Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on Emerging Therapies for the Treatment of Patients With Vestibular Schwannomas

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MEDICAL THERAPY

Target Population: Adults with histologically proven or suspected vestibular schwannomas with neurofibromatosis type 2 (NF2).

Question: What is the role of bevacizumab in the treatment of patients with vestibular schwannomas?

Recommendations: Level 3: It is recommended that bevacizumab be administered in order to radiographically reduce the size or prolong tumor stability in patients with NF2 without surgical options.

Level 3: It is recommended that bevacizumab be administered to improve hearing or prolong time to hearing loss in patients with NF2 without surgical options.

Question: Is there a role for lapatinib, erlotinib, or everolimus in the treatment of patients with vestibular schwannomas?

Recommendations: Level 3: Lapatinib may be considered for use in reducing vestibular schwannoma size and improvement in hearing in NF2.

Level 3: Erlotinib is not recommended for use in reducing vestibular schwannoma size or improvement in hearing in patients with NF2.

Level 3: Everolimus is not recommended for use in reducing vestibular schwannoma size or improvement in hearing in NF2.

Question: What is the role of aspirin, to augment inflammatory response, in the treatment of patients with vestibular schwannomas?

Target Population: Any patient with a vestibular schwannoma undergoing observation.

Recommendation: Level 3: It is recommended that aspirin administration may be considered for use in patients undergoing observation of their vestibular schwannomas.

Question: Is there a role for treatment of vasospasm, ie, nimodipine or hydroxyethyl starch, perioperatively to improve facial nerve outcomes in patients with vestibular schwannomas?

Target Population: Adults with histologically proven or suspected vestibular schwannomas.

Recommendation: Level 3: Perioperative treatment with nimodipine (or with the addition of hydroxyethyl starch) should be considered to improve postoperative facial nerve outcomes and may improve hearing outcomes.

PREHABILITATION

Question: Is there a role for preoperative vestibular rehab or vestibular ablation with gentamicin for patients surgically treated for vestibular schwannomas?

Target Population: Adults with histologically proven or suspected vestibular schwannomas.

Recommendations: Level 3: Preoperative vestibular rehabilitation is recommended to aid in postoperative mobility after vestibular schwannoma surgery.

Level 3: Preoperative gentamicin ablation of the vestibular apparatus should be considered to improve postoperative mobility after vestibular schwannoma surgery.

SURGICAL THERAPY

Question: Does endoscopic assistance make a difference in resection or outcomes in patients with vestibular schwannomas?

Target Population: Vestibular schwannoma patients, who are surgical candidates. Inclusion in this analysis required resection utilizing the endoscope, either as the primary operative visualization or microscopic assistance with more than 20 patients treated.

Recommendation: Level 3: Endoscopic assistance is a surgical technique that the surgeon may choose to use in order to aid in visualization.

The full guideline can be found at: https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_9.

KEY WORDS: Acoustic neuroma, Emerging therapies, Endoscope, Novel drug therapies, Vestibular schwannoma

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Vestibular schwannomas (VS) are commonly managed well with observation, surgery, and radiation. However, treating physicians continue to investigate new and emerging therapies for treatment-resistant cases as well as to aid in improved patient outcomes.

METHODS

Details of the systematic literature review are provided in the full text of this guideline (https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_9) and within the methodology article (https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_1) of this guideline series. The task force collaborated with a medical librarian to search for articles published from January 1, 1966 to December 31, 2014. Two electronic databases, PubMed and the Cochrane Central Register of Controlled Trials, were searched. The task force made every effort to obtain a complete set of relevant articles to ensure the guideline is not based on a biased subset of articles.

Seventy-eight citations were manually reviewed by the team with specific inclusion and exclusion criteria. Two independent reviewers reviewed and abstracted full-text data for each article, and the 2 sets of data were compared for agreement by a third party. Inclusion and exclusion criteria can be viewed on the full version online. Evidence was then classified according to criteria for evidence on therapeutic effectiveness as detailed in the Joint Guidelines Committee guideline development methodology (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

ABBREVIATIONS: NF2, neurofibromatosis type 2; **VS,** vestibular schwannomas

RESULTS

Twenty-two studies met inclusion criteria for analysis in this diverse group. No level 1 evidence existed. One study met criteria for level 2 evidence; all others provided level 3 data. Level 3 data exist supporting bevacizumab as a medical therapy to radiographically reduce the size of VS, it further lengthens time to hearing loss and may improve hearing in neurofibromatosis type 2 (NF2). Less is known regarding the effectiveness of imatinib, mesylate, lapatinib, erlotinib, and everolimus; however, lapatinib has shown some success in VS tumor shrinkage in NF2. In patients with sporadic VS, level 3 evidence supports the use of acetylsalicylic acid to potentially prevent growth in appropriate patients. Agents aimed at vasospasm prevention (ex nimodipine) have level 3 evidence for the potential to improve postoperative facial function in surgery and may be considered. Level 3 evidence suggests prehabilitation for vestibular training or preoperative gentamycin ablation of the vestibular apparatus may aid in postoperative recovery.

DISCUSSION

The clinical and preclinical work done, thus far, in regards to emerging therapies in VS treatment has not provided data that immediately translates into level 1 recommendations at this time. Some progress has been made in medical therapies for treatment-resistant VS and applies most usefully to patients with NF2 where preservation of function is key. Bevacizumab has made the most progress and appears to be a viable treatment option for patients with NF2 and growing tumors or loss of hearing. In these patients, bevacizumab recovers some useful hearing function and results in tumor reduction; however, the effect is ultimately lost with time succumbing to the natural tendency of the tumor to grow, opening doors for combination or other therapies. Lapatinib also

appears to have some effectiveness in tumor size reduction and hearing preservation.

CONCLUSIONS

Other direct molecular inhibitors are also being investigated, and it appears phosphoinositide 3-kinase and mammalian target of rapamycin pathway inhibitors hold the most promise. Further options for treatment include vasoactive treatments perioperatively to improve postoperative outcome and aspirin therapy in those patients undergoing observation in preventing growth. What is clear when considering medications being useful for VS is that much more work is needed, and tumor consortiums should focus their efforts on promoting multi-institutional studies investigating these therapies. Furthermore, there are ongoing trials formally evaluating prehab and preoperative gentamicin ablation. Hopefully, these will define the role of these therapies in improving postoperative balance functions and aiding patients' postoperative recovery. In terms of endoscopic surgery for VS or its use as an adjunct at the time of surgery, the jury is still out; however, for those comfortable with these techniques, there may be an advantage in improving facial and cochlear nerve outcomes, as well as reducing cerebrospinal fluid leaks. It is important to note as a community of surgeons treating these conditions, it is critical to promote well-designed clinical trials to answer these questions and improve the outcomes of patients.

Disclosure

These evidence-based clinical practice guidelines were funded exclusively by the Congress of Neurological Surgeons, the Tumor Section of the Congress of Neurological Surgeons, and the American Association of Neurological Surgeons, which received no funding from outside commercial sources to support the development of this document.

Conflict of Interest

The Vestibular Schwannoma Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the full-text introduction and methods manuscript (https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_1).

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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