CASE REPORT

Long-term survival of an adolescent glioblastoma patient under treatment with vinblastine and valproic acid illustrates importance of methylation profiling

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Received: 11 February 2021 / Accepted: 29 June 2021 / Published online: 26 July 2021 © The Author(s) 2021

Abstract

Glioblastoma (GBM) is an exceptionally aggressive brain tumor with a dismal prognosis, demanding fast and precise classification as a base for patient-specific treatment strategies. Here, we report on an adolescent patient with a histologically bona fide GBM that shows a molecular methylation profile suggesting a low-grade glioma-like subgroup. Despite an early relapse, intolerance of temozolomide, and change of treatment strategy to vinblastine and valproic acid (VPA), the patient is now in good clinical condition after more than 5 years since initial diagnosis. This case stresses the merit of methylation array data for clinical prognosis and treatment planning.

Keywords Glioblastoma · Vinblastine · Valproic acid · Methylation profiling

Introduction

High-grade glioma accounts for 10–15% of pediatric CNS tumors [1]. Gross surgical resection and radiotherapy are essential for survival. A rational base for chemotherapy treatment, however, is still missing [2]. The current German HIT HGG 2013 study investigates an additive effect of valproic acid (VPA) to temozolomide and radiotherapy [3]. But despite multimodal therapy approaches, the prognosis of pediatric glioblastoma patients with high-grade GBM is extremely poor. As prognosis varies significantly in dependence of clinical and biological features, identification of reliable prognostic parameters for treatment response and clinical outcome of individual patients is urgent [4].

DNA methylation profiling contributes to define molecular subgroups in pediatric GBM that are clinically and prognostically important [5, 6]. Two independent investigations in 2015 and 2017 describe that a subset of H3/IDH wild-type GBM showed methylation profiles resembling low-grade glioma (LGG-like) or pleomorphic xanthoastrocytoma (PXA-like). The LGG-like tumors occurred mainly in infants under the age of 1 year and showed a significantly better prognosis than other H3/IDH wild-type GBM [5, 6].

Case report

The 15-year-old female patient presented at the Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf with several weeks of frontotemporal headache and was admitted to the hospital with transient weakness and paresthesia of the left extremities. The cranial MRI showed a right-frontal tumor with surrounding edema (Fig. 1a, f).

After macroscopically complete tumor resection, a small residual tumor was suspected in the postoperative
Histomorphologic assessment by local and reference pathologists confirmed the diagnosis of IDH-mutant GBM. The tumor region was irradiated with a target volume dose of 60 Gy following the HIT HGG-2007 protocol with concomitant daily temozolomide, followed by a temozolomide monotherapy in monthly cycles of 5 days (treatment overview in Fig. 2). Seven months after diagnosis, the tumor reoccurred (Fig. 1c, h). After the initial treatment regimen, a second surgical resection and additional radiation therapy were performed (Fig. 1f, g). Despite these interventions, the tumor continued to progress, and the patient eventually developed disease progression (Fig. 1d, i). Seven months after progression, MRI images show stable disease (Fig. 1e, j): stable non-enhancing FLAIR hyperintensities (arrow) in the left cingulate gyrus e.

**Fig. 1** Cranial MRIs before and during treatment: T2 fluid-attenuated inversion recovery (FLAIR) a–e and contrast-enhanced T1 weighted f–j MRI sequences. Upon initial diagnosis a, f: heterogeneous mass on the right frontal lobe with perifocal edema a, ring enhancement f, a slight midline deviation and the presence of satellite lesions f. Post-operative imaging b, g: 2 days after tumor resection showing typical perifocal edema b and a focal nodular enhancement g at the anteromedial resection margin (broad arrow) suggesting possible residual tumor. Upon relapse 7 months after tumor resection c, h: frontal defect with discrete perifocal edema c and relapsing contrast-enhancing lesions (triangles) adjacent to the resection area h. Upon progression d, i: larger post-resection parenchyma defect on the right frontal lobe after repeated tumor resection and progressive hyperintense signal in the FLAIR d in the contralateral cingulate gyrus (arrow). Note the absence of enhancement (star) in the post-contrast images i.

**Fig. 2** Time line showing patient’s treatment. Chemotherapeutical treatment: oral temozolomide (green) was given concomitant to radiotherapy and then as a monotherapy first 150 mg/m$^2$/day (5 days every 4 weeks), then 100 mg/m$^2$/day and was terminated due to severe side effects. Valproic acid (blue) 300 mg/m$^2$/day in 2 daily oral doses and vinblastine 3 mg/m$^2$ treatment (red) was added first as weekly infusions and then in longer intervals of 2–3 weeks. Dosages remained unchanged for the entire treatment period.
second surgical resection, a residual tumor at the dor-
sal resection border could not be excluded. We initiated
adjuvant therapy with oral valproic acid (VPA) and due
to slight progression of the residual mass, we added treat-
ment with weekly vinblastine. At the time of 4.5 years after
the first diagnosis, Vinblastine and VPA dosage remained
unchanged but vinblastine applications were stretched to
3-week intervals in order to reduce adverse reactions.

Five years after initial diagnosis and 6 months after
decreasing the treatment intensity, MRI imaging showed
a progressive hyperintense signal in the FLAIR sequence
in the contralateral cingulate gyrus, indicating a new
non-enhancing tumor lesion (Fig. 1d, i). The patient
was clinically well and very hesitant towards intensified
chemotherapy or surgery. Therefore, and with respect to
the slow progression, we decided to continue the previ-
ous treatment schedule with VPA and vinblastine and to
closely surveille the tumor by MRI imaging. The tumor
showed no further progression on MRI for the following
7 months (Fig. 1e, j).

Neuropathological and molecular workup

We investigated the biological characteristics of the
tumors in more detail (Figs. 3 and 4). The initial his-
tology showed a glial tumor with vascular proliferation,
areas of necrosis, and increased proliferation. Tumor
cells were positive for GFAP and MAP2c and negative
for IDH-1 (R132H) and mutation-specific Histone H3.
DNA sequencing ruled out mutations in codon 27 or 34
of the \textit{H3F3A} gene.

We conducted Illumina Human Methylation 850 K
Bead Chip array analysis of primary and relapse tumor
tissue. Both tumors showed an unmethylated MGMT pro-
moter. The tumor did not show a definite match with any
of the reference brain tumor entities on the Heidelberg
brain tumor classifier [7]. The initial tumor had a cali-
brated score of 0.4, and the relapse tumor did not score
above 0.3. We then performed t-distributed stochastic
neighbor embedding (\textit{t-SNE}) analysis alongside 2,801
brain tumor cases as published [7]. Initial and relapse

Fig. 3 Histology of initial tumor (left) and relapse tumor (right): glial tumor with vascular proliferation and necrosis a–c. Positive staining of
GFAP d, 10–20\% Ki67-positive cells in initial and recurrent tumor e, f. Histological diagnosis: Glioblastoma (°IV)
tumor clustered closely with low-grade glioma, comparable to published methylation data of LGG-like GBM by Mackay et al. [6] (Fig. 4).

**Discussion**

Despite an early relapse and a residual tumor, the adolescent patient remained with stable disease for over 5 years under treatment with vinblastine and VPA.

Weekly vinblastine has previously proven successful in treatment of recurrent LGG [8]. Vinca alkaloids showed activity in early chemotherapy studies [9, 10] and are a key element in previous and current treatment strategies [11].

VPA is a well-established anti-epileptic drug but was also found to induce an anti-tumor response in vitro and in GBM patients and has been proposed to have sensitizing effects during radiation therapy [12–15]. Due to promising preclinical and clinical reports, treatment with VPA is currently tested in the running German HIT-HGG 2013 trial [3].

Methylation analysis did not detect a clear match with any brain tumor methylation class, but t-SNE analysis of the methylation profile suggested similarity to low-grade glioma. The correct diagnosis of glioblastoma is strongly supported by the aggressive tumor biology and the clear histological features. However, the methylation profile in combination with the good response to VPA and Vinblastine treatment point towards this glioblastoma having some LGG-like features as described previously [5, 6].

Whether the good treatment response of our patient is due to an intrinsically less aggressive tumor biology, as suggested by the LGG-like methylation profile, or if the applied treatment strategy also contributed to the long-term survival remains unknown and will have to be put into context with detailed clinical data from comparable patients.

With respect to the devastating prognosis of GBM, we stress the importance of methylation profiling for risk stratification and treatment. Adolescent patients with GBM clustering in the LGG-like subgroup and an above-average prognosis might be more common than suggested by previous reports. Clustering of tumors in the LGG-like subgroup might even supply evidence for alternative treatment strategies including vinblastine and VPA.
Funding Open Access funding enabled and organized by Projekt DEAL. C.K. was sponsored by a fellowship of the University Cancer Center Hamburg (UCCH). Further funding from the Fördergemeinschaft Kinderkrebszentrum Hamburg is provided to U.S. The HIT-MED trial center in Hamburg and the reference center for Neuroradiology in Würzburg are supported by the Deutsche Kinderkrebsstiftung.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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