Potent clinical and radiological response to larotrectinib in first case of TRK fusion high grade glioma

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TRK fusion cancer

- Somatic oncogenic fusions involving the NTRK1, NTRK2, and NTRK3 genes (NTRK gene fusions), which encode the TRKA, TRKB and TRKC receptor tyrosine kinases, occur in a broad range of solid tumors.
- Beyond embryogenesis, TRK proteins are primarily expressed in the nervous system.
- The 3 neurotrophin receptors regulate specific normal functions: NTRK1 encodes TRKA → Pain, thermoregulation; NTRK2 encodes TRKB → Movement, memory, mood, appetite, body weight; NTRK3 encodes TRKC → Proprioception.
- NTRK gene fusions are generally rare, but are recurrent oncogenic drivers.

Larotrectinib

- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC50 in cellular assays).
- It is highly selective, with little or no interaction with other kinase and non-kinase targets.
- Liquid formulation allows dosing of children as young as 1 month of age and delivers equivalent pharmacokinetics to capsules.
- Larotrectinib is highly active in children and adults with TRK fusion solid tumors, eliciting durable responses in both.

Efficacy in TRK fusion cancer

- Larotrectinib is the first selective TRK inhibitor in clinical development:
  - An overall response rate of 80% has been reported in a series of pediatric and adult patients with TRK fusion cancer.
  - However, no patients in this cohort had a TRK fusion high grade glioma.

Case history prior to larotrectinib

- Patient is a 3-year-old girl who was diagnosed with a brain tumor at 5 months of age.
- Presented initially with vomiting and seizures; MRI showed a heterogeneous mass measuring 6 × 3 × 2 cm in the right lateral ventricle.
- Following gross total resection, pathology showed a high grade glioma and she was treated with 20 cycles of chemotherapy.
- 4 months after completing treatment, she had disease progression in the tumor bed with multiple nodules in the lateral and third ventricles. Further tumor debulking confirmed recurrent disease.
- After 6 months, a new mass in the tumor bed was subtotally resected; patient received focal radiotherapy of 54 Gy to the tumor bed. In parallel, the resected tumor underwent molecular testing on a pilot personalized medicine study, to inform therapeutic options for potential future disease progression:
  - Whole genome sequencing of tumor DNA revealed a somatic ETV6-NTRK3 gene fusion (Figure 1); RNA sequencing showed that the ETV6-NTRK3 fusion was robustly expressed.
  - 3 months following completion of radiation therapy she re-presented with difficulty walking, drowsiness, vomiting and irritability. MRI showed widespread progressive disease with increased enhancement at the resection site, and enlarging suprasellar and subependymal nodules in the lateral and third ventricles (Figure 2A, B).
- Given the presence of an NTRK gene fusion, the patient was referred for larotrectinib compassionate access.

Treatment with larotrectinib

- Larotrectinib compassionate access was obtained and treatment was commenced at a dose of 100 mg/m2 BID:
  - After 4 weeks the patient had no further lethargy, drowsiness, headaches or vomiting, was eating well, and had started talking clearly.
  - After 6 weeks she was able to walk independently, was speaking in 2–3-word sentences, and had normal energy levels.
  - By week 8 she was running, dancing, and continued to gain new words and language.
  - MRI scans at 2 and 5 months demonstrated a sustained radiological response (Figure 2C–F).
  - At the time of this report the patient continues on treatment with no adverse events.

Conclusion

- The dramatic response in this patient shows that larotrectinib can penetrate the blood brain barrier and may have potent activity in patients with high grade gliomas harboring NTRK gene fusions.

References


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