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Precision Medicine Clinic: Molecular Tumor Board

Treatment of Pediatric Glioblastoma with Combination Olaparib and Temozolomide Demonstrates 2-Year Durable Response

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

For pediatric patients with high-grade gliomas, standard-of-care treatment includes surgery, chemotherapy, and radiation therapy; however, most patients ultimately succumb to their disease. With advances in genomic characterization of pediatric high-grade gliomas, the use of targeted therapies in combination with current treatment modalities offer the potential to improve survival in this patient population. In this report, we present the case of a 3-year-old girl with glioblastoma who continues to experience an exceptional and durable response (>2 years) to the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib. Our patient presented with persistent and progressive seizure activity that upon workup was the result of a large heterogeneously enhancing, mixed cystic and solid mass in the left frontal-parietal-temporal region. Histopathologic analysis of resected tumor tissue confirmed the diagnosis of glioblastoma, and comprehensive genomic profiling demonstrated absence of any *BRAF* or *H3F3A* mutations. Genomic profiling, however, did reveal a probable germline heterozygous *BRCA2* Lys3326Ter (K3226*) nonsense variant. After debulking surgery, the patient received standard-of-care treatment with radiation and temozolomide. Nine months later the PARP inhibitor olaparib was administered in combination with temozolomide for 16 cycles. This regimen was well tolerated by the patient and serial imaging showed reduction in tumor size. Since completion of the regimen, the patient remains neurologically intact with no evidence of tumor recurrence. To our knowledge, this represents the first case of a pediatric glioblastoma that maintains a durable response to a therapeutic strategy that included the PARP inhibitor olaparib and more generally highlights the potential clinical utility of incorporating these agents into the treatment of pediatric high-grade gliomas. ***The Oncologist*** 2020;25:e198–e202

Key Points

- Germline mutations detected in pediatric gliomas may represent a cancer predisposition syndrome.
- Integrating molecular testing into routine clinical care for pediatric patients with glioma is critical to identify therapeutic targets and patients with a cancer predisposition syndrome.
- Patients with glioma with defects in DNA repair pathway components (e.g., *BRCA1/2*) may show increased responsiveness to poly (ADP-ribose) polymerase (PARP) inhibitors.
- Combining PARP inhibitors with temozolomide (standard-of-care treatment) revealed no adverse events or toxicities over the course of 18 months.

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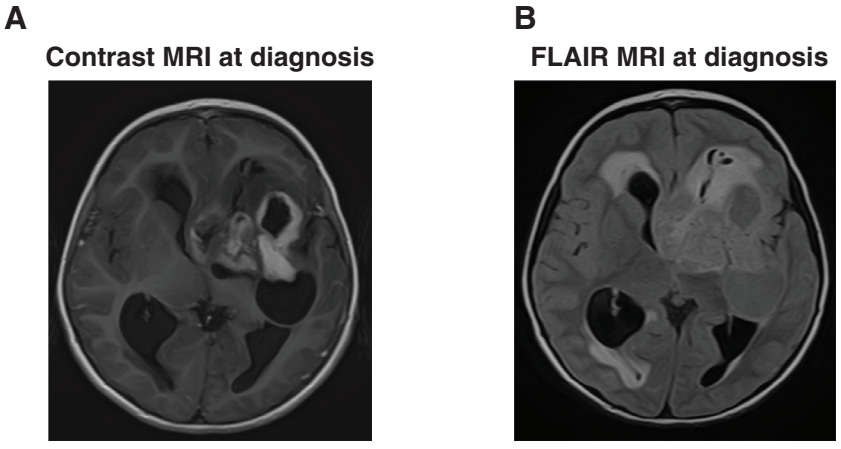

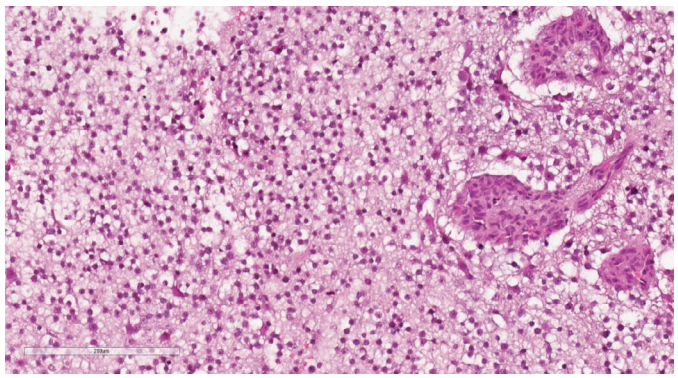

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Gene	Alteration	Coding Sequence Effect	Allele Frequency (%)
VHL	T100A	298A>G	46
BRCA2	K3326*	9976A>T	49
FGFR3	S736Y	2207C>A	48
MLL2	L3734_Q3735insQ	11201_11202insGCA	29

Figure 1. Clinical presentation and analysis of patient's glioblastoma. **(A):** Contrast MRI at diagnosis illustrating a mass that extends into the internal capsule, thalamus, and basal ganglia and across the corpus callosum into the right frontal region. **(B):** FLAIR MRI demonstrates a solid mass with restricted diffusion. **(C):** Hematoxylin and eosin image of the tumor mass demonstrates a densely cellular glioma with frequent mitosis, microvascular proliferation, and necrosis. Scale bar, 200 μm. **(D):** Mutations and metrics identified in the tumor by next-generation sequencing.
Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Patient Story

A 3-year-old girl presented in July 2015 with multiple daily episodes of absence seizures lasting up to 10 seconds. Persistent seizure activity was noted in November 2015 associated with increased duration (20–30 seconds) and was accompanied by repeated swallowing movements, lethargy, and loss of interest in toys and games. In January 2016, she reported occasional headaches, and the structure of attacks appeared dystonic. These attacks increased in frequency to five times daily and lasted up to 60 seconds, requiring initiation of anticonvulsant therapy with valproic acid (250 mg b. i.d.) in February 2016.

In February 2016 additional diagnostic workup for her seizures included magnetic resonance imaging (MRI), which revealed a large (8.7 × 6.0 × 6.0 cm), heterogeneously enhancing, mixed cystic and solid mass in the left frontal-parietal-temporal region. The mass extended into the internal capsule, thalamus, and basal ganglia and across the corpus callosum into the right frontal region (Fig. 1A, B).

In March 2016, a partial resection was performed to remove tumor tissue from the frontal and temporal lobes and the lateral portion of the left basal ganglia. Postoperative MRI scans showed significant residual tumor in the left frontal-temporal region, so the patient underwent a second debulking surgery. Postoperative MRI scans showed residual tumor in the insula, internal capsule, and left frontal region, and spinal MRI scans showed no evidence of drop metastases. The patient exhibited mild right-sided hemiparesis postoperatively but no other neurologic deficits.

Histopathologic review of the tumor revealed a densely cellular glioma composed of cells with abundant eosinophilic-to-clear cytoplasm and eccentrically displaced nuclei (Fig. 1C). Mitoses, microvascular proliferation, and necrosis were present. Immunohistochemical analysis showed that tumor cells were diffusely positive for glial fibrillary acidic protein. INI-1 staining demonstrated intact nuclear expression, and the Ki-67 proliferation index was 15%–20%. Tissue was submitted to Foundation Medicine, Inc., for comprehensive genomic profiling

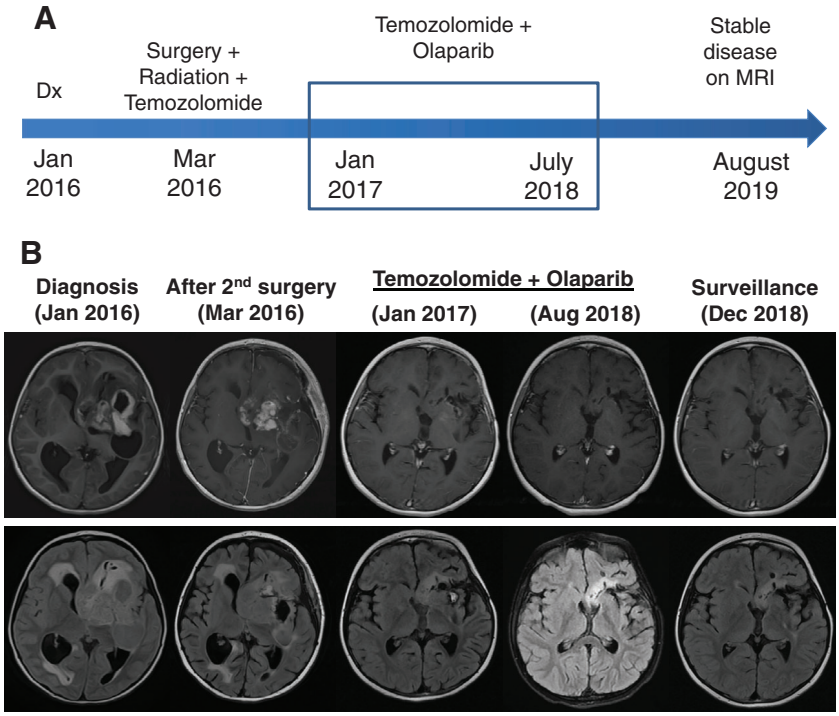

Figure 2. Therapeutic course and serial neuroimaging studies. **(A):** Schematic illustrating the timing of tumor resection and treatments for the patient. **(B):** Contrast MRI (top) and fluid-attenuated inversion recovery MRI (bottom) images during the course of treatment from January 2016 to December 2018.
Abbreviations: Dx, diagnosis; MRI, magnetic resonance imaging.

using a hybrid-capture-based next-generation sequencing assay interrogating 315 cancer related genes as well as introns of 28 genes involved in rearrangements. Sequencing revealed *VHL* (T100A), a known pathogenic variant, as well as variants of uncertain significance involving *BRCA2* (K3326*), *FGFR3* (S736Y), and *MLL2* (L3734_Q3735insQ) (Fig. 1D). Investigational application of somatic-germline-zygosity analysis demonstrated the *BRCA2* (K3326*) variant to be a heterozygous germline alteration. Microsatellite instability (MSI) analysis revealed the tumor to be MSI stable, and *MGMT* promoter methylation analysis was negative for methylation.

The patient was started on standard-of-care treatment consisting of 60 Gy focal radiation to the tumor bed in combination with temozolomide (75 mg/m^2) over a 6-week period. After a 4-week treatment-free interval, she received six additional cycles of temozolomide monotherapy (150 mg/m^2/day cycles 1–2, 200 mg/m^2/day cycles 3–6) administered over a 28-day period. The treating clinician added olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, to her treatment regimen starting in January 2017. In total, she received 16 cycles of temozolomide (125 mg/m^2) and olaparib (100 mg/m^2), with discontinuation of therapy in June 2018 (Fig. 2A). Routine MRI studies showed a gradual reduction of tumor size, reduction of contrast enhancement, and decreased ^{11}C-methionine accumulation on positron emission tomography–computed tomography (PET-CT) (Fig. 2B, data not shown). Importantly, no significant side effects from the combination therapy have been reported, apart from grade 4 hematological toxicity after the seventh cycle, which was associated with a concurrent viral infection.

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BRCA2 encodes a tumor suppressor gene that mediates homologous recombination as a repair mechanism in response to DNA damage. Similar to BRCA1 and RAD51, the BRCA2 protein relocates to replication sites following exposure of cells in S phase to hydroxyurea or UV irradiation, which generates DNA double-strand breaks. Inherited mutations in either *BRCA2* or *BRCA1* have been well established to predispose individuals to various malignancies, most notably breast and ovarian cancers; however, there is increasing evidence that these individuals are also susceptible to developing other cancers such as pancreatic cancer, prostate cancer, and melanoma [1]. Additionally, recent reports indicate that *BRCA2* mutations also predispose individuals to gliomas, although these are not as frequent as the abovementioned tumors [2–4]. In one study, 3% (11/364) of individuals with primary brain cancer harbored a germline mutation in *BRCA2*, and interestingly, in eight cases the primary brain tumor was the first presentation of a malignancy [5].

For pediatric patients, tumors arise as a result of a cancer predisposition syndrome (CPS) in at least 10% of cases [6]. For gliomas, Li-Fraumeni syndome, constitutional mismatch repair disorder, and neurofibromatosis (NF1 and NF2) are the most well-established CPSs; however, as awareness increases of the importance of documenting family history, age of onset, and occurrence of bilateral, multifocal, or multiple cancers, additional risks as a result of other cancer predisposition syndromes, such as *BRCA2* mutation, may be elucidated. There is growing evidence that identifying these patients is critical for accurate identification of tumor subtype, gauging prognosis, guiding genomically targeted therapies, and screening other potentially affected family members [7, 8].

Genotyping Results and the Interpretation of the Molecular Results

DNA was extracted from the patient's formalin-fixed, paraffin-embedded glioblastoma (GBM) tissue and subjected to clinical sequencing of 315 cancer related genes as well as introns of 28 genes involved in rearrangements, including *BRCA2*. Sequencing revealed a *BRCA2* p.Lys3326* (c.9976A>T) nonsense mutation that prematurely truncates the protein. The wild-type BRCA2 protein consists of 3,419 amino acids, and the p.Lys3326* (K3326*) mutation results in truncation of the distal C-terminal 93 amino acids. As of December 2018, this exact nonsense mutation has been reported six times in the Catalogue of Somatic Mutations in Cancer (COSMIC) database, including five adenocarcinomas of unknown primary and one pleural mesothelioma sample. Within the cBioPortal data set (cbioportal.org, December 2018), ten tumors harboring the K3326* variant were identified, including nine cases (four ovarian carcinomas, five prostate carcinomas) with the variant designated a germline alteration and one case of an adenoid cystic carcinoma with the variant designated somatic. The pathogenicity of the *BRCA2* K3326* variant remains uncertain, especially in the context of hereditary breast and ovarian cancer syndrome, given a 1% minor allele frequency in the European (Finnish) population and functional studies in mouse embryonic stem cells suggesting this variant has little effect on BRCA2 functions [9]; however, several studies re-evaluating this variant demonstrate its association with a modestly higher risk of breast, ovarian, squamous cell lung, and upper aero-digestive tract cancers [10–13].

Potential Strategies to Target the Pathway and Implications for Clinical Practice

Olaparib is an oral PARP inhibitor that, in the setting of *BRCA*-deficient cells, functions as a cytotoxic agent by blocking base excision repair, which eventually leads to double-strand breaks, subsequent DNA replication fork stalling, and cell death [14]. In certain cancer types with high mutation rates in genes involved with homologous recombination components, such as high-grade serous ovarian, triple-negative breast, metastatic prostate, or pancreatic tumors, PARP inhibitors have proven to be effective treatment strategies [15–18].

Emerging evidence suggests that PARP inhibitors may also be a novel therapeutic option for patients with GBM, given the upregulation of DNA repair genes like *ATM*, *ATR*, *CHK1*, and *PARP* as well as the high capacity for DNA repair in glioma stem cells [19]. Additionally, several studies have demonstrated the radiosensitizing effects of PARP inhibition on glioma cell lines, specifically in actively dividing cells [20]. As a result of these and other preclinical studies, one phase I/II dose escalation trial is now open to evaluate the efficacy of combined radio-chemotherapy with olaparib for adult patients with high-grade glioma (NCT03212742) [21].

For pediatric patients with high-grade glioma, treatment options are limited and fail to provide significant improvement in progression-free or overall survival. Indeed, 2-year survival rates are <15% for pediatric patients with high-grade glioma [22, 23]. Moreover, current standard-of-care treatment, including radiation therapy, often provides symptomatic relief but results in devastating damage to the still-developing central nervous system [24]. Although clinical trials to evaluate targeted or novel therapies such as MAPK inhibitors or H3F3A peptide vaccines are underway, the available treatment options are limited for pediatric patients with glioma (NCT02960230) [25]. Preclinical studies are providing important insights into potential targeted therapeutics, including PARP inhibitors for pediatric high-grade gliomas. A recent study demonstrated the efficacy of two PARP inhibitors, olaparib and niraparib, in reducing cell growth and viability of patient-derived pediatric high-grade glioma models [26].

This report highlights the value of combining standard-of-care treatment with PARP inhibitors in primary gliomas. Our patient experienced no adverse events or toxicities following the addition of olaparib to her treatment plan and continues to experience a durable response to treatment.

Patient Update

From the initiation of care, the patient received a total of 22 cycles of temozolomide, of which 16 cycles (January 2017 to June 2018) included combination with olaparib. Cytostatic treatments were discontinued in July 2018, and a clinical plan was established to monitor tumor status by MRI every 3 months. The December 2018 baseline MRI showed stable disease with no evidence of tumor progression, which was supported by a follow-up MRI at the end of May 2019. Additionally, a PET scan in July 2019 demonstrated no progression of disease. In the 13 months since monitoring was initiated, she remains clinically stable and neurologically intact. She is preparing to attend school in September 2019 and participates in music classes.

Glossary of Genomic Terms and Nomenclature

PARP: poly adenosine diphosphate-ribose polymerase
BRAF: B-Raf proto-oncogene, serine/threonine kinase
H3F3A: H3 Histone Family Member 3A
BRCA2: BRCA2 DNA repair associated
FGFR: Fibroblast growth factor receptor
VHL: von Hippel-Lindau tumor suppressor
MLL2 (KMT2D): lysine methyltransferase 2D

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Disclosures

David E. Kram: Foundation Medicine, Inc. (E, OI); **Eric Severson:** Foundation Medicine, Inc. (E, OI); **Amanda Hemmerich:** Foundation Medicine, Inc. (E, OI); **Claire Edgerly:** Foundation Medicine, Inc. (E, OI); **Daniel Duncan:** Foundation Medicine, Inc. (E, OI); **Nicholas Britt:** Foundation Medicine, Inc. (E, OI); **Richard S.P. Huang:** Foundation Medicine, Inc. (E, OI); **Julia Elvin:** Foundation Medicine, Inc. (E, OI); **Vincent Miller:** Foundation Medicine, Inc. (E, OI), Revolution Medicines (C/A); **Jeffrey S. Ross:** Foundation Medicine, Inc. (E, OI); **Laurie Gay:** Foundation Medicine, Inc. (E, OI); **Joshua McCorkle:** Foundation Medicine, Inc. (E, OI); **Andrew Rankin:** Foundation Medicine, Inc. (E, OI); **Rachel L. Erlich:** Foundation Medicine, Inc. (E, OI); **Yakov Chudnovsky:** Foundation Medicine, Inc. (E, OI); **Shakti H. Ramkissoon:** Foundation Medicine, Inc. (E, OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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