Successful Treatment of an Adult Diffuse Midline Glioma With Olaparib Combined With Bevacizumab

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Research Article

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Abstract

Diffuse midline gliomas (DMGs), characterized by malignant, fast growing and carrying a poor prognosis, are a rare subtype of glial tumor. Majority of DMGs harboring H3 K27-mutation are a novel entity with a worse prognosis 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 treatment is limited in DMG, the need for effective therapeutic strategies is urgent. Olaparib is one of Poly-ADP-Ribose Polymerase (PARP) inhibitors and has been reported in inhibiting glioma in some preclinical trials and clinical trial in glioblastoma. Olaparib plus bevacizumab have been successfully used in ovarian cancer. However, the olaparib application in DMGs has not been reported yet. Herein, we firstly reported that an adult DMG patient benefited from olaparib combined with bevacizumab. This report provides a promising treatment option for DMG patients.

Introduction

A rare subtype of glial tumor, diffuse midline gliomas (DMGs), are malignant, fast growing and carrying a poor prognosis [1]. The majority of DMGs harbor the H3 K27 mutations, including the historical diffuse intrinsic pontine gliomas (DIPGs) [2, 3]. K27 mutations occur in *H3F3A* gene or *HISTIH3B/C* gene and both genes encode histone H3 [4]. However, H3 K27 mutations are associated with a worse prognosis when compared to H3 wildtype [5–7]. Due to DMGs with H3 K27M mutation have unique characteristics of molecular signature and clinical features, they are recognized as a separate entity of central nervous system (CNS) tumors in 2016 World Health Organization (WHO) Classification [1, 8]. Histone-mutated DMGs occur more commonly in children and less frequently in adults, which are characterized by a midline location (such as thalamus, pons, brain stem, and spinal cord) and categorized as a grade IV glioma [9]. Despite a lot of clinical trials in past decades, overall survival didn't improve and treatment is limited in DMG, so the need for effective therapeutic strategies is urgent [10].

Olaparib, one of Poly-ADP-Ribose Polymerase (PARP) inhibitors, has been reported in inhibiting glioma in some preclinical trials [11, 12]. A phase I/IIa study OLA-TMZ-RTE-01 showed that combining olaparib with radiotherapy and chemotherapy in glioblastoma may improve survival outcomes [13]. Olaparib plus bevacizumab as maintenance therapy provided a significant progression-free survival (PFS) benefit in patients with advanced ovarian cancer [14]. However, the clinical application of olaparib monotherapy or combination in DMGs has not been reported. Herein, we firstly reported that an adult DMG patient benefited from olaparib combined with bevacizumab.

Case Report

A 37-year-old female presented to Beijing Tiantan Hospital in October 2019 with double vision and poor physical activity for more than two weeks. Magnetic resonance images (MRI) of the brain was performed and showed the pons tumor in the brainstem. After elimination of surgical contraindications, the pons tumor was removed under general anesthesia. Postoperative pathology showed astrocytoma (WHO

Grade II) with diffuse slightly dense cells, H3K27M (-), IDH (-), ATRX (+++), 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%), *TP53* exon7 p.M237I (AF 80.27%) was identified.

The patient was admitted to our hospital one month after surgery in November 2019. Three-dimensional conformal radiotherapy (58Gy/ 29F) for intracranial tumors and concurrent temozolomide chemotherapy (75mg/m^2 per day) were administered. Then after 3 4-week cycles of 200mg/m^2 adjuvant temozolomide chemotherapy given on days 1–5, brain MRI showed progressed. Then olaparib (300mg bid) combined with bevacizumab (5mg/kg, once in every 28 days) were administered at 2020-4-15. After one month the dose of olaparib was halved due to the grade II myelosuppression. Two months later, brain MRI showed significant lesion reduction and four months later, MRI showed the pons tumor disappeared, which was evaluated as complete remission (CR). The MRI changes during treatment were shown in Fig. 1.

Discussion

In our case, we found two valuable points. First, the patient with DMG responded to olaparib combined with bevacizumab and achieved complete remission. Radiotherapy is the main treatment for DIPG and treatment method of DMG is limited at present, so it's urgent to explore effective therapeutic strategies. PARP inhibitors have been used well in ovarian cancer, breast cancer and prostate cancer [15]. Recently, multiple studies on PARPi have highlighted that therapeutic responses are irrespective of *BRCA1/2* status or HRD [16–19]. This new evidence may extend the clinical use of PARPi toward a wider group of patients, especially those with *BRCA1/2* wild-type. Olaparib plus bevacizumab have been used in ovarian cancer [14]. Hypoxia caused by antiangiogenic therapy can induce or at least increase homologous recombination deficiency (HRD), which means that bevacizumab may increase HRD positive tumor patients [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 repair, and the *TP53* mutations may benefit from olaparib therapy. M237I is located in TP53 DNA binding domain, which can result in the reduction of TP53 trans-activation activity [21]. *TP53* was reported as the candidate biomarkers of PARPi-mediated radiosensitization [22]. Clinical trial (NCT02576444) is under way 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 the adult DMG patient. DMGs with H3 K27M-mutant are a novel entity, which previous diffuse intrinsic pontine glioma belongs to and a mean survival of this tumor is only ~9 months [23]. H3 K27M-mutation are common in adult midline gliomas, but survival may be similar or improved if the mutation is present [24]. It is important to identify H3 K27M-mutation accurately for accurate diagnosis, prognostication, and may also for treatment selection. Clinical trials with mutation-specific are ongoing (NCT03295396, NCT02717455, NCT03696355).

K27M mutation always occurred in *H3F3A* gene or *HIST1H3B/C* gene. K27I in *H3F3A* has been reported that also created a loss of trimethylation [25]. *H3F3B* gene, like *H3F3A*, is also encodes histone H3.3 and expressed throughout the cell cycle. This is the first report of identification of the novel *H3F3B* K27I mutation in an adult DMG patient by NGS, which may expand the detection gene spectrum of DMG patients. However, the effect of the *H3F3B* K27I mutation on histone H3 and on glioma grading needs further study.

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

Declarations

Ethics approval and consent to participate

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

Consent for publication

A written informed consent was obtained from the patient for publication.

Availability of data and materials

Not applicable.

Competing interests

The authors have declared no competing interest.

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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.

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Compliance with ethical standards

Disclosure of potential conflicts of interest

All authors have no conflicts of interest to disclose.

Research involving Human Participants and/or Animals

This study does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from the patient for the publication of this case report.

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Figures

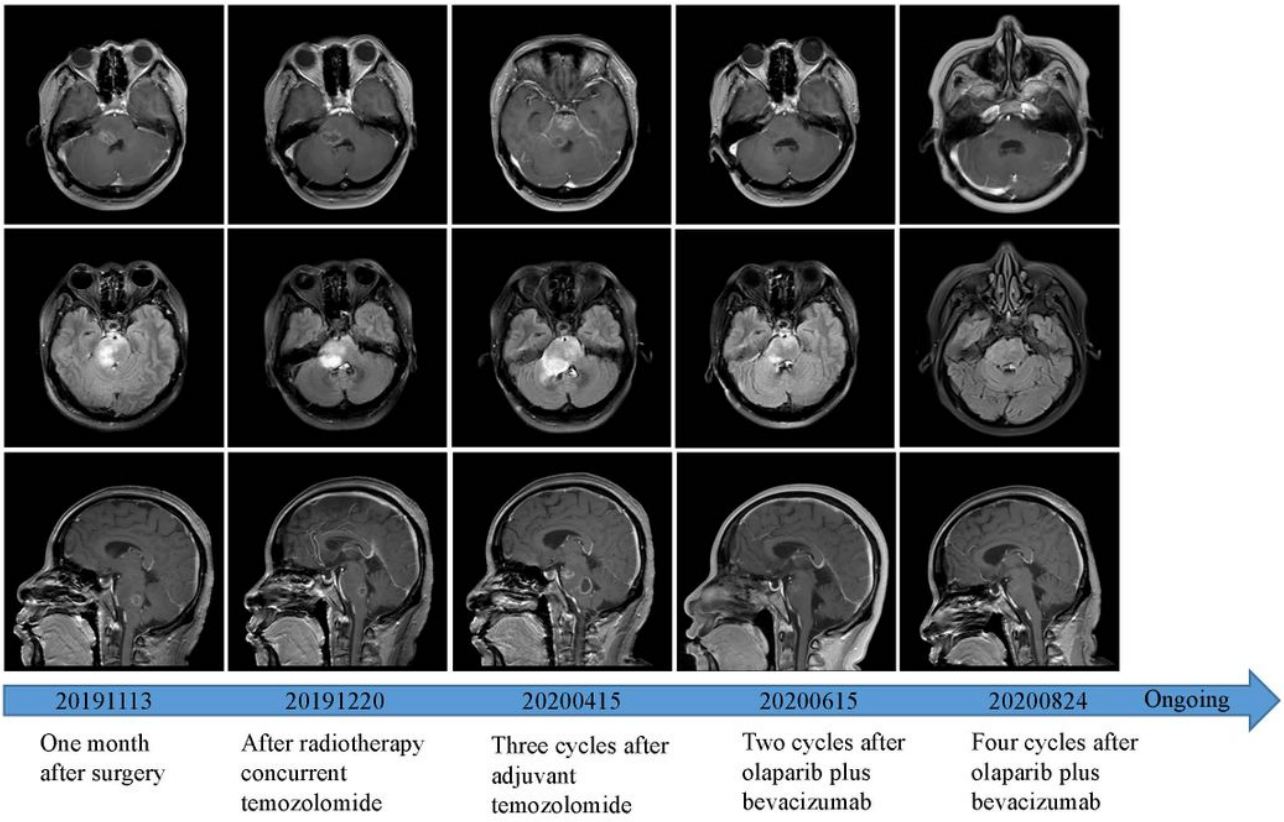

Figure 1

Time line of treatments of the patient after postoperative recurrence and changes in MRI of the brain during treatments.