

Larotrectinib Response in NTRK3 Fusion-Driven Diffuse High-Grade Glioma

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Keywords

Tumor agnostic · Targeted therapy · Precision medicine · Brain cancer · Glioblastoma

Abstract

High-grade glioma (HGG) and glioblastoma are the most common adult malignant brain tumors. The standard treatment consists of surgical resection followed by radiochemotherapy with temozolomide. The prognosis and the therapeutic options of these malignant brain tumors however are limited. Here, we describe a case of a patient with HGG with a previously unknown NTRK3 fusion that showed an extraordinary response to treatment with larotrectinib. This case supports regular testing for NTRK fusion proteins.

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Published by S. Karger AG, Basel

Introduction

The prevalence of neurotrophic tyrosine receptor kinase (NTRK) fusions in adult glioma or glioblastoma is very low [1]. Due to the paucity of cases with NTRK fu-

sion-positive primary CNS malignancies, reports on tropomyosin receptor kinase (TRK)-inhibition in these patients are rare. Here, we report a case of a patient with unresectable high-grade glioma (HGG) harboring a previously unknown NTRK3-ARHGEF7 gene fusion. Treatment with larotrectinib showed rapid clinical benefit and radiological response.

Diffuse HGGs including glioblastoma, IDH wildtype, are malignant brain tumors leading to death within several months to a few years despite multimodal treatment. Optimal standard treatment consists of total gross resection, radiotherapy, and concomitant chemotherapy with temozolomide, followed by 6 cycles of temozolomide [2]. The addition of tumor-treating fields can increase median overall survival. Only few molecular alterations can be targeted in patients with diffuse HGG including glioblastoma [2]. As an example, therapy with BRAF-inhibition or combined BRAF/MEK-inhibition has been active in patients with glioma harboring BRAF V600E mutations [2]. For patients with NTRK-fused HGG, there are only a few published cases of successful TRK-inhibition [3, 4], likely due to the rarity of these alterations and the novelty of TRK-inhibitors.

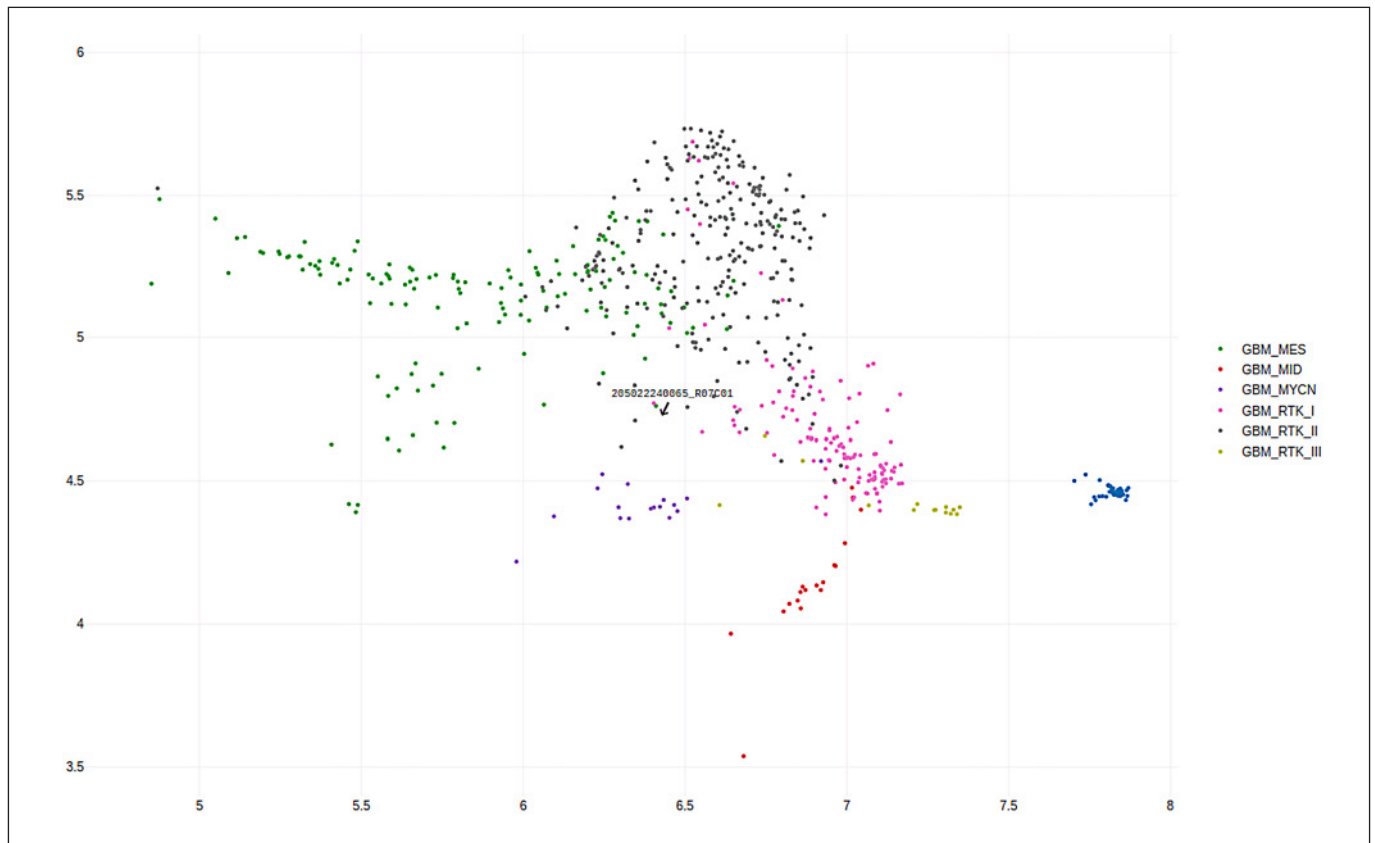


Fig. 1. Position in a pan-cancer dimension reduction plot generated with the www.epidip.org tool.

Materials and Methods

Patient

The patient was treated at the University Hospital Basel, Switzerland. We obtained the consent from the patient to use her clinical data for research. The patient was followed within a post-approval safety study (Clinicaltrials Identifier: NCT04142437).

Methylation Analysis

Whole-genome methylation analysis was done on the Illumina Infinium HumanMethylation450 BeadChip (450k) arrays according to the manufacturer's instructions. Tumor type and chromosomal copy number changes were determined as published by Capper et al. [5].

Determination of Fusion Transcripts

Targeted RNA sequencing was performed by a customized Archer fusion panel (Archer™ FusionPlex™ Custom V2 Panel) that enables detection of fusions without prior knowledge of fusion partners. RNA extraction was performed after enrichment of tumor cells to a level of at least 20% (60% in our case). Our institution's customized Archer panel includes fusion transcripts of 63 genes (including NTRK 1, 2, and 3).

Results

Here, we describe the case of an HGG-patient with a novel NTRK3 fusion as an oncogenic driver alteration. An 80-year-old woman presented with progressive gait disorder, dizziness, and generalized weakness. Clinical examination was notable for right-sided hemiparesis, dysmetria, and the tendency to fall to the right. Magnetic resonance imaging (MRI) of the brain raised the suspicion of a multifocal HGG. Predominant left-parietal lesions with perilesional edema were consistent with the neurological picture. Extracranial imaging did not show any primary solid tumors or systemic metastases. Morpho-molecular analysis of a left-parietal biopsy revealed an IDH-wildtype HGG (NOS, yet compatible with WHO grade 4). Its DNA methylome did not match to any of the defined glioblastoma, IDH wildtype, subgroups [5], and lacked the prototypical +7/-10 chromosomal signature of glioblastoma, IDH wildtype; highest classifier v11b4 calibrated scores for glioblastoma, IDH wildtype (0.38, no match; cut-off ≥ 0.9), subclass RTK I (0.25). Dimension reduction showed

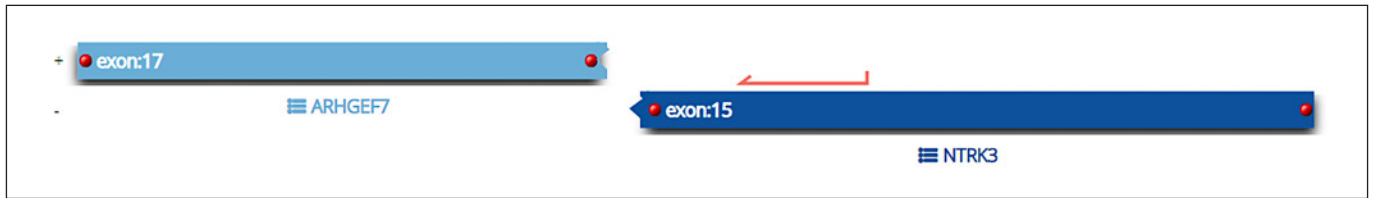


Fig. 2. Schematic representation of the NTRK3-ARHGEF7 fusion.

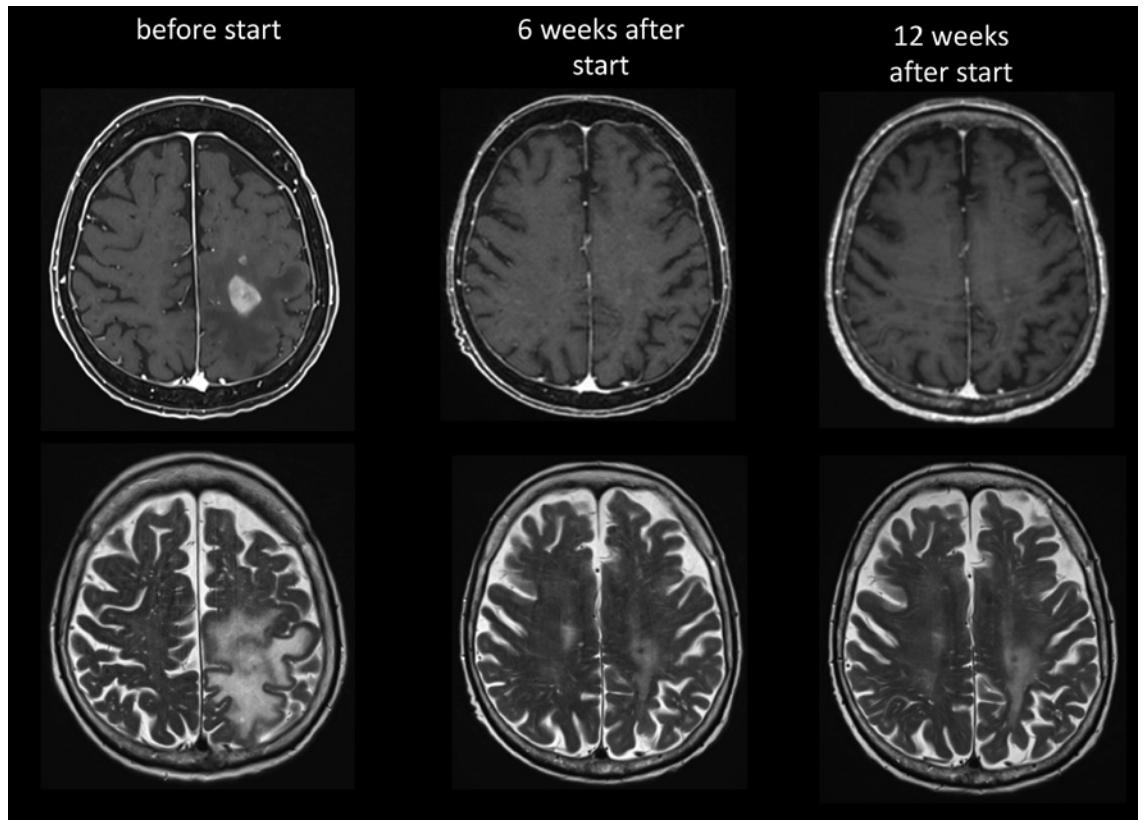


Fig. 3. T1-weighted (upper panel) and T2-weighted MRI of the brain (gadolinium administration) before and after larotrectinib treatment.

some similarity to glioblastoma, IDH wildtype but did not fall into any of the distinct clusters (Fig. 1). The 6-methylguanine-DNA methyltransferase promoter status was unmethylated. Targeted RNA sequencing identified an NTRK3 (exon 15) – ARHGEF7 (exon 17) fusion (Fig. 2). Such a fusion protein between NTRK3 and the Rho guanine nucleotide exchange factor 7 (ARHGEF7) has not yet been described. As the multifocal tumor was unresectable, the patient underwent cerebral radiotherapy of the tumor area with a total dose of 39.9 Gy (15×2.66 Gy). Additionally, the patient received a short course of high-dose steroids (with an initial dose of 16 mg daily dexamethasone)

for symptomatic brain edema. Dexamethasone was tapered over 17 days with initial dosing of 12 mg, then 8 mg, and then 4 mg daily. Treatment with larotrectinib was started shortly after the completion of radiotherapy. A clinical benefit was apparent within 2 weeks of larotrectinib-therapy, as reflected by significantly improved mobility due to hemiparesis regression. Moreover, remarkable cognitive improvement was noted. High-dose steroid treatment was tapered to physiological dose 1 month after the start of larotrectinib-therapy. Six weeks after treatment initiation, a brain MRI revealed partial response according to RANO criteria (Fig. 3). As the patient had re-

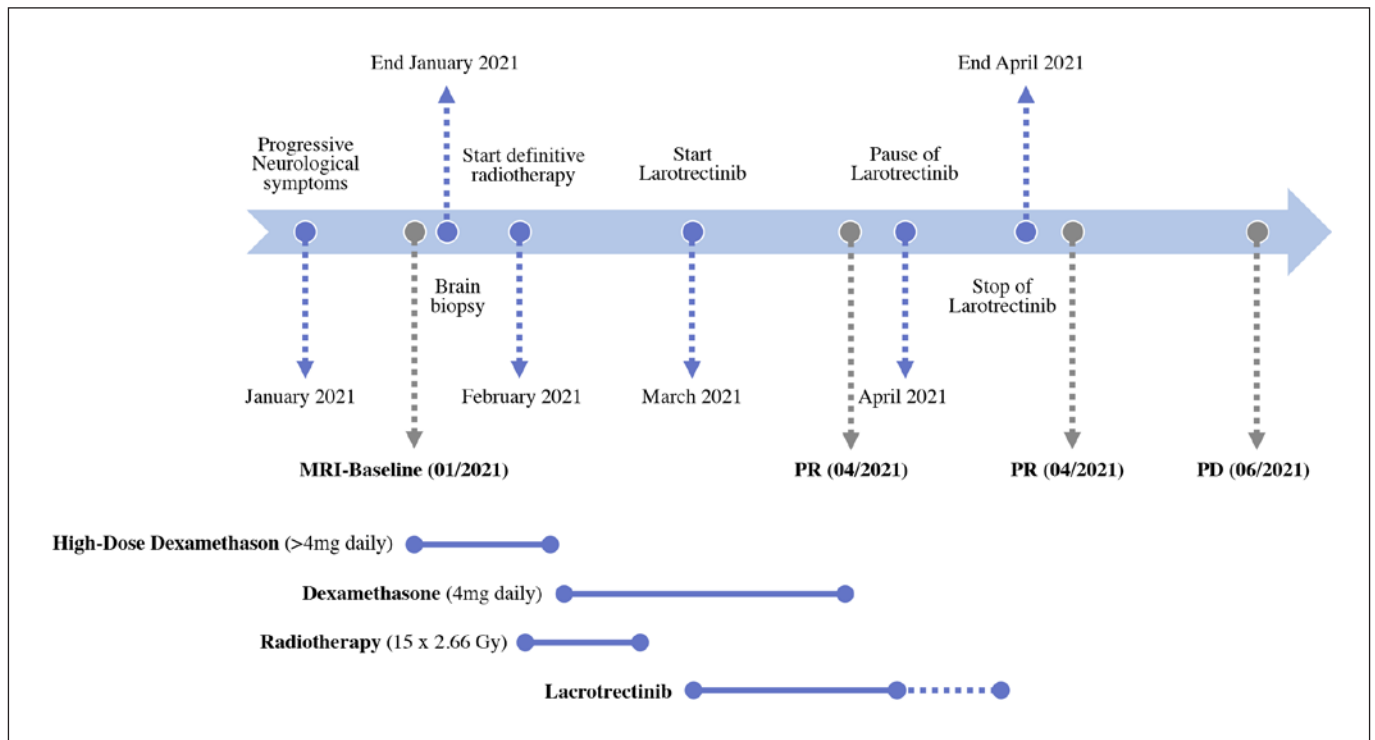


Fig. 4. Timeline of interventions and treatments.

ceived cerebral radiotherapy, we cannot distinguish between the effect of radiation and that of the NTRK inhibitor. A follow-up MRI after 3 months of treatment showed continuous remission, paralleled by continuing clinical benefits, although larotrectinib treatment had to be paused due to reversible grade 4 hepatotoxicity. Sustained clinical benefit was preserved 2 months after stop of larotrectinib and 6 months after diagnosis (Fig. 4).

Discussion/Conclusion

NTRK fusions act as oncogenic drivers in various tumor types [6]. NTRK fusions are frequently found in some rare cancer entities such as secretory breast carcinoma, cancers of the salivary glands, papillary thyroid cancer, and congenital fibrosarcoma. They only rarely occur in adult HGG, while their prevalence is higher in pediatric HGG and diffuse intrinsic pontine gliomas [6]. Numerous NTRK fusions have been described across different tumor types [7]. Most patients have NTRK1 or NTRK3 rearrangements and the most frequently represented gene fusion is ETV6-NTRK3 [6]. In primary CNS malignancies, NTRK fusions involving each of the NTRK

genes have been described [7]. Most potent TRK-inhibition has been observed for the first-generation inhibitors larotrectinib [8] and entrectinib [9], characterized by a high overall response rate (79% and 57%) and rapid onset of response. Of note, both larotrectinib and entrectinib have been tested in a tumor-agnostic setting. Pivotal pooled analysis excluded patients with primary CNS malignancies. A recent report describes 33 patients with CNS tumors treated with larotrectinib [4]. Most patients were pediatric patients (26 patients), and a response rate of 30% was observed. None of the adult patients had an NTRK3 fusion. Interestingly, the DNA methylome in our patient did not match any of the defined glioblastoma subtypes, and due to the paucity of cases, it is currently unknown whether this cluster is associated with NTRK fusion-driven HGG.

Here, we describe an adult patient with a diffuse, NTRK3 fusion-driven HGG who was successfully treated with larotrectinib. Although we assume that cerebral radiotherapy contributed to the response observed in our patient, the rapid onset of clinical benefit after start of larotrectinib-therapy (as often seen for targeted therapy in other driver-dependent solid tumors) suggests an important role of TRK-inhibition. The rapid treatment re-

sponse to larotrectinib is consistent with the reported time to response in other patients [7]. The uniform (radiological) response argues against tumor heterogeneity. Due to the short treatment period, the durability of larotrectinib treatment was not assessable.

The underlying NTRK3-ARHGEF7 fusion in our report has not been previously described in any tumor entity, although ARHGEF7 is known as a fusion partner for other drivers. In a pediatric medulloblastoma patient, a gene rearrangement involving ARHGEF7 and MYO16 has been reported [10]. ARHGEF7 (Rho guanine nucleotide exchange factor 7) belongs to Ras-like family of Rho proteins and has an important role during neuronal development [11]. Upregulation of ARHGEF7, also known as β Pix (Pax-interacting exchange factor beta) or Cool1 (Cloned out of library 1), might play a key role in glioblastoma cell invasion [12].

Given the still very limited prognosis with current standard treatment options in patients with HGG and the new treatment options for NTRK-gene fusions, testing for these alterations should be considered, especially in patients whose methylome analysis does not match the standard glioma or glioblastoma type. Efficacy data of TRK-inhibition in patients with CNS malignancies should be pooled and regulatory status evaluated.

Acknowledgment

The authors thank the patient for allowing us to report her clinical information and data.

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Statement of Ethics

The patient has given written informed consent for the publication of her case including publication of images. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

David König, Jürgen Hench, Ivana Bratic Hench, and Stephan Frank had no conflicts of interest to declare. Laura Dima is employed by Bayer. Heinz Läubli received travel grants and consultant fees from Bristol-Myers Squibb (BMS) and Merck, Sharp & Dohme (MSD). Received research support from BMS, Novartis, GlycoEra, and Palleon Pharmaceuticals.

Funding Sources

There was no financial support/funding for this article.

Author Contributions

David König and Heinz Läubli treated the patient and wrote the manuscript. Jürgen Hench, Ivana Bratic Hench, and Stephan Frank performed histological and molecular analysis. Laura Dima helped writing the manuscript. All authors have approved the final version for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.