Genome-wide analysis of vestibular schwannomas: is medical management possible?

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Introduction

- Vestibular Schwannomas (VS) are benign, typically encapsulated tumors of the cranial nerve VIII sheaths, usually commencing in the internal auditory meatus
  - Symptoms are typically related to the compression of adjacent cranial nerves, brainstem, or posterior fossa structures
- The majority of VS are unilateral and sporadic, whereas 5% of all schwannomas are bilateral and part of neurofibromatosis type 2 (NF2)
- VS are treated by surgical resection, stereotactic radiotherapy, or close observation
- There has been recent discussion about the possibility of treating vestibular schwannomas using chemotherapeutic agents:
  - inhibitors of RKT, Akt, MTOR, and CXCR4
  - Anti-inflammatory medications
  - Anti-VEGF antibody: tumor shrinkage and hearing improvement have been identified after the administration of bevacizumab
- We performed a targeted genomic analysis on a series of sporadic unilateral VS
  - This analysis, which assesses for many known cancer-associated genetic mutations, is paired with literature-based suggestions for targeted medical therapy

Methods

- Genomic analysis was performed on tissue samples of individual vestibular schwannomas between 2017-2021 at a single institution
- Tissue samples were sent to Jackson Laboratory where they were analyzed using ActionSeq™ 2.0 which incorporates a targeted-enrichment sequencing assay comprising 501 cancer-related genes for which all coding exons are sequenced and clinically significant variants in 209 genes are reported
- Evidence of association between genomic variants and potential therapeutic, prognostic and/or diagnostic outcomes was then obtained from peer-reviewed literature, clinical practice guidelines, FDA labels, publicly available databases and the JAX Clinical Knowledgebase (JAX-CKB)
  - Current data includes gene and variant descriptions, drug indication status, clinical trials, treatment efficacy, evidence support response or resistance to treatments by indication
  - Variants were classified into four tiers: tier I (strong clinical significance), tier II (potential clinical significance), tier III (unknown clinical significance), tier VI (benign or likely benign variants)
- The electronic medical record of each patient was retrospectively reviewed for prior NF2 diagnosis, previous VS resection/recurrence, tumor location, presenting symptoms and demographic factors

Results

- Eight VS were resected and sequenced
- Average age at resection was 48.4 years old
- None of the patients had prior NF 2 diagnosis, prior separate schwannoma diagnosis, or prior history of malignancy of any kind

Results

Variable	
Male, n (%)	5 (62.5%)
Race, n (%)	
Caucasian	8 (100%)
Ethnicity, n (%)	
Not Hispanic/Latino (a)	8 (100%)
Tumor location, n (%)	
Cerebellopontine angle and internal auditory canal	8 (100%) 2 (25.0%)
Brainstem involvement	
Presenting symptoms, n (%)	
Dizziness/balance issues	3 (37.5%)
Facial/ear pain	2 (25.0%)
Asymmetric hearing loss	6 (75.0%)
Tinnitus	1 (12.5%)
Prior retrosigmoid craniotomy, n (%)	1 (12.5%)
Prior translabrynth debulking, n (%)	2 (25.0%)

Table 1: Patient demographics, clinical presentation, and prior VS surgical history. The clinical presentation includes symptomatic presentation and tumor location.

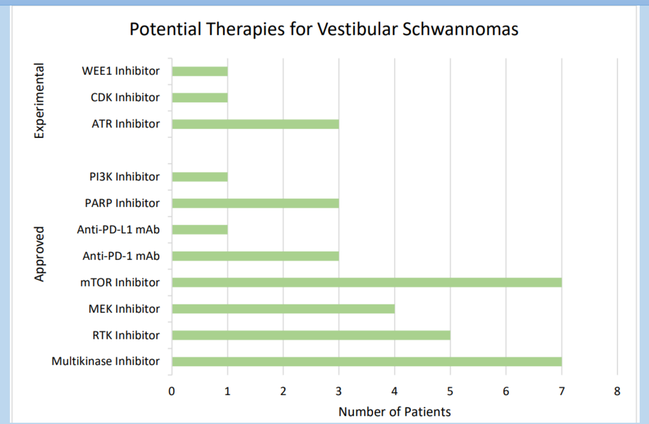

Figure 1: Number of patients with VS theoretically susceptible to potential medical therapies (both experimental and FDA-approved therapies).

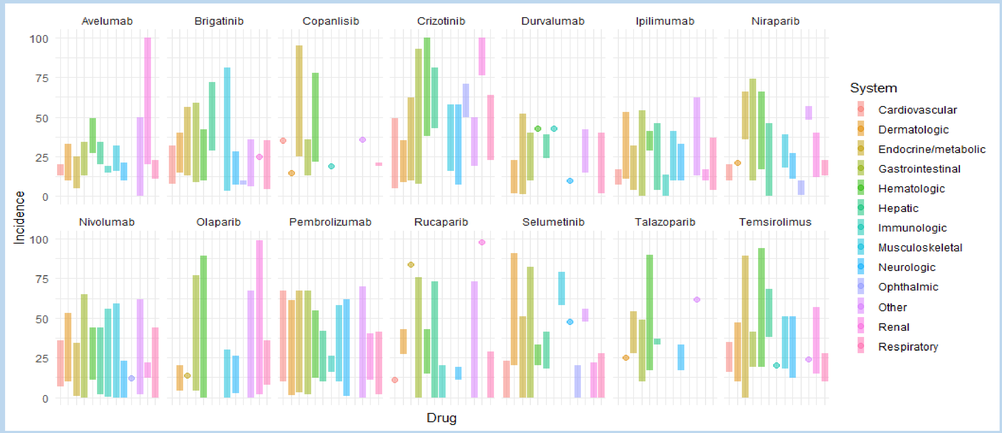

Figure 2: Incidence of medication side effects categorized by body system.

Discussion/Conclusions

- The efficacy and response of several of the therapeutic agents have already been studied in VS, both *in vivo* and *in vitro*
- The use of chemotherapeutic agents to treat VS is a promising approach to limit risks associated with radiation and surgery
- It is important to consider the adverse effects that can be caused by each of these chemotherapies (**figure 2**) as well as discuss these risks and benefits in comparison to the standard of care with the patient
  - At this time, it may not be reasonable to use these therapeutic agents in otherwise healthy patients with VS due to the significant adverse effects
- Future directions:
  - Sequencing VS for cancer-related gene variants may be used in the future as a routine test following tumor resection to potentially guide targeted medical therapy in appropriate patients, as well as further knowledge on potential co-drivers of VS
  - The data may also help guide the development of in-vitro experiments to examine the proposed therapies

Subject	Genomic Markers	Potential Therapies	FDA Approved – Different Indication
1	NF2 p.R262 c.784C>T NF2 p.K413 c.1237A>T	Multikinase Inhibitor RTK Inhibitor MEK Inhibitor mTOR Inhibitor	Brigatinib Crizotinib Selumetinib Temsirolimus
2	NF2 p.Q147fs c.441_442delinsC RAD51 Deletion (one copy)	Multikinase Inhibitor RTK Inhibitor MEK Inhibitor mTOR Inhibitor Anti-PD-1 mAb PARP Inhibitor o ATR Inhibitor	Brigatinib Crizotinib Selumetinib Temsirolimus Avelumab Niraparib Rucaparib
3	NF2 p.R196 c.586C>T NF2 p.D513 c.1536_1539delTGAC CHEK2 Deletion (one copy)	Multikinase Inhibitor RTK Inhibitor MEK Inhibitor mTOR Inhibitor Multikinase Inhibitor RTK Inhibitor MEK Inhibitor mTOR Inhibitor Anti-PD-1 mAb PARP Inhibitor o ATR Inhibitor	Brigatinib Crizotinib Selumetinib Temsirolimus Brigatinib Crizotinib Selumetinib Temsirolimus Avelumab Olaparib Rucaparib
4	NF2 p.Q362 c.1084C>T RAD51 Deletion (one copy) BRCA2 p.G2748D c.8243G>A	Multikinase Inhibitor mTOR Inhibitor Anti-PD-1 mAb PARP Inhibitor o ATR Inhibitor Anti-PD-1 mAb PI3K Inhibitor Anti-PD-L1 mAb Anti-CTLA-4 mAb PARP Inhibitor o CDK Inhibitor o ATR Inhibitor o WEE1 Inhibitor	Brigatinib Temsirolimus Avelumab Olaparib Rucaparib Avelumab Copanlisib Durvalumab Ipilimumab Niraparib Nivolumab Olaparib Pembrolizumab Rucaparib Talazoparib
5	CHEK2 Deletion (one copy) NBN p.S53fs c.156_157delTT	Anti-PD-1 mAb PARP Inhibitor o ATR Inhibitor Anti-PD-1 mAb PARP Inhibitor o ATR Inhibitor	Avelumab Rucaparib Avelumab Niraparib Rucaparib Talazoparib
6	NF2 p.R25 c.71_72dupTG	Multikinase Inhibitor RTK Inhibitor mTOR Inhibitor	Brigatinib Crizotinib Temsirolimus
7	NF2 p.K88fs c.263delA	Multikinase Inhibitor RTK Inhibitor MEK Inhibitor mTOR Inhibitor	Brigatinib Crizotinib Selumetinib Temsirolimus
8	NF2 p.R57 c.169C>T	Multikinase Inhibitor mTOR Inhibitor	Brigatinib Temsirolimus

Table 2: Genomic markers, potential therapies, and proposed FDA-approved medications for each genotyped VS.

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