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SHORT REPORT

Successful treatment of an adult patient with diffuse midline glioma employing olaparib combined with bevacizumab

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Summary

Diffuse midline gliomas (DMGs), which are malignant, fast-growing and entail a poor prognosis, are a rare subtype of glial tumor. DMGs harboring H3 K27-mutation are a novel entity with a poorer prognosis than the H3 wildtype and are categorized as a grade IV glioma. Histone-mutated DMGs characterized by a midline location occur more commonly in children and less frequently in adults. Considering the DMG treatment is limited, there is an urgent need for effective therapeutic strategies. Olaparib is a poly-adenosine diphosphate-ribose polymerase inhibitor, which has been reported to inhibit glioma in preclinical and clinical trials. Olaparib plus bevacizumab has been successfully used in ovarian cancer. However, the application of olaparib in DMGs has not been reported yet. Herein, we firstly reported that an adult DMG patient benefited from olaparib combined with bevacizumab and achieved complete remission. The duration of response and overall survival was 8 months and 16 months respectively. This report provides a promising treatment option for patients with DMG.

Keywords Diffuse midline gliomas · H3 K27-mutation · Olaparib combined with bevacizumab · Complete remission

Introduction

Diffuse midline glioma (DMG), a rare subtype of glial tumor, is malignant, fast-growing and entails a poor prognosis [1]. Most DMGs, including historical diffuse intrinsic pontine gliomas (DIPGs), harbor the H3 K27 mutations [2, 3]. K27 mutations occur in the *H3F3A* and *HISTIH3B/C* genes, both of which encode histone H3 [4]. However, H3 K27 mutations are associated with a poorer prognosis compared with the H3 wildtype [5–7]. Given that DMGs with H3 K27M mutation have unique molecular signature characteristics and clinical features, they are recognized as a separate entity of central nervous system tumors in 2016 World Health Organization (WHO) Classification [1, 8]. Histone-mutated DMGs occur more often in children than in adults, are characterized by a midline location (such as thalamus, pons, brain stem, and spinal cord), and are categorized as grade IV gliomas [9]. Despite the numerous clinical trials in recent decades, the overall survival (OS) of DMG has not improved and treatment is limited; effective therapeutic strategies are therefore urgently needed [10].

Olaparib, a poly-adenosine diphosphate-ribose polymerase (PARP) inhibitor, has been reported to inhibit gliomas in a number of preclinical trials [11, 12]. The phase I/IIa study OLA-TMZ-RTE-01 showed that combining olaparib with radiotherapy and chemotherapy in glioblastoma can improve survival outcomes [13]. Olaparib plus bevacizumab as maintenance therapy provided a significant progression-free survival benefit for patients with advanced ovarian cancer [14]. However, the clinical application of olaparib monotherapy or combination therapy in DMGs has not yet been reported.

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Herein, we firstly reported that an adult DMG patient benefited from olaparib combined with bevacizumab and achieved complete remission.

Case report

A 37-year-old female presented to Beijing Tiantan Hospital in October 2019 with double vision and poor physical coordination for more than 2 weeks. Magnetic resonance imaging (MRI) of the brain showed a pons tumor in the brainstem. After elimination of surgical contraindications, the pons tumor was removed under general anesthesia. Postoperative pathology revealed the tumor to be a diffuse astrocytoma (WHO Grade II) with slightly dense cells, H3K27M (−), IDH (−), ATRX (+++), and ki-67 (10%). Next-generation sequencing (NGS) 539-gene panel (Simceredx) profiling was performed using postoperative tissue and *H3F3B* exon2 p.K27I (allele frequency, AF 57.64%), as well as *TP53* exon7 p.M237I (AF 80.27%) were identified.

The patient was admitted to our hospital 1 month after surgery in November 2019 and underwent three-dimensional conformal radiotherapy (58Gy/29F) for intracranial tumors and concurrent temozolomide chemotherapy (75 mg/m^2 per day). After three 4-week cycles of 200 mg/m^2 adjuvant temozolomide chemotherapy performed on days 1–5, a brain MRI showed progress. Then olaparib (300 mg bid) combined with bevacizumab (5 mg/kg, once every 28 days) were administered on April 15, 2020. After 1 month, the olaparib dosage was halved due to grade II myelosuppression. Two months later, a brain MRI showed significant lesion reduction; 4 months later, an MRI showed the pons tumor had disappeared, which was evaluated as complete remission. However, the patient relapsed on December 22, 2020 and died on February 1, 2021, with an OS of 16 months. The disease-free survival and duration of response using olaparib plus bevacizumab were 4 months and 8 months, respectively. The MRI changes during treatment are shown in Fig. 1.

Discussion

In our case, there were 2 valuable points. First, the patient with DMG responded to olaparib combined with bevacizumab and achieved complete remission with an OS lasting 16 months. Given the DMG treatment method is limited at present, there is an urgent need to explore effective therapeutic strategies. PARP inhibitors have been widely used in ovarian cancer, breast cancer and prostate cancer [15]. Recently, multiple studies on PARP inhibitors have indicated that therapeutic responses are irrespective of *BRCA1/2* status or homologous recombination deficiency (HRD) [16–19]. This new evidence may extend the clinical use of PARP inhibitors toward a wider group of patients, especially those with *BRCA1/2* wild-type. Olaparib plus bevacizumab has been used in ovarian cancer [14]. Hypoxia caused by antiangiogenic therapy can induce or at least increase HRD, which means that bevacizumab may increase HRD positive tumors [14, 20].

TP53 is a tumor suppressor gene in DNA damage pathway by preventing cells from entering the DNA synthesis phase, inhibiting cell division and proliferation, and allowing sufficient time for DNA damage to be repaired; thus, *TP53* mutations might benefit from olaparib therapy. M237I is located in TP53 DNA binding domain, which can result in the reduction of TP53 transactivation activity [21]. *TP53* has been reported as the candidate biomarker of PARP inhibitor-mediated

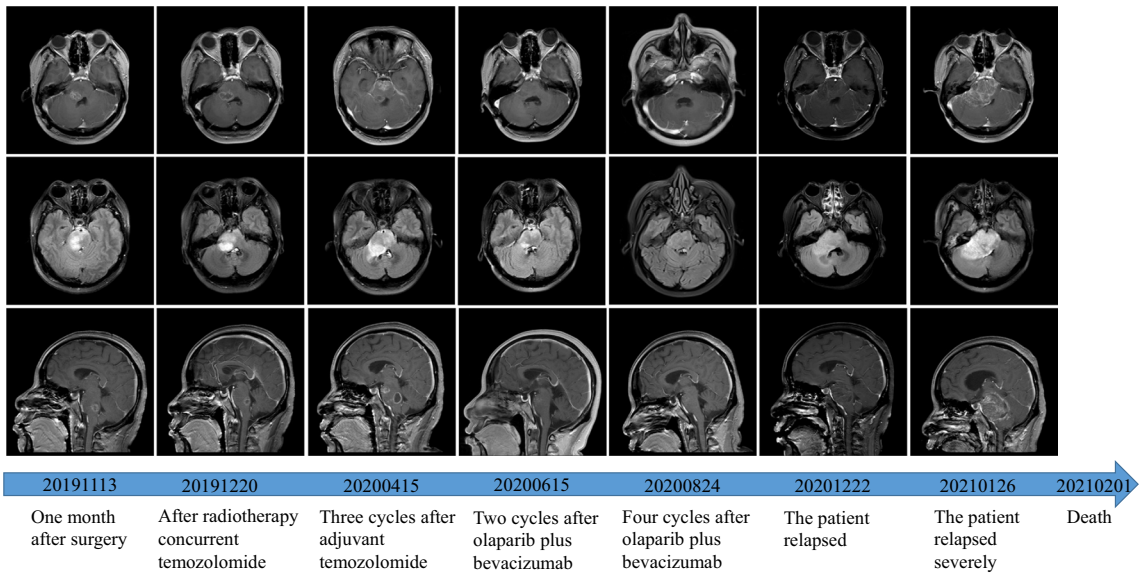

Fig. 1 Timeline of the patient's postoperative treatments and changes observed in the brain magnetic resonance imaging during treatments

radiosensitization [22]. A clinical trial (NCT02576444) is underway for AZD1775 plus olaparib to treat patients with tumors harboring *TP53* mutations.

Second, we firstly identified a novel *H3F3B* K27I (the same as K28I) mutation in an adult patient with DMG. DMGs with H3 K27M mutation are a novel entity, to which previous DIPG belongs, and the mean survival of this tumor is only ~9 months [23]. H3 K27M mutations are common in adult midline gliomas, but survival may be similar or improved if the mutation is present [24]. It is important to correctly identify H3 K27M-mutation for an accurate diagnosis, prognosis, and treatment selection. Mutation-specific clinical trials are ongoing (NCT03295396, NCT02717455, and NCT03696355).

K27M mutation always occurrs in *H3F3A* gene or *HISTIH3B/C* gene. K27I in *H3F3A* has also been reported to be associated with a loss of trimethylation [25]. The *H3F3B* gene, like *H3F3A*, also encodes histone H3.3 and is expressed throughout the cell cycle. To our knowledge, this is the first report to identify the novel *H3F3B* K27I mutation in an adult patient with DMG by NGS, which may expand the detected gene spectrum of patients with DMG. However, the effect of the *H3F3B* K27I mutation on histone H3 and glioma grade needs further study.

In conclusion, this is the first report of a patient with DMG responding to olaparib combined with bevacizumab. The patient achieved complete remission and the OS lasted for 16 months. Our case report provides a promising option for patients with DMG and provides direction for the design of future clinical trials.

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Code availability Not applicable.

Authors' contributions YW, JX: treated the patient and writing the manuscript. NL, CQ: analysis and interpretation of data. RT: treated the patient, conceptualized the study, and approved the final manuscript version.

Data availability Not applicable.

Declarations

Ethics approval The research was approved by the Institutional Ethics Review Board of Shandong Cancer Hospital.

Consent to participate Informed consent to participate was obtained from the patient.

Consent for publication A written informed consent was obtained from the patient for publication of this case report.

Conflict of interest The authors have declared no conflicts of interest.

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