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REVIEW

A Review of Drug Therapy in Vestibular Schwannoma

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Abstract: Vestibular schwannomas (VSs, also known as acoustic neuromas) are benign intracranial tumors commonly managed with observation, surgery, and radiotherapy. There is currently no approved pharmacotherapy for VS patients, which is why we conducted a detailed search of relevant literature from PubMed and Web of Science to explore recent advances and experiences in drug therapy. VSs feature a long course of disease that requires treatment to have minimal long-term side effects. Conventional chemotherapeutic agents are characterized by neurotoxicity or ototoxicity, poor effect on slow-growing tumors, and may induce new mutations in patients who have lost tumor suppressor function, and therefore are unsuitable for treating VSs. Along with the well-investigated molecular pathophysiology of VS and the increasingly accessible technology such as drug repositioning platform, many molecular targeted inhibitors have been identified and shown certain therapeutic effects in preclinical experiments or clinical trials.

Keywords: vestibular schwannomas, drug therapy, therapeutic targets, VEGFR inhibitor

Introduction

As the most common tumors of the cerebellopontine angle and the fourth most common intracranial neoplasms, vestibular schwannomas (VSs) are histopathologically benign neoplasms that typically originate from Schwann cells lining cranial nerve VIII (vestibular nerve). Neurosurgeons have determined that hearing loss, deafness, and tinnitus are common clinical manifestations in the early stages of VSs, and that progressive VSs are likely to impact lower cranial nerves and the brainstem, leading to facial paresthesia, ataxia and vertigo.[1] With the progress of diagnosis and treatment technology, the main purpose of VS management has changed from saving patients' lives to preserving complete neurological function and improving their quality of life.

VSs can occur unilaterally, as sporadic lesions, or bilaterally, as a part of autosomal dominantly inherited disorder neurofibromatosis type 2 (*NF2*). About 60% of unilateral VSs and 90% of bilateral cases demonstrate the mutation of the *NF2* gene and the dysfunction of its transcription product, merlin (Moesin-ezrin-radixin-like protein).[2,3] Strategies for managing patients with sporadic VS are observation, surgery, and radiotherapy. Over the 3.6-year follow-up, the average growth rate for sporadic tumors was 1.1 mm/year, suggesting that "wait and rescan" with serial MRIs is a safe choice for small and stable tumors (<2cm), as well as for elderly patients, whose treatment is associated with a higher mortality rate.[4] However, this tactic is associated with risk of tumor growth and poor hearing

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outcomes. Surgical treatment can cause significant trauma to patients, thus it is only preferable in patients with symptoms of brainstem compression or with small but fast-growth tumors. Radiotherapy is suitable for small growing tumors and small tumors with an irregular outline. Additionally, pseudo progression, damage to cochlear hair cells, delayed hearing loss, and surgically challenging post-stereotactic radiosurgery should be taken into consideration.[5–7] *NF2*-VSs are more lobulated, grow more quickly, present at a younger age, tend to be larger, envelop adjacent cochlear and facial nerves, and may coexist with schwannomas of the facial and cochlear nerves, making the cleavage plane between the facial nerve and the tumor difficult to determine, thus higher risk of nerve damage secondary to surgery.[8,9] It is widely accepted that radiotherapy is less effective in treating *NF2*-VSs than treating sporadic VSs.[10]

The growing understanding of the mechanisms by which merlin dysregulation induces disease, as well as of signal pathways related to VS growth, has raised hopes for the application of targeted therapies. Merlin plays a significant role in regulating the process mediated by the actin cytoskeleton, adhesion junction formation, and cell proliferation.[11] Recent studies have suggested that merlin can regulate multiple pathways implicated in tumorigenesis including retrovirus-associated DNA sequences (Ras)/rapidly accelerated fibrosarcoma (Raf)/mitogen extracellular signal-regulated kinase (MEK)/extracellular-signal-regulated kinases (ERK), mammalian target of rapamycin complex 1 (mTORC1), Rac/p21-activated kinase (PAK)/C-Jun kinase, phosphoinositide 3-kinase (PI3K)/Akt and the intranuclear E3 ubiquitin ligase CRL4 (DCAF1) (Figure 1).[12–17] All of these proposed sites are potential therapeutic targets of VS.

Methods

To conduct this literature review, we searched the databases of PubMed and Web of Science to identify studies published between 2010 and 2020, which included the terms "vestibular schwannoma" or "acoustic neuroma," in addition to "drug," "medicine," "therapy," or "treatment." Additionally, we manually searched the reference list of the retrieved articles and summarized therapeutic targets currently under consideration and pharmacotherapy in cell studies, animal experiments, and clinical trials in vestibular schwannoma.

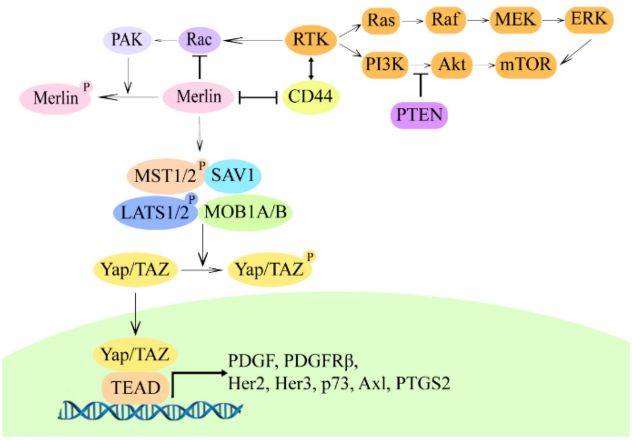

Figure 1 Signal pathways related to merlin dysregulation.
Notes: After merlin inactivation, RTK and its downstream Ras/Raf/MEK/ERK and PI3K/Akt/mTOR signaling pathways are abnormally activated. In addition, merlin inhibits the phosphorylation of Yap/TAZ downstream of the Hippo pathway, allowing more Yap/TAZ into the nucleus and binds to TEAD, promoting the transcription of PDGF, PDGFRβ and PTGS2.
Abbreviations: PAK, p21-activated kinase; RTK, receptor protein tyrosine kinase; Ras, retrovirus-associated DNA sequences; Raf, rapidly accelerated fibrosarcoma; MEK, mitogen extracellular signal-regulated kinase; ERK, extracellular-signal-regulated kinases; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; Yap, Yes-associated protein; TAZ, TEAD; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PTGS2, prostaglandin G/H synthase 2.

Results

Protein Tyrosine Kinase Inhibitor

The transfer of the phosphate groups on adenosine triphosphate (ATP) to determined target proteins is catalyzed by kinases, which are the primary mediators in cell signal transduction that regulate cell differentiation, growth, migration, and apoptosis. As a type of kinase that catalyzes the transfer of phosphate from ATP to protein tyrosine residues, protein tyrosine kinase (PTK) can be divided into receptor protein tyrosine kinases (RTKs) and non-receptor protein tyrosine kinases (nrPTKs) according to their structure.[18]

RTKs usually consist of an extracellular domain, a transmembrane region, and an intracellular kinase domain. They are not only cell surface receptors for many growth factors and cytokines but also catalyze the phosphorylation of tyrosine residues of their target proteins.[19] Uncontrolled RTK signals lead to cell growth disorders and cancer, which provided the rationale for the development of strategies for the prevention and interception of RTK signaling as a way to treat cancer. A number of RTKs have been shown to be associated with VS, such as ErbB, platelet-derived growth factor (PDGF), fibroblasts growth factor (FGF), insulin-like growth factor-1

(IGF-1), and vascular endothelial growth factor (VEGF).[20–25]

Additionally, nrPTKs, including Src, BCR-ABL, and the JAK/STAT pathway, are not receptors per se. They generally do not have an extracellular domain, but are coupled to the cell membrane or exist in the cytoplasm, and their tyrosine kinase activity can be activated after binding to the activated receptor.[26] The activation of nrPTKs and downstream signal transduction pathways can promote cell proliferation, cell apoptosis resistance, and oncogenesis. Further, over-activation of the Src pathway has been found in *NF2*.[27]

ErbB Family Protein Inhibitors

The ErbB family's cell membrane receptors include EGFR (HER1/erbB-1), HER2 (neu/erbB-2), HER3 (erbB-3), and HER4 (erbB-4). When specific ligands bind to the extracellular domain, they induce a conformational change in the transmembrane region, causing ErbB family members to form heterodimers and simultaneously activate the intracellular kinase domain.[28] Activation of ErbB receptors was considered a common feature of both sporadic and *NF2*-related VS, and EGFR expression levels correlated directly with VS tumor size and inversely with patient age.[29,30] Besides, an intriguing finding is that EGF was upregulated in all *NF2*-related VS, but not so in any of the sporadic VS.[29] Moreover, *NF2*-related VS tend to present in young patients experiencing a growth phase with greater levels of circulating EGF, implying that an EGFR inhibitor might have greater efficacy in *NF2* patients.

The predominant ErbB receptor dimerization pattern in VS is EGFR and ErbB2 heterodimers.[31] Trastuzumab, a humanized anti-ErbB2 monoclonal antibody, can significantly reduce VS cells' proliferation and VS xenografts' growth; however, this antibody does not ensure a significant increase in VS cells' death.[32]

Lapatinib is a potent and reversible tyrosine kinase inhibitor that has been widely used in the treatment of metastatic breast cancer.[33] It has a dual inhibitory effect on EGF activation of EGFR/ErbB2, thus, it may be effective at abrogating the growth effects of EGF in VS In a preclinical VS model, molecular targeted therapy with lapatinib can inhibit ErbB2 phosphorylation and survivin upregulation.[30] A Phase II study showed that lapatinib carries minor toxicity and has the effect of reducing tumor volume and improving hearing in *NF2* patients with progressive VS.[34]

Additionally, another study demonstrated that lapatinib is less potent for inhibiting the proliferation of schwannoma cells, compared with erlotinib, which may be due to the upregulation of ErbB3 that is caused by lapatinib's inhibition of ErbB2.[35,36] Erlotinib is a reversible, small molecule EGFR-specific tyrosine kinase inhibitor. It can significantly reduce the growth of VS xenografts in nude mice and increase cell death.[32] However, an erlotinib strategy in 11 *NF2*-related VS was found to be clinically ineffective for tumor size reduction and improving hearing responses.[37]

PDGFR Family Protein Inhibitor

The PDGFR family includes PDGFR-α, PDGFR-β, colony-stimulating factor1-receptor (CSF1-R), fetal liver kinase-2 (Flk-2), and c-kit. Compared with normal nerves, the expression and activation of c-kit, PDGFR-α and PDGFR-β in sporadic and *NF2*-related VS are all increased.[38] Therefore, they are all candidates as VS therapeutic targets. Imatinib mesylate (STI571) is an inhibitor of the BCR-ABL fusion kinase designed to treat chronic myelogenous leukemia (CML). In vitro studies using the immortalized *NF2*-null VS cell line HEI-193 showed that imatinib mesylate inhibits the activation of c-KIT, PDGFR-α, and PDGFR-β and its downstream signaling pathways, leading to increased apoptosis, cell cycle arrest, and decreased cell viability in a dose-dependent manner (IC_{50} 5–10 μmol/L).[21,38] Moreover, corneal angiogenesis assay revealed that imatinib has an inhibitory effect for angiogenesis in both sporadic and *NF2*-related VS.[39] This dual inhibition of tumorigenesis and angiogenesis potentializes imatinib in the treatment of VS.

Nilotinib (AMN107) is a second-generation RTK inhibitor with a target profile similar to that of imatinib, but has increased potency, decreased toxicity, and greater tissue permeability, making it easier to penetrate the blood-brain barrier.[40] Nilotinib is currently used to treat imatinib-resistant CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Nilotinib has been shown to inhibit cell proliferation more effectively than imatinib in a primary human schwannoma cell in vitro model, indicating that this compound has a therapeutic effect on merlin-deficient tumors.[41] In HEI-193 cells, nilotinib can reduce cell viability, inhibit proliferation and increase apoptosis; these anti-tumorigenic effects are related to the inhibition of PDGFR-α and PDGFR-β, as well as their downstream signaling mediators, Akt and mTOR.[42]

Ponatinib (AP24534) is a third-generation inhibitor of BCR/ABL tyrosine kinase that is considered as a pan-BCR -ABL inhibitor with potent anti-tumorigenic properties in other cancers.[43] Alejandra et al observed that ponatinib can reduce cell viability of primary VS cells with *NF2* mutations and stimulate a robust G1 cell cycle arrest of merlin-deficient human Schwann cells (HSC) by decreasing the highly phosphorylated PDGFRα/β in merlin-deficient HSC and VS samples. Therefore, ponatinib might have significant therapeutic value for VS.[44]

VEGFR Inhibitor

The VEGFR family mainly includes VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4), which are important regulators of physiological or pathological angiogenesis. Merlin deletion can lead to down-regulation of the protein semaphoring3F (SEMA3F) that inhibits VEGF-mediated angiogenesis.[45,46] Studies have shown that the concentration of VEGF and VEGFR-1 is related to the growth rate of VS, which warrants further research regarding the anti-VEGF monoclonal antibody bevacizumab for VS treatment.[47] In 2009, Plotkin reported that, for patients with *NF2* and progressive VSs, bevacizumab (5mg/kg/2 week) treatment can lead to tumor shrinkage in up to 90% of cases patients, as well as durable hearing response in over half of cases.[48] Subsequently, a variety of studies validated that bevacizumab can benefit progressive *NF2*-VS patients in terms of hearing improvement and tumor-volume reduction.[49–52] Although bevacizumab has achieved promising and satisfactory results in progressive and large tumors, its therapeutic effect seems to have population differences. First, its efficacy in pediatric *NF2*-VS patients is quite controversial. A previous study showed that the average annual tumor growth rate in children (median age at inclusion was 15 years) was reduced from 138% to 36% after one year of treatment.[53] However, follow-up studies have revealed that although bevacizumab can delay pediatric patients' hearing loss, it has minimal effect on objective radiological response compared with adult participants.[50,52,54] Second, bevacizumab did not cause tumor residuals regression or hearing improvement in any of the 9 young *NF2*-VS patients after partial resection, indicating this pharmacotherapy might have poorer efficacy in smaller and slow-growth tumors, thus, new treatment strategies are required.[55]

The DCE-MRI data suggested bevacizumab can normalize the function of tumor vessels and potentially restore the normality of the blood-nerve barrier, while also improving vascular perfusion and oxygen delivery, thereby reducing tumor edema and enhancing the efficacy of radiotherapy.[48,56] The volumetric response to bevacizumab therapy can be predicted by the mean apparent diffusion coefficient at baseline, while hearing improvement is inversely correlated with the baseline plasma hepatocyte growth factor (HGF) level.[48,57]

Compared with malignancies, the medication time of bevacizumab in the treatment of benign tumors is usually prolonged, making drug tolerability an issue to consider. The main causes for bevacizumab adverse reactions are intravenous route of administration and dose accumulation. A retrospective study showed that for 33 *NF2*-related VS or ependymoma patients treated with bevacizumab (5 mg/kg biweekly, IV), 58% developed hypertension and 62% developed proteinuria, implying an urgency to find an optimal dosing schedule.[58] The super-selective intra-arterial infusion of bevacizumab, after temporary disruption of the blood-brain barrier, was capable of improving drug concentrations at the tumor site, leading to better therapeutic effect in *NF2*-VS patients.[59] By reducing the dose of bevacizumab from 5 mg/kg biweekly to 2.5 mg/kg bi- or tri-weekly, the adverse effects of hypertension or proteinuria in three *NF2*-VS patients disappeared with sustained clinical response, indicating that the low-dose regimen is more desirable in the long-term treatment with bevacizumab.[60]

The role of bevacizumab in *NF2*-VS has been well documented. An adult female patient with progressive sporadic VS also exhibited excellent imaging response to bevacizumab, providing a new treatment alternative for sporadic VS patients who are not suitable for standard treatment.[61] The safety and preliminary efficacy of the VEGFRs peptide vaccine demonstrated in *NF2* patients promises a new hope for the immunotherapy of *NF2*-VS.[62]

HGFR Inhibitor

The hepatocyte growth factor (HGF) receptor, also known as c-MET (c-mesenchymal-epithelial transition) is a glycosylated receptor tyrosine kinase that expressed on the cell surface and plays a central role in driving tumorigenesis.[63] Numerous studies have shown that the over-activation of c-MET may initiate the transformation of normal cells into tumor cells, and further drive subsequent events such as invasion and metastasis. The activation of the HGF/c-MET pathway in sporadic VS can mobilize the inflammation network in the brain microenvironment and promote the progression of cancer.[64,65] This

pathway can also protect cells from DNA fragmentation and apoptosis induced by chemotherapy or radiotherapy through PI3K/Akt signaling, and is related to the resistance of radiotherapy, chemotherapy and targeted therapy.[66–68]

The c-MET and anaplastic lymphoma kinase inhibitor crizotinib (CRZ, PF-02341066) can enhance radiation-induced DNA damage of *NF2* schwannoma cells, thereby enhancing tumors' radio-sensitivity, which is conducive to reducing the dose of radiotherapy and protecting patients' hearing.[69] The study in animal models of *NF2* delineate the potential target of CRZ is focal adhesion kinase 1 (FAK1), with inhibition of this target can suppress tumorigenesis and rescue the treatment effects of the CRZ-resistant forms of FAK1.[70] A Phase II clinical trial of CRZ for *NF2* and progressive VS in children and adults is ongoing (NCT04283669). Simultaneous use of the c-MET inhibitor cabozantinib and the Src inhibitor saracatinib can cause caspase-dependent apoptosis in merlin-deficient mouse Schwann cells (MD-MSC) and reduce the viability of human VS cells with *NF2* mutation by 40%, which is more effective than using either inhibitor alone.[71]

There is a crosstalk between c-MET and VEGFA in VS, as described in other pathological types of cells. Using c-MET-targeted siRNA, Sonam et al found that c-MET and VEGFA protein levels decreased, while VEGFA-targeted siRNA reduced c-MET expression; this discovery highlights combined inhibition of VEGFA and c-MET as an effective pharmacotherapy.[64]

Small Molecule Inhibitors of Akt Signal Transduction

A better understanding of the underlying mechanisms of VS tumorigenesis can help design new targeted therapies. The most studied abnormality in VS is the PI3K/Akt pathway, which is manifested by elevated Akt mRNA and protein levels, as well as higher Akt phosphorylation levels in VS samples.[72,73] Because the PI3K/Akt pathway is the confluence point of many growth stimuli and controls cellular processes and responses (such as cell survival, cell proliferation, insulin response, stress response and differentiation) through its downstream substrates, its activation may contribute to tumorigenesis.[74] Therefore, the PI3K/Akt pathway is the most attractive therapeutic target for VS, and small molecule inhibitors of Akt signaling may have therapeutic potential to inhibit the growth of benign VS and malignant schwannomas.

OSU-03012 (AR-12) is a phosphoinositide-dependent kinase-1 (PDK1) inhibitor that can induce apoptosis of several types of cancer cells. Although OSU-03012 is a novel derivative of the cyclooxygenase 2 (COX-2, also known as prostaglandin G/H synthase 2, PTGS2) inhibitor celecoxib (Celebrex™), it has no COX-2 inhibitory activity. By dose-dependent reduction of Akt phosphorylation in VS cells, OSU-03012 inhibits VS cell growth and promotes apoptosis.[75]

Additionally, OSU-HDAC42 (AR-42), a novel phenylbutyrate-derived histone deacetylase inhibitors (HDACIs), can inhibit the downstream Akt expression of PI3K and PDK1 through protein phosphatase-1-mediated Akt dephosphorylation, showing the effect of G2 cell cycle arrest and VS cell apoptosis induction in both cell and animal experiments.[76] Further, an in vitro study demonstrated that AR-42 potently inhibits primary VS cell growth ($IC_{50} \approx 500$ nM) at doses correlating with Akt pathway inhibition, which indicates that AR-42 could be a promising molecular targeted agent for VS.[77]

mTORC1 Inhibitor

mTOR is a downstream signal of the PI3K/Akt pathway that can integrate signals from multiple upstream pathways as well as the local intracellular environment and serve as a hub in the intracellular communication cascade. Merlin was reported to negatively regulate mTORC1, inhibition of the constitutive activated mTORC1 pathway in merlin-deficient tumors may be a useful targeted therapy for VS.[17]

Using the mTORC1 inhibitor rapamycin (also known as sirolimus) to treat merlin-deficient schwannoma cell lines, allogeneic *NF2*-/- mice models, and genetically engineered mouse models of *NF2* schwannomas, previous studies have found that rapamycin are cytostatic for *NF2*-/- schwannoma cells, and that it can also inhibit the growth of merlin-deficient tumors in vivo. Consistent with this, rapamycin can lead to tumor volume reduction in *NF2* patients with growing VS.[78]

Everolimus (RAD001), a derivative of rapamycin, can not only inhibit mTORC1 but also reduce tumor angiogenesis.[79] Although a phase II study found that everolimus was ineffective in progressive *NF2*-related VS patients, another study showed that taking everolimus reduced the median annual tumor growth rate in 55.6% of patients with *NF2*-related VS, from 67% before treatment to 0.5% during treatment.[80,81]

Chemokine Receptor-4 (CXCR4) Inhibitor

CXCR4 is a G protein-coupled receptor of the chemokine receptor subfamily, with a molecular weight of 40kDa. It plays an important role in the development of the nervous, hematopoietic, and cardiovascular systems during embryogenesis, and in pathological processes like infection and tumor development.[82,83] CXCR4 is also considered to be correlated with the tumorigenesis and functional impairment of sporadic and *NF2*-related VS.[84]

CXCR4-directed positron emission tomography/computed tomography (PET/CT) imaging with radiolabeled CXCR4-targeted ligand [68Ga] Pentixafor in VS patients can be used to evaluate CXCR4 expression in VS patients.[85] These results provide a possibility for the use of Plerixafor (AMD3100), a CXCR4-targeting drug, in individualized therapeutic tactics of VS patients.

Inflammatory Factor Inhibitors

COX2 Inhibitor

Several studies have shown that the expression of COX-2 is associated with sporadic and *NF2*-related VS proliferation.[86,87] Mutations in the *NF2* gene can activate the Hippo pathway, in which the effector molecule YAP can promote the transcription of the key enzyme COX-2 for prostaglandin biosynthesis. Prostaglandin E2 (PGE2) catalyzed by COX-2 has multiple roles in cell proliferation, apoptosis, angiogenesis, inflammation, and immune monitoring.[88] This suggests that COX-2 inhibitors may have the potential to inhibit the growth of VS A significant negative correlation between aspirin users and sporadic VS growth has been found, indicating the potential therapeutic role of aspirin in sporadic VS management.[89]

However, other studies on celecoxib, aspirin, and COX-2 inhibitors in non-steroidal anti-inflammatory drugs (NSAIDs), found that there is no expected growth inhibitory effect for celecoxib on *NF2* or aspirin on VS.[90–92] Other studies have shown that NSAIDs, glucocorticoids, or other immunosuppressive drugs could not alter the expression of COX-2 in VS, and that NSAIDs were not significantly correlated with VS growth, tumor diameter, and average VS growth rate.[92–94]

In addition to inhibiting COX-2, aspirin can also suppress the activated NF-κB pathway in VS, which is another potential mechanism of the therapeutic effect of aspirin.[95,96] Aspirin is recommended by the Congress of Neurosurgeons for "wait and scan" VS patients to prevent tumor proliferation.[97]

NF-κB Inhibitor

Mifepristone (RU486) is a progesterone and glucocorticoid receptor antagonist used for medical abortion. It is well tolerated via oral administration and can be used for the palliative treatment of glioblastoma multiforme.[98,99] The screening by computational drug repositioning platform ksRepo found that mifepristone has the potential to treat VS. Moreover, Ingenuity Pathway Analysis (IPA) results infer that mifepristone acts on the upstream of VS inflammation markers, such as NF-κB.[100] Further cell experiments demonstrated that mifepristone inhibited the metabolic and proliferative activity of VS cells in a dose-dependent manner, and this effect was independent of whether the *NF2* gene was mutated.[101]

Discussion

For a long time, the unpredictable course of VS has presented unique management challenges. Currently, local treatment is the main option for VS, and there is no level I evidence to support systematic treatment of VS. In addition to the aforementioned drugs, the inhibitory effects of LiCl, cucurbitine D and Goyazensolide on the proliferation of *NF2* deficient schwannoma cells, tanshinone IIA, and Ailanthone on the proliferation of VS cells have been confirmed.[102–105] The delivery of tumor necrosis factor (TNF)-targeted siRNA by nanoparticles can reduce the VS- sensorineural hearing loss-related protein concentration.[106] The use of the *NF2*-VS growth model based on the early tumor volume dynamics and the VS growth model when treated with bevacizumab and everolimus alone or in combination, established by Ouerdani et al, opens up the prospect of individualized treatment for *NF2* patients.[107]

The research on the pathways in which the *NF2* gene product interacts provides a pharmacological basis for the development of VS targeted drugs. Compared with traditional chemotherapy, targeted therapy possesses less vascular nerve damage and has good application prospects. *NF2* gene mutation and merlin dysfunction is a typical characteristic of *NF2*-VS and often occurs in sporadic VS.[2,3] Therefore, drugs based on this mechanism have the potential to treat both *NF2*-VS and sporadic VS As we summarized, imatinib mesylate, bevacizumab, and aspirin have shown efficacy in sporadic VS, suggesting the potential of targeted therapy in sporadic VS.[39,61,89] The loss of merlin results in

Table 1 Summary of Drugs Under Research

Class	Therapeutic Target	Drug	Features	Ref
PTK inhibitors	ErbB	Trastuzumab	Inhibit cells proliferation without significant increase in VS cells death.	[32]
		Lapatinib	Reduce tumor volume and improve hearing in *NF2*-VS patients in a phase II study.	[34]
		Erlotinib	Can inhibit the growth of VS and increase cell death in nude mice, but ineffective in *NF2*-VS patients.	[32,37]
	PDGFR	Imatinib mesylate	Increased apoptosis and decrease cell viability in a dose-dependent manner in HEI-193 cell line. Imatinib also has an angiogenesis inhibitory effect in both the sporadic and *NF2*-VS by corneal angiogenesis assay.	[21,38,39]
		Nilotinib	Inhibit proliferation and increase apoptosis in HEI-193 cell line.	[42]
		Ponatinib	Reduce cell viability of primary *NF2*-VS cells and induce G1 cell cycle arrest of merlin-deficient HSC.	[44]
	VEGFR	Bevacizumab	Benefit *NF2*-VS patients in hearing improvement and tumor shrinkage. A sporadic case of imaging reaction to bevacizumab was also reported.	[48–52,61]
	HGFR	Crizotinib	Enhance radiosensitivity of *NF2* schwannoma cells, a phase II clinical trial in progressive VS patients is ongoing.	[69]
		Cabozantinib	Combination with Src inhibitor saracatinib can reduce *NF2*-VS cell viability.	[71]
		c-MET targeted siRNA	Decrease both c-MET and VEGFA protein levels.	[64]
Akt inhibitors	Akt	OSU-03012	Inhibit cells proliferation and promote apoptosis.	[75]
		OSU-HDAC42	Induce G2 cell cycle arrest and VS cell apoptosis in both in vitro and in vivo study.	[76,77]
mTORC1 inhibitors	mTORC1	Rapamycin	Result in tumor volume reduction in *NF2*-VS patients.	[78]
		Everolimus	One study believes that everolimus is ineffective in *NF2*-VS, but in another study, it can reduce the median annual tumor growth rate in *NF2*-VS patients	[80,81]
CXCR-4 inhibitors	CXCR-4	CXCR4 inhibitor	/	[84]
Inflammatory factor inhibitors	COX2	Aspirin	A study confirmed an inverse correlation between aspirin users and sporadic VS growth, but another study suggested aspirin had no expected growth inhibitory on VS patients.	[89,92]
		Celecoxib	No expected growth inhibitory on genetically engineered murine model of *NF2*.	[91]
	NF-κB	Mifepristone	Inhibit the metabolism and proliferation activity of VS cells.	[101]

the activation of a variety of signals related to cell survival, growth, and proliferation, and these abnormally expressed molecules are also potential drug therapeutic targets, of which VEGF has made the most progress.[108] Table 1 shows the major categories of drugs currently in development. The complex interlinked signaling pathways in the pathogenesis of VS suggest that a combination therapy may provide an ideal therapeutic effect. Besides, due to the long duration of VS, the potential adverse reactions and toxicity of long-term use of the drug should also be considered.

Conclusions

Targeted therapy has shown efficacy in both sporadic VS and *NF2*-VS. Widely accepted treatment options,

including long-term observation, surgery, and radiation therapy, plus targeted therapies currently under research, are tailored for patients with different tumor characteristics. Further multidisciplinary cooperation will help to choose the best treatment plan for individual patients and maximize the protection of nerve function.

Abbreviations

ATP, adenosine triphosphate; c-MET, c-mesenchymal-epithelial transition; CML, chronic myelogenous leukemia; COX2, cyclooxygenase 2; CSF1-R, colony-stimulating factor1-receptor; CXCR4, chemokine receptor-4; ERK, extracellular-signal-regulated kinases; FAK1, focal adhesion kinase 1; FGF, fibroblasts growth factor; Flk-2, fetal liver kinase-2; HDACIs, histone deacetylase inhibitors; HGF, hepatocyte growth factor; HSC, human Schwann cell; IGF1, insulin-like growth factor-1; IPA, Ingenuity Pathway Analysis; MD-MSC, merlin-deficient mouse Schwann cells; MEK, mitogen extracellular signal-regulated kinase; mTORC1, mammalian target of rapamycin complex 1; *NF2*, neurofibromatosis type 2; nrPTKs, non-receptor protein tyrosine kinases; NSAIDs, non-steroidal anti-inflammatory drugs; PAK, p21-activated kinase; PDGF, platelet-derived growth factor; PDK1, phosphoinositide-dependent kinase-1; PET/CT, positron emission tomography/computed tomography; PGE2, prostaglandin E2; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; PI3K, phosphoinositide 3-kinase; PTGS2, prostaglandin G/H synthase 2; PTK, protein tyrosine kinase; Raf, rapidly accelerated fibrosarcoma; Ras, retrovirus-associated DNA sequences; RTKs, receptor protein tyrosine kinases; SEMA3F, semaphoring3F; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VSs, vestibular schwannomas.

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Disclosure

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