Systemic Bevacizumab for Severe Recurrent Respiratory Papillomatosis

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May 20, 2022

Abstract

Recurrent respiratory papillomatosis (RRP) is the most common benign pediatric laryngeal neoplasm. Various adjuvant medical therapies have failed to reliably decrease surgical frequency in this challenging airway disease. Recently, systemic bevacizumab has shown promise in advanced, treatment-resistant papillomatosis. We describe the use of systemic bevacizumab in two children with severe RRP unresponsive to other therapies. Voice and breathing improved dramatically in both patients with minimal side effects. Both patients have not required surgery in 23 months and 15 months, respectively. Systemic bevacizumab is a promising long-term treatment for severe RRP, with oncology playing an important role in patient care.

Introduction

Recurrent respiratory papillomatosis (RRP), a viral disease caused by human papillomavirus (HPV) serotypes 6 and 11, is the most common benign pediatric laryngeal neoplasm and is characterized by recurrent proliferation of squamous papillomas within the airway.[1] The disease is commonly progressive with age at diagnosis <5 years associated with aggressive disease.[2] There is no cure, and the recurrent nature has a significant negative impact on quality of life due to voice disturbance and airway obstruction. Surgery remains the standard of care, though up to 20% of patients require adjuvant medical therapy due to having more than four surgeries per year, rapid regrowth of papillomas with airway compromise, or distal multisite spread of disease.[1]

Bevacizumab (Avastin, Genentech, San Francisco, CA) and its biosimilar bevacizumab-awwb (Mvasi, Amgen) are recombinant humanized monoclonal antibodies that target vascular endothelial growth factor (VEGF) to inhibit angiogenesis. Despite well-established clinical efficacy in adult oncology, bevacizumab use remains limited in pediatrics.[3,4] Intralesional bevacizumab injections show inconsistent results with limited efficacy in multifocal disease.[5-8] Recently, systemic bevacizumab has shown promise in advanced, treatment-resistant papillomatosis.[8-13] However, questions remain regarding best protocols. Here, we describe the long-term use of IV bevacizumab for severe RRP among two pediatric patients.

Case Report 1

An 8-year-old boy who presented at 22 months of age with hoarseness since birth was diagnosed with RRP (HPV serotype 6). He required 26 surgeries for aggressive laryngeal recurrence by 6 years of age, averaging two months between procedures. He failed adjuvant medical therapies including recombinant HPV vaccine (types 6, 11, 16, 18) and nineteen intralesional bevacizumab injections. Given the subglottic extension of disease despite frequent procedures, systemic bevacizumab-awwb treatment was planned under the supervision of pediatric oncology. Direct laryngoscopy prior to first bevacizumab cycle showed extensive papillomas along

the epiglottis, bilateral aryepiglottic folds, and bilateral true and false cords with subglottic extension (Panel A). There was no tracheal involvement, and a chest CT scan showed no pulmonary disease. In June 2020, the patient underwent his first intravenous bevacizumab-awwb infusion of 10 mg/kg, ultimately receiving four cycles every three weeks. After cycle one, the patient had significant improvement in voice. Direct laryngoscopy after cycle three showed only few small papillomas on the laryngeal surface of the epiglottis (Panel A). After cycle four, time between infusions was increased by three weeks after each set of three cycles (i.e., 3 cycles at 6-week intervals followed by 3 cycles at 9-week intervals followed by 3 cycles at 12-week intervals). The only side effect was a mild stomachache that resolved after cycle one. As of May 2022, the patient completed his final 12-week interval cycle and remains asymptomatic with last surgery in July 2020. His infusions will be spaced to 3 cycles at 16-week intervals starting June 2022 before reaching a planned stable infusion interval at every 6 months.

Case Report 2

A 7-year-old girl who presented at 18 months of age with hoarseness since birth was diagnosed with RRP (HPV serotype 11). She required 30 surgeries for aggressive laryngeal recurrence by 6 years of age, averaging 2-3 months between procedures. She failed adjuvant medical therapies including recombinant HPV vaccine (types 6, 11, 16, 18), six intralesional modified vaccinia Ankara E2 virus vaccine injections, and four intralesional bevacizumab injections. Given the need for frequent procedures, systemic bevacizumab-awwb treatment was planned under the supervision of pediatric oncology. Direct laryngoscopy prior to first bevacizumab cycle showed extensive papillomas along the left true cord, ventricle, and false cord extending to the laryngeal surface of the epiglottis (Panel B). There was no tracheal extension, and a chest CT scan showed no pulmonary disease. In February 2021, the patient presented for surgical debridement and, five days later, underwent her first systemic bevacizumab-awwb infusion of 10 mg/kg, ultimately receiving four cycles every three weeks. After cycle one, the patient had significant improvement in voice and breathing. Direct laryngoscopy after cycle four showed no evidence of laryngeal papillomas and a scar band in the posterior glottis (Panel B). Subsequently, time between infusions was increased as in Case 1. The only side effect was trace proteinuria that resolved after cycle one. As of May 2022, the patient completed her final 9-week interval cycle and remains asymptomatic with last surgery in February 2021. Her infusions will be spaced to 12 weeks apart beginning June 2022 with plans to continue spacing per Case 1.

Discussion

Recurrent respiratory papillomatosis is a challenging airway disease, especially in children who generally present with more aggressive disease and have higher recurrence rates than adults.[14] Multiple surgeries are often necessary to maintain airway patency and laryngeal anatomy. The mean number of yearly surgical procedures per child is 5.1 with an average of 20 procedures in a child's lifetime.[15] Many adjuvant medical therapies, including interferon-alfa, celecoxib, intralesional cidofovir, and intralesional bevacizumab, have failed to reliably decrease surgical frequency.[8]

Recently, systemic bevacizumab has been shown to decrease papilloma burden and reduce surgical frequency. Bevacizumab targets VEGF to inhibit angiogenesis, indirectly inhibiting papilloma growth. Studies have shown strong expression of VEGF in papilloma epithelium and VEGFR-1 and VEGFR-2 in underlying vascular endothelium in patients with RRP.[16] However, bevacizumab does not affect the underlying viral infection, and risk of recurrence after stopping treatment is possible.[9,11,17] While current evidence supports the use of bevacizumab for RRP, *in vitro* and *in vivo* models of RRP are difficult to establish, limiting the identification of other potential therapeutic targets.[18]

In this article, we present two children who received systemic bevacizumab-awwb given significant disease recurrence. The biosimilar bevacizumab-awwb is structurally, functionally, and clinically similar to bevacizumab.[19] Both patients received identical 10 mg/kg initiation and maintenance dosing schedules with a follow-up of 23 months and 15 months, respectively. Immediate improvement in respiratory and vocal symptoms was observed after just one cycle. Normal vocal quality often correlates with significant reduction of laryngeal lesions which was observed during follow-up laryngoscopies.[13]Both patients remain asymp-

tomatic without need for surgical intervention after more than a year of treatment. The only side-effects observed were trace self-resolving proteinuria and stomachache, consistent with prior studies demonstrating tolerability of bevacizumab among children.[4]

Systemic bevacizumab is still a novel therapy for RRP, and standardized treatment protocols are lacking. Recently, an international consensus statement on ideal patient and treatment center characteristics was proposed. Consensus was reached that multiple disciplines, including pediatric oncology, are necessary to optimize systemic bevacizumab administration for RRP, highlighting a novel treatment paradigm for this benign but aggressive airway tumor.[20] However, long-term effects of systemic bevacizumab and appropriate dosing schedules, including treatment endpoint, remain unknown. Anecdotal evidence suggests spacing cycles as detailed above from every 3 months to every 4 months to every 6 months and holding at that interval. If symptoms recur at any point, treatment frequency can be increased. Accumulated clinical experience through multidisciplinary partnerships, including primarily pediatric oncology and otolaryngology, may facilitate future multi-institutional efforts to standardize bevacizumab administration. Unfortunately, given the rarity and potential severity of RRP, randomized placebo-controlled trials are not feasible or ethically justified. A national registry of patients treated with systemic bevacizumab detailing treatment schedules and disease progression would be essential to inform future therapy decisions.

Conclusion

Systemic bevacizumab is a promising long-term treatment for severe RRP, with pediatric oncology playing an important role in patient care.

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Legend List

Panel A

Extensive papillomas along the epiglottis, bilateral aryepiglottic folds, and bilateral true and false cords with extension into the subglottis (left) and residual small papillomas on the laryngeal surface of the epiglottis after 2 months and 3 cycles of bevacizumab (right).

Panel B

Severe laryngeal papillomas of the left larynx (left) and disappearance of disease after 3 months and 4 cycles of bevacizumab (right). There is a small scar band in the posterior glottis (black arrow).