Targeted Therapies for Vestibular Schwannoma

Subjects: Oncology

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Vestibular schwannoma (VS) is a benign tumor that originates from Schwann cells in the vestibular component. Surgical treatment for VS has gradually declined, especially for small tumors. Gamma knife radiosurgery has become an accepted treatment for VS, with a high rate of tumor control. For neurofibromatosis type 2 (NF2)-associated VS resistant to radiotherapy, vascular endothelial growth factor (VEGF)-A/VEGF receptor (VEGFR)-targeted therapy (e.g., bevacizumab) may become the first-line therapy. A clinical trial using a VEGFR1/2 peptide vaccine was also conducted in patients with progressive NF2-associated schwannomas, which was the first immunotherapeutic approach for NF2 patients. Targeted therapies for the gene product of SH3PXD2A-HTRA1 fusion may be effective for sporadic VS. Several protein kinase inhibitors could be supportive to prevent tumor progression because merlin inhibits signaling by tyrosine receptor kinases and the activation of downstream pathways, including the Ras/Raf/MEK/ERK and PI3K/Akt/mTORC1 pathways. Tumor-microenvironment-targeted therapy may be supportive for the mainstays of management. The tumor-associated macrophage is the major component of immunosuppressive cells in schwannomas.

Keywords: schwannoma ; NF2 ; bevacizumab ; VEGF ; molecular targeted therapy

1. Introduction

Schwann cells originate from neural crest cells, which migrate with growing neurites during nerve development. Schwann cells, which form the myelin sheath of an axon, support neuronal function and regeneration [1].

Schwannoma (Sch) is one of the common benign intracranial tumors with an incidence of 1 per 100,000 [2]. Sch often presents between the ages of 40 and 60 years [2]. Among these cases, 80–90% originate from the vestibular nerve. About 5–10% of vestibular Schs (VSs) are observed as bilateral in neurofibromatosis 2 (NF2) patients. A total of 95% of NF2 patients show bilateral VSs [3]. About 60% of unilateral VSs and 90% of bilateral VSs show NF2 gene mutation and the dysfunction of its transcription product, moesin–ezrin–radixin-like (merlin) protein [4].

The mainstays of management are observation, surgery, and radiosurgery. Surgery with facial and auditory monitoring remains the only curative treatment for growing VSs of all sizes. Stereotactic radiosurgery is considered as a widely accepted treatment option for small-sized VSs. For larger tumors, combined treatment strategies are mostly recommended. In particular, gamma knife radiosurgery (GKRS) has become an accepted treatment for VS [5]. However, additional treatment is needed for some refractory cases. Tumor volume ≥15 cm^3 is a significant factor predicting poor tumor control following GKRS [6]. There is no approved medical therapy for VS. For refractory VS with high risks of surgical treatment or GKRS, medical therapies that can slow tumor growth are urgently needed.

2. Inflammation and Stress Reaction

2.1. COX2

The expression of cyclooxygenase 2 (COX-2) is associated with sporadic and NF2-related VS proliferation. Mutations in the NF2 gene can activate the Hippo pathway, in which YAP can promote the transcription of COX-2 for prostaglandin production. Prostaglandin E2 (PGE2) catalyzed by COX-2 has multiple roles in cell proliferation, apoptosis, angiogenesis, inflammation, and immune monitoring. COX-2 inhibitors may have the potential to inhibit the growth of VS [7][8].

A negative correlation between aspirin users and sporadic VS growth has been demonstrated [9][10]. In addition to inhibiting COX-2, aspirin can also suppress the activated NF-κB pathway in VS, which may be another potential mechanism. However, other studies demonstrated that there is no growth inhibitory effect for celecoxib on NF2-related VS or aspirin on sporadic VS [9][10]. Other studies have shown that NSAIDs, glucocorticoids, and other immunosuppressive drugs could not alter the expression of COX-2 in sporadic Sch [11].

2.2. Hsp90

Heat shock protein 90 (HSP90) is a ubiquitous molecule. The absence of Hsp90 results in proteasomal degradation [12]. The dysregulation of the Hippo pathway is necessary for schwannomagenesis, and MAPK signaling acts as a modifier for Sch formation. Furthermore, the pharmacological co-inhibition of YAP/TAZ transcriptional activity and MAPK signaling shows a synergistic size reduction in a mouse Sch model [13].

In a recent study, a novel small-molecule inhibitor compound of HSP90, NXD30001 (pochoxime A), was able to show reduced growth of NF2-deficient tumors in vivo. There are no current clinical trials using an HSP90 inhibitor [14].

The molecular patterns and mutations described for VS are summarized in **Table 1**.

Table 1. Molecular patterns and mutations currently described for VS.

Targeted Pathway	
	NF2 (merlin)-related pathway
1	**Ras/Raf/MEK/ERK signaling**
2	**PI3K/Akt/mTORC1 signaling**
	SH3PXD2A-HTRA1-fusion-related pathway
1	**MAPK signaling**
	Protein-kinase-related pathway
1	**VEGF-A/VEGFR signaling**
2	**ErbB family signaling**
3	**PDGF/PDGFR signaling**
4	**HGF/HGFR (c-MET) signaling**
	Cytokines and chemokines
1	**CXCL12/CXCR4 signaling**
2	**IL-1β, IL-6, IL-34, M-CSF, TNF-α**
	Tumor microenvironment
1	**Tumor-associated macrophage**
2	**Regulatory T cell**
3	**PD-1/PD-L1**
4	**Hypoxia**
	Inflammation and stress reaction
1	**COX2**
2	**Hsp90**

c-MET, c-mesenchymal–epithelial transition; COX2, cyclooxygenase 2; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; ERK, extracellular-signal-regulated kinases; HGFR, hepatocyte growth factor receptor; Hsp90, heat shock protein 90; IL, interleukin; MAPK, mitogen-activated protein kinase; M-CSF, macrophage colony-stimulating factor; MEK, mitogen extracellular signal-regulated kinase; mTORC1, mammalian target of rapamycin complex 1; NF, neurofibromatosis; PDGFR, platelet-derived growth factor; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; Raf, rapidly accelerated fibrosarcoma; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

3. Drug Repositioning

Mifepristone (RU486), a progesterone and glucocorticoid receptor antagonist that has already been approved for medical abortion, was chosen as the most promising candidate drug [15]. In a preclinical study, mifepristone reduced cellular

proliferation in primary human VS cultures regardless of NF2 mutation. A phase II clinical trial on mifepristone in VS is currently being planned [15].

In VS, genes associated with NLRP3 were significantly upregulated in patients with poor hearing. NLRP3 mutation is associated with cochlear autoinflammation in conjunction with DFNA34-mediated hearing loss and age-rated hearing loss. The activation of NLRP3 triggers the production of IL-1β [16]. A recombinant human IL-1 receptor antagonist reversed the hearing loss observed in a family with sensorineural hearing loss and NLRP3 mutations [17].

4. Gene Therapy

Gene therapy offers the potential to treat a wide range of inherited and acquired human diseases. The direct modulation of affected genes in specific cell types represents the most powerful treatment strategy for NF2 patients. Delivery platforms typically include viral vectors, such as retroviruses, adenoviruses, and adeno-associated viruses (AAVs), as well as nonviral vectors, including nanoparticles and polymers [18].

A direct injection of an AAV serotype 1 vector encoding caspase-1 (ICE) under the Schwann-cell specific promoter led to the regression of Sch in a mouse model. Recently, a direct injection of AAV1 encoding the apoptosis-associated speck-like protein reduced tumor growth and resolved tumor-associated pain in a human xenograft Sch model [19].

Nonviral vectors, such as liposomal-, polymeric-, and peptide-based nanoparticles, offer an attractive alternative for gene delivery. Liposomes were used to deliver genome-editing agents to the cochlea of neonatal mice with dominant genetic deafness. By decorating the nanoparticle surface with a peptide targeting Schwann cells, peptide-based nanoparticles were used to deliver genetic materials, resulting in a decreased secretion of an ototoxic inflammatory cytokine from tumor cells [20].

5. Ongoing Clinical Trials

Table 2 shows ongoing clinical trials using multimodal treatment strategies for Sch. The superselective intraarterial infusion of bevacizumab is performed to control tumor progression (NCT01083966). Because of the promising results found with bevacizumab, it may be safely used by direct intracranial superselective intraarterial infusion up to a dose of 10mg/kg in order to enhance survival and hearing function. Another six trials are using medical treatment strategies. Crizotinib, AR-42 (OSU-HDAC42), everolimus, selumetinib (MEK 1/2 inhibitor), and tanezumab (a monoclonal antibody against nerve growth factor as a treatment for pain) are being evaluated in the trials. A previous meta-analysis suggests that there is insufficient evidence to recommend aspirin usage in patients with VS [21][22]. High-quality trials are warranted to determine the efficacy of aspirin in reducing VS growth (NCT03079999).

Table 2. Active and recruiting clinical trials using medical therapeutic approaches for schwannoma.

ClinicalTrials.Gov Identifier	ID	RP	EE	Age	TS
NCT01083966	8, 2011	Lenox Hill Brain Tumor Center	30	≥18	Superselective intraarterial intracranial infusion of bevacizumab
NCT04283669	2, 2020	University of Alabama at Birmingham	19	≥6	Crizotinib
NCT03079999	6, 2018	Massachusetts Eye and Ear Infirmary	300	≥12	Aspirin
NCT02282917	9, 2015	Massachusetts Eye and Ear	5	≥18	AR-42 (OSU-HDAC42)
NCT01345136	7, 2015	University of California	4	16–65	Everolimus
NCT03095248	5, 2017	Children's Hospital Medical Center	34	3–45	Selumetinib
NCT04163419	4, 2020	Massachusetts General Hospital	46	≥18	Tanezumab

ER, estimated enrollment; ID, initiation date; RP, responsible party; TS, treatment strategy.

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