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Case Report

Larotrectinib Use in A Patient with A Diffuse High-Grade Glioma with NTRK2 Fusion

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Abstract:

High-grade gliomas, particularly in the pineal region, present challenges due to their aggressive nature and the lack of established treatment regimens. Molecular profiling allows clinicians to identify mutations that may be actionable to improve progression-free and overall survival. This report presents the case of a 59-year-old male with a high-grade glioma of the pineal region harboring an NTRK2 fusion who was successfully treated with larotrectinib. His tumor has remained stable for over 24 months, and he is tolerating therapy well, with manageable fatigue and no other significant adverse effects. This case confirms the importance of obtaining molecular profiling to enable administration of targeted treatment options which can in turn improve patient outcomes.

Key words: larotrectinib; NTRK2 fusion; high-grade glioma; molecular profiling

Introduction

High-grade gliomas are difficult to treat due to both the aggressive nature of the tumor as well as the limited number of treatment options. Additionally, if these tumors are unable to be surgically resected, morbidity is increased. The molecular make-up of these tumors is also complex and variable, making current approved treatment options even more challenging for use across the entire patient population. Current standard-of-care treatment, including radiation and chemotherapy, is associated with myelosuppression, fatigue, and gastrointestinal or other toxicities and results in overall survival of around 12-15 months (Stupp et al., 2005). Fortunately, many therapies which target certain fusions are much better tolerated and do not come with the toxicities of traditional therapies alone.

High-grade gliomas of the pineal region are particularly rare, accounting for less than 0.5% of all gliomas (Price et al., 2024), and often cannot be completely resected due to their location adjacent to critical brainstem structures. Given their rarity in the adult population, there is little known about optimal treatment strategies; however, discovering certain tumor mutations can enable treatment with targeted therapy, improving survival in selected patients.

Advances in molecular profiling have led to the discovery of glioma mutations that respond to certain therapies. One such mutation is the Neurotrophic Tyrosine Receptor Kinase (NTRK) fusion. NTRK fusions are rare in gliomas; they have been found in less than 2% of all adult and pediatric central nervous system (CNS) tumors (Torre et al., 2020). However, once discovered, treatment of this mutation with TRK-targeted therapy, such as larotrectinib, can lead to prolonged progression-free and overall survival. Larotrectinib, the first tissue-agnostic molecular targeted therapeutic approved by the FDA (FDA, 2018), received accelerated FDA approval for treating solid tumors with an NTRK gene fusion in adult and pediatric patients. Larotrectinib is a highly selective TRK

inhibitor that targets the CNS (Hong et al., 2023). Its use has been shown to have rapid disease control, durable response, and a favorable side effect profile when used to treat many rare solid tumors (Drilon et al., 2018; Waguespack et al., 2022). This case study describes the (a) significance of an NTRK2 fusion in an adult patient with high-grade pineal glioma and (b) the tolerability and efficacy of larotrectinib in this patient's treatment.

Case Presentation

A 59-year-old adult male presented to his primary care office with a 4-week history of progressively worsening sleepiness, brain fog, short-term memory impairment, headaches, decreased physical coordination, delayed reaction time, confabulation, and episodes of near falls. A brain MRI revealed a heterogeneously enhancing pineal region mass and associated tri- ventricular obstructive hydrocephalus with periventricular edema. Biopsy of the mass identified a high-grade glial/glioneuronal neoplasm not elsewhere classified, characterized by multiple mitoses, necrosis, and a Ki-67 index of approximately 20% (Figure 1). By immunohistochemistry, the tumor cells were positive for Olig2 and synaptophysin; IDH1 R132H, H3 K27M, and BRAFV600E were negative; ATRX, BAF47, and BRG1 were retained; and the Ki-67 index was approximately 30%. Chromosomal microarray analysis demonstrated chromothripsis events involving chromosomes 9, 12, and 18; homozygous loss of CDKN2A/B (9p21.3); MDM2 amplification (12q15); and multiple additional copy number abnormalities including loss of 13q (RB1) and 17p (TP53). Next-generation sequencing was negative for IDH1/2, H3F3A, and TERT promoter mutations. Methylation profile testing was unable to result due to insufficient DNA yield.

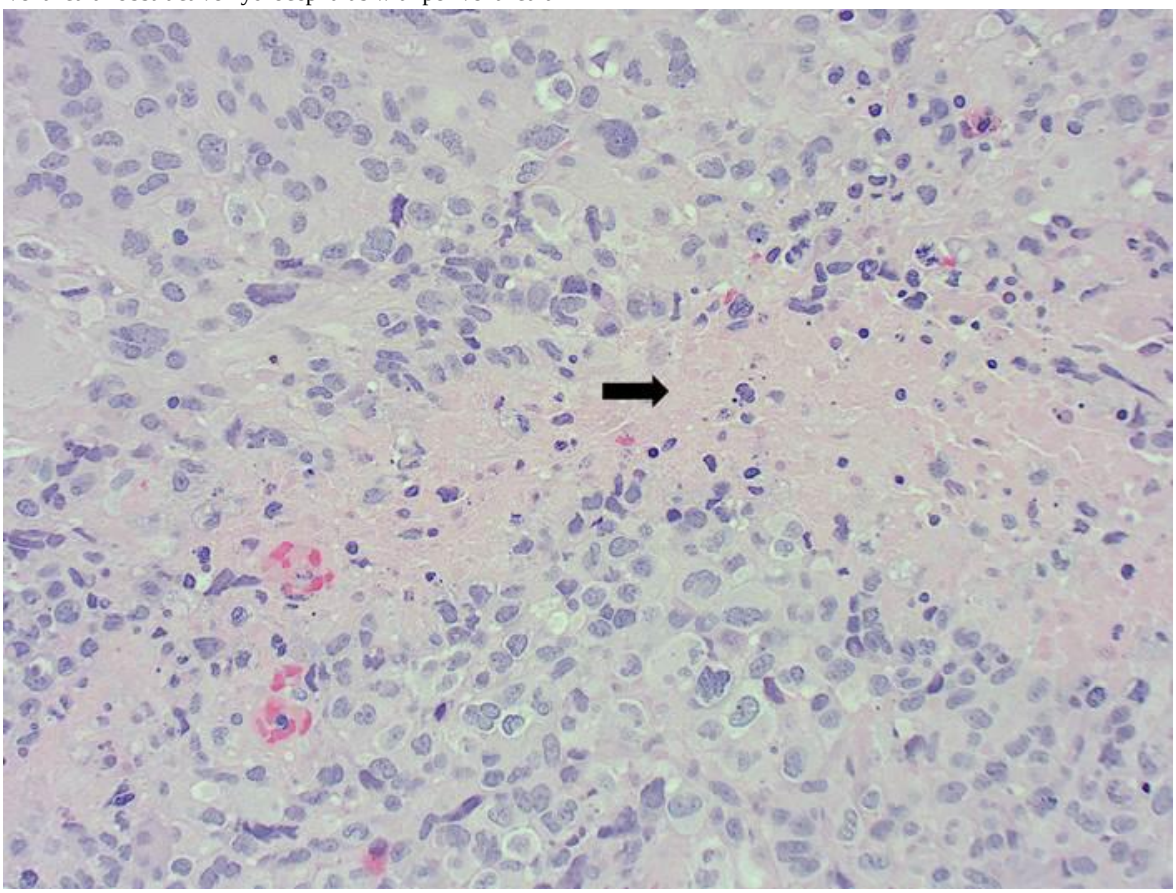

Figure 1: High-grade glial/glioneuronal neoplasm with necrosis (hematoxylin and eosin, original magnification x 20).

Six weeks of temozolomide and radiation per Stupp protocol were initiated (Stupp et al., 2005). Chemoradiotherapy was well-tolerated, with only mild fatigue. The patient required 1 to 2 mg of dexamethasone to help with bilateral tinnitus throughout radiation and temozolomide. His symptoms resolved with dexamethasone, and he was able to taper off therapy prior to completion of the standard 6 weeks of radiation.

The biopsy tissue was sent to Caris for molecular profiling, which identified a GKAP1: NTRK2 fusion; therefore, the process for approval of larotrectinib was initiated. Twenty-six days after completion of chemoradiotherapy, the patient proceeded with larotrectinib 100 mg by mouth twice daily (Vitravaki, 2023).

Upon drug initiation, the patient was monitored closely with a complete blood count with differential and comprehensive metabolic panel every other week for two months followed by monthly, along with a clinic visit with an oncology advanced practice provider, where he was evaluated for both neurologic symptoms as well as toxicity related to larotrectinib. He underwent routine brain MRIs with and without contrast every 2 months. Two months after initiating larotrectinib therapy, the tumor shrank. This initial shrinkage was likely due to the initial effects of radiation; however, over the course of nine months, the tumor continued to shrink, with stability ultimately noted at that time. No significant radiographic changes to the tumor were noted for the following 17 months. At 2.5 years after diagnosis, the patient's MRI continued to show a stable size of the pineal region mass with a resolution of enhancement and associated hydrocephalus (Figure 2).

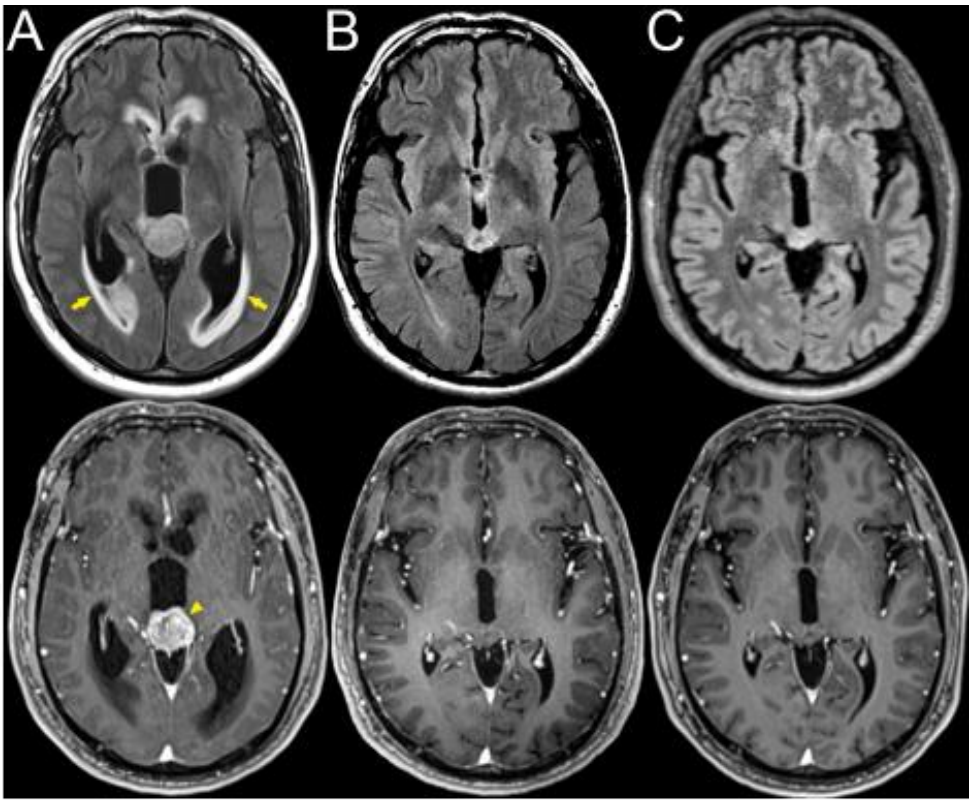

Figure 2: Axial T2/FLAIR weighted (top row) and T1-weighted post-contrast (bottom row) MR images at the level of the pineal region from the date of original diagnosis (A), at 1 year post- treatment (B), and 2.5 years post-treatment (C). Images at the time of diagnosis (A) show a heterogeneously enhancing pineal region mass (arrowhead) and associated triventricular obstructive hydrocephalus with periventricular edema (arrows). Post-treatment images (B and C) show decreased size of the pineal region mass with resolution of enhancement and associated hydrocephalus.

After 18 cycles of larotrectinib, the patient had not experienced any of the following common side effects: nausea, dizziness, vomiting, hepatotoxicity, cough, bowel changes (Vitrakvi, 2023). He had developed only mild fatigue (requiring a 1- to 2-hour nap daily), which, with ongoing use of larotrectinib, increased to about 3 hours of napping daily by month 24. The patient expressed that this fatigue did not interfere with his activities of daily living, and he was willing to continue the medication. Given the potential risk for fractures and ongoing use, a bone density test was ordered for close monitoring of the patient.

At the completion of 2 years of therapy with larotrectinib, the case was presented at tumor board, and the question was posed as to whether to continue therapy. Although data support that there is a positive impact on survival for patients with brain tumors treated with 2 years of traditional chemotherapy (Jaoude et al., 2019), chemotherapy is often discontinued after 2 years due to resistance concerns and/or risk for chemotherapy toxicities that may be additive over time. Given the patient's manageable fatigue, the decision was made to continue the targeted therapy until his disease progressed or unmanageable toxicity was experienced. This recommendation was extrapolated from using TRK-targeted therapy in other disease groups, particularly lung cancer (Hong et al., 2023).

Discussion

Larotrectinib proved effective in treating patients with CNS tumors in the largest study to date (Doz et al., 2022). However, as this study was performed on patients with a median age of 8.9 years, uncertainties remain regarding its efficacy and side effect profiles in the adult patient population. Additionally, much of the research regarding the efficacy of larotrectinib has been performed on solid tumors (including thyroid, lung cancer and breast cancer) other than gliomas (Rosen et al., 2019; Waguespack et al., 2022; Drilon et al., 2018).

Since its FDA approval in 2018, larotrectinib has allowed patients with NTRK fusions to achieve better tumor control/response without traditional chemotherapy's challenging side effect profiles (FDA, 2018). This case confirms the importance of obtaining tumor molecular profiling on all patients with primary CNS tumors, particularly those with high-grade gliomas, as both progression-free and overall survival can be improved if an actionable mutation such as NTRK2 is identified. This case demonstrates how a patient can achieve a quick and durable response to TRK therapy along with the excellent tolerance of the medication. Limitations to utilization of Larotrectinib in patients with high grade glioma revolve around the length of use and the risk of resistance. Without confirmed length of treatment, there is unknown as to how long to use the drug for treatment of the tumor. However, there is also concern that with prolonged use, there is potential for resistance. Although low frequency, when NTRK2 is identified in patients with gliomas, it is imperative to initiate targeted treatment and consider potential resistance should dosing need to be altered (Amatu et al., 2016). There is a concern for the potential resistance of first-generation TRK inhibitors as resistance is mediated by on-target mutations (Parrish & Szulzewsky, 2024). In such cases, utilization of a second-generation inhibitor may be considered (Parrish & Szulzewsky, 2024).

Conclusion

High-grade gliomas, particularly those located in the pineal region, can present treatment challenges given their rarity and lack of established treatment regimens. Utilizing molecular profiling, an NTRK fusion may be identified, which can lead to targeted treatment of these tumors with a TRK inhibitor such as larotrectinib.

This case highlights larotrectinib as safe and efficacious in treating an adult patient with a high- grade glioma that harbors an NTRK fusion. Continued research is warranted to further understand the long-term efficacy and safety of larotrectinib use in this population. This case confirms that molecular profiling and targeted therapy can have a promising effect on this rare and potentially life-threatening cancer.

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