Diffuse mid-line glioma with H3K27M mutation

Sonikpreet
PGY5 Hematology/Oncology fellow
Mayo Clinic, Florida
Learning objectives

• Case discussion

• Diffuse mid-line glioma with H3K27M mutation.

• Molecular biology.

• Potential targeted treatment options: Histone deacetylase inhibitors (HDACi).
Chief complaint

“Gradual weakness of bilateral upper and lower extremities”.
Case description – Part A

- Ms X is a 50 year-old-female who presented with numbness and weakness of her right upper extremity (RUE) progressing to right lower extremity (RLE), numbness around her trunk, and urinary hesitance/incontinence over a period of 9 months.

- Medical history: none

- Surgical history: none

- Family history: no significant familial/medical history

- Social history: a small business owner, non-smoker, non-drinker, lives with her parents and 4 sisters.

- ROS: negative except as above.
Case description – Part A (contd)

- Labs: Unremarkable
- Physical examination:
- Hemodynamically stable
- Neurological examination: awake, alert and oriented to time, place and person; motor strength - 3/5 RUE, 2/5 RLE; right hand contractures, sensation intact bilaterally, standing with assistance.
• Surgery: Cervical laminectomy C4-T3 and subtotal resection of intradural intramedullary spinal cord tumor C5-T2.

• Pathology: spinal cord pilocytic astrocytoma IDH-1 negative and MIB-1 10%.
Fast forward 6-10 months: progressive symptoms of left hand stiffness with contractures. She still has residual right upper and lower extremity weakness.
Management

• Revised pathology based on new criteria and molecular testing: Diffuse midline glioma H3 K27M-mutant WHO grade IV.

• Surgery was not recommended.

• Treatment: concurrent chemotherapy (Temozolomide), Valproic acid and radiation therapy.

• Physical therapy.
Loss of the K27 methylation mark (IHC for K27-methylation)
Diffuse mid-line gliomas H3K27M

- 2016 WHO classification of CNS tumors - Diffuse midline glioma, H3 K27M-mutant Grade IV (new entity).
- Mutation in histone H3 at position amino acid 27 resulting in the replacement of Lysine by methionine (K27M).
- Can occur in mid-brain, pons, and spinal cord.
- Mostly occur in children and rare in adults.

Molecular biology

PRC2 methyltransferase

KDM6 demethylase

KDM6 demethylase

PRC2 methyltransferase
Targeted therapy

• GSKJ4 has \textit{in-vitro} and \textit{in-vivo} anti-tumor activity against K27M mutant tumors.

• Vorinostat: pan-HDACi showed benefit in pre-clinical data.

• Panobinostat: better activity than Vorinostat \textit{in-vitro}.

• Trial of Panobinostat in Children With Diffuse Intrinsic Pontine Glioma (PBTC-047) is currently open.

• In-vitro: combination of Panobinostat and GSKJ4 has shown synergistic effect.

• Valproic acid: can be a potential therapeutic agent

Summary

- Diffuse mid-line glioma with H3K27M Grade IV tumors are defined as separate clinical entity in WHO classification in 2016 with aggressive course and poor prognosis.

- We have better understanding of the epigenetic pathways.

- Currently, pre-clinical data has shown some benefit with histone deacetylase inhibitors.

- Further clinical trials are required to assess their efficacy and effect on PFS/OS.
Thank you.

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