not been investigated. We hope our case could provide a reference for clinicians in this region.

Keywords: Apatinib; Case Report; Radiotherapy; Recurrent High-Grade Glioma; Temozolomide

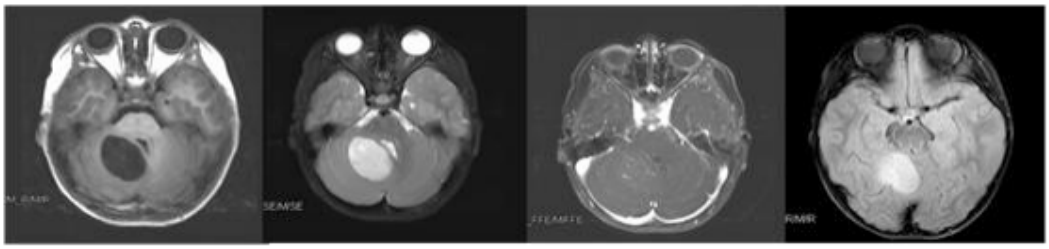
Introduction

Compared with adult patients, the incidence rate of High-Grade Gliomas (HGGs) in pediatric patients is relatively low, affecting approximately 0.85 children per 100,000 annually. Pediatric HGGs are comprised primarily of anaplastic astrocytomas (AA, WHO grade III) and glioblastomas (GBM, WHO grade IV) [1,2]. The survival for patients with recurrent pediatric HGGs remains poor with 5.6 months Overall Survival (OS) regardless of therapy [3]. The standard treatment for adult HGGs is maximally safe surgical resection, followed by concurrent Radiation Therapy (RT) and Temozolomide (TMZ) for 6 weeks, then adjuvant TMZ for 6 months [4]. However, RT is often avoided for children under 3-years-old due to increased risk of several adverse events, and TMZ failed to provide clinical benefits in pediatric HGGs compared with other regimens [5,6]. There are

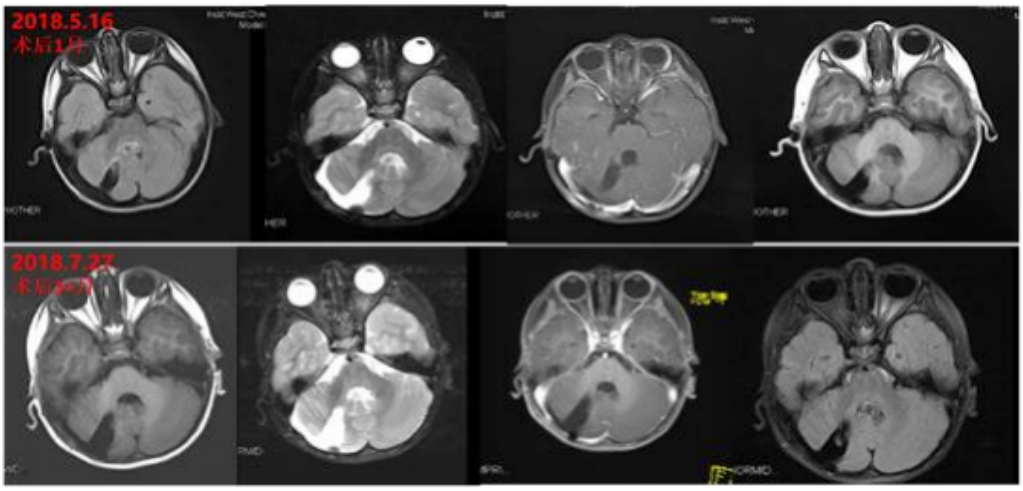
no standard treatment regimens for pediatric HGGs. Nowadays, inhibitors of Vascular Endothelial Growth Factor (VEGF) or receptor (VEGFR) such as bevacizumab have been approved by FDA in treating recurrent HGGs [7]. Apatinib, an orally administered small molecular Tyrosine Kinase Inhibitor (TKI) to VEGFR2, has been proved to be effective when combined with TMZ in treating adult recurrent HGGs patients, but the clinical benefit in pediatric patients has not been validated. Herein, we report a case describing a pediatric patient with recurrent HGGs who received combination therapy of Apatinbi plus TMZ and achieved a durable response.

Case Presentation

A 3-year-old boy was admitted to the Department of Neurosurgery, West China Hospital due to gait disturbance and occasionally headache on March 2, 2018. Long T1 and long T2 signals measuring 3.9×2.9cm with a few vessels were observed in the right cerebellum by brain magnetic resonance imaging (MRI). The lesion was heterogeneously enhancing and pushing the fourth ventricle. On April 3, 2018, gross-total resection of cerebellum lesions and decompressive craniectomy was performed under general anesthesia. The postoperative pathology revealed elongated tumor cells, visible mitotic figures, mucoid degeneration of the stomal cells with branching vessels, confirmed the diagnosis of high-grade gliomas. Immunohistochemistry (IHC) showed Cyclin D1 (+), BOCR2 (+), SATB2 (+), WT-1 (-), CMYC (-), ERG (-), desmin (-), myogenin (-), S100 (+), P63 (-), PCK (-), SMA (-), GFAP (-), INI-1 (-), Oligo-2 (+), ATRX (-), H3K27M (-), P53 (+), EMA (-), NeuN (-), Ki-67 (MIB-1 20%). PCR revealed no mutation of in IDH2 gene. PCR assay revealed no mutation of H3F3A codon 27 gene and HIST1H3B codon 27. In October, 2018, the patient was referred to Beijing International Hospital presented with gait disturbance, nausea and vomiting. Brain MRI revealed a mass in cerebellum with abnormal enhancement, considering tumor with brain tumor associated strokes (BTS). Craniotomy for tumor resection was conducted under general anesthesia. The postoperative pathology revealed heterogenous tumor cells with visible mitotic figures and pseudopalisading necrosis, which suggest of HGGs. IHC showed GFAP (+), OligII (+), NeuN (+), Syn (-), CD34 (vessel +), EMA (-), IDHR132H (-), P53(+), ATRX(+), Ki-67(~20%+), INI1(+), NF(-), Inhibin-a(-), NSE(+), S-100(+), STAT6(-), MAP2(+). The patient was diagnosed as high-grade gliomas (WHO IV) after consulting to Beijing neuro research on November 13, 2018 and our hospital. Clinicians suggest the patient to test BCOR and CIC gene, but refused by the patient's family.

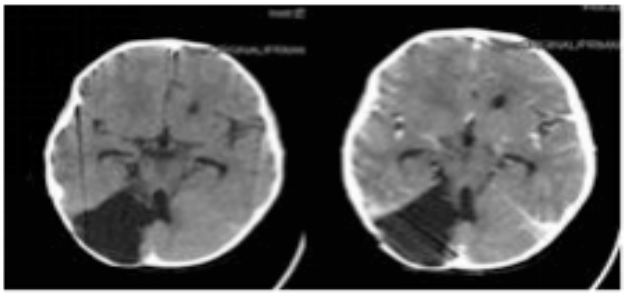


CT



CT

On January 1, 2019, MRI revealed local recurrence located from right brainstem to ventral braincase; lesions in anterior horns and body of left ventricle; diffuse in ventricle. On February 8, 2019, the patient admitted in a Japanese hospital and started receiving proton beam radiation therapy in a dose of 45 Gy (RBE), followed by 14.4Gy local radiotherapy and concurrent chemotherapy of TMZ (50mg/m^2, qd×28d, ivgtt) and dexamethasone (1.5mg, bid). The total does was 59.4Gy. After 12 days, follow-up MRI showed enlarged recurrent lesions and diffusion in braincase and the recurrence continue to progress after 26 days. Then the patient discontinued the treatment due to severe headache and nausea. The total dose was 32.4 Gy in 18 fractions. From April, 2019 to May 2019, the patient received additional radiotherapy in a dose of 24Gy/2cGy/12F in our hospital. On March 20,2019, the patient started taking Apatinib (83mg, qd, p.o.) combined with TMZ (50mg/m2, qd×5d, ivgtt) in a 28-days cycle. At the time of writing, the follow-up period has reached 14 months and the patient was still alive with well-tolerable adverse events.



MRI (2020.9.2)

Discussion

Previous studies have demonstrated postoperative adjuvant chemotherapy could extend Overall Survival (OS) of pediatric HGGs and the addition of TMZ to radiotherapy has a favorable effect than radiotherapy alone in newly diagnosed adult HGGs [7,8]. Though TMZ showed no improvement compared with other chemotherapy regimens in pediatric HGGs, the addition of lomustine to TMZ as adjuvant therapy revealed significantly improved outcomes in a phase II clinical trial [6,9]. However, none of these studies focus on pediatric recurrent HGGs, and most of the studies recruited HGGs patients of both grade IV and grade III, which have a better prognosis. Despite various therapeutic approaches and ongoing clinical trials, there are still no effective treatments for recurrent pediatric HGGs. The outcomes in pediatric HGGs patients remain very poor with OS of 8.5 months between 2006-2016 [3]. As HGGs is characterized by a microenvironment of intense angiogenesis, and inhibition of Vascular Endothelial Growth Factor (VEGF) pathway in recurrent HGGs patients has demonstrated promising clinical benefit, thus Bevacizumab (BVZ) was approved by the FDA to treat recurrent HGGs [10]. The combination of TMZ plus thalidomide have been proven to be safe and well-tolerated in newly diagnosed pediatric Diffuse Pontine Glioma (DPG) patients, besides, Apatinib combined with TMZ was effective in PFS and was well tolerated after appropriate dose reduction in the Chinese population tested of rGBM [11,12]. Therefore, we believed combination therapy of Apatinib and TMZ can be used as a salvage treatment for pediatric patients with grade IV gliomas who experienced multiple recurrences. In the present case, our patient did not receive any adjuvant treatment after surgical resection and experienced relapse within 7 months. He presented with gait disturbance and vomit which may be related to BTS, thereafter, surgical resection was performed again to relieve the symptoms. However, the tumor recurrent within a short period. Then the patient was treated with radiation therapy accompanied with TMZ and Apatinib, and showed a durable response to this regimen with manageable adverse events. Given an oral dose of TMZ could have an equivalent intravenously infusion does with mild and transient adverse events, and it's more convenient for pediatric patients to receive drugs intravenously, we recommend clinicians to use TMZ intravenously instead of orally when treating pediatric patients [13,14]. Limitations of this study include that it is a single case report, so further clinical trials are needed to validate the effect of this regimen, and we could not find a specific biomarker to predict the prognosis of this treatment.

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