Use of Adjuvant Intralesional Bevacizumab for Aggressive Respiratory Papillomatosis in Children

Derek J. Rogers, MD; Shilpa Ojha, MBChB; Rie Maurer, MA; Christopher J. Hartnick, MD, MS Epi

Importance: Juvenile recurrent respiratory papillomatosis (RRP) can be an aggressive disease process necessitating frequent trips to the operating room with multiple anesthetics for tumor debulking and airway preservation. Adjuvant therapy, such as that which is reported in this article, may help reduce the number of operative procedures affected children need each year and therefore may also affect their overall quality of life (QOL).

Objective: To describe our experience with intralesional bevacizumab (Avastin) treatment for children with severe RRP by comparing median number of surgical procedures per year, median duration of time between procedures, Derkay staging, and voice QOL before and after bevacizumab treatment.

Design: Prospective, consecutive case series.

Setting: Tertiary care aerodigestive center.

Participants: Ten children, aged 18 months to 18 years, with severe RRP necessitating more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to intralesional bevacizumab treatment.

Interventions: Intralesional bevacizumab administered at concentration of 2.5 mg/mL for 3 consecutive injections (with 532-nm pulsed KTP [potassium titanyl phosphate] laser when necessary) at intervals of 2 to 3 weeks.

Main Outcome Measures: Time between surgical procedures, number of procedures per year, Derkay staging, total Pediatric Voice-Related Quality of Life (PVRQOL) score, Emotional PVRQOL score, and Physical PVRQOL score defined by comparing the year leading up to first of 3 bevacizumab injections with the year following the third bevacizumab injection.

Results: The median duration of time between surgical procedures increased by 5.9 weeks after bevacizumab (P = .002). The median number of procedures per year decreased by 4 (P = .002). Derkay staging decreased by 6 (P = .03). The median total PVRQOL score increased by 25.5 (P = .02), the median Emotional PVRQOL score increased by 11.3 (P = .047), and the median Physical PVRQOL score increased by 14.3 (P = .047).

Conclusions and Relevance: Intralesional bevacizumab treatment may increase duration of time between surgical procedures and decrease number of procedures per year, while improving voice QOL.

ECURRENT RESPIRATORY PAPILLOMATOSIS (RRP) represents the most common neoplasm of the pediatric larynx. The disease is characterized by repeated growth of multiple warts involving the larynx as well as other parts of the upper respiratory tract. The incidence of RRP in the United States is about 0.2 to 1.1 per 100 000 children per year, and its prevalence is estimated to be 1.7 to 2.6 per 100 000 children. Recurrent respiratory papillomatosis is most commonly caused by human papilloma virus (HPV) types 6 and 11. Occasionally, RRP is caused by HPV types 16 and 18. Infrequently, papillomas may undergo malignant transformation. Most children with RRP present with hoarseness, making RRP the second most common cause of hoarseness in the pediatric population. Some children may present with stridor from airway obstruction by the papillomas.

Children with RRP usually require multiple surgical procedures to eradicate their disease. The National Registry of Children with RRP noted an average of 4.4 procedures per year, totaling over 10,000 surgical procedures annually for children with RRP in the United States. Scarring and vocal fold webbing may occur in these children after repeated procedures. Recurrent respiratory papillomatosis resolves in
most children, but some continue to have disease into adulthood.9 Depending on the prevalence, the annual medical costs of juvenile-onset RRP in the United States are estimated at $42 million to $67 million.10 Children diagnosed as having RRP before age 3 years are 3.6 times more likely to have more than 4 surgical procedures per year and almost twice as likely to have 2 or more anatomic sites affected.2 Although several studies have suggested that HPV type 11 is associated with more aggressive disease, HPV type may only be weakly associated with disease course when simultaneously accounting for patient age.11 A child born to a young primiparous mother with condylomas is at high risk for developing RRP.12

Recurrent respiratory papillomatosis remains primarily a surgically treated disease at the present time. Surgical options include cold steel excision, microdebrider, 532-nm KTP (potassium titanyl phosphate) laser, carbon dioxide laser, 585-nm pulsed-dye laser, flushed pumped-dye laser, and photodynamic therapy. The primary goal of surgery is to completely remove the papillomas while preserving normal structures. Although the carbon dioxide laser has become quite popular in recent years, the most common method of papilloma removal has now become the microdebrider.13

While surgery is currently the mainstay of treatment for RRP, approximately 20% of cases require adjuvant therapy.1 Adjuvant therapy may include oral indole-3-carbinol, mumps vaccine, heat shock protein (HSP) E7, interferon, and intralesional cidofovir. Indications for adjuvant therapy are the need for more than 4 surgical procedures per year, rapid regrowth of papillomas with airway compromise, or distal multisite spread of disease.1

Although historically interferon was a common adjuvant therapy for RRP, cidofovir has been the most widely described injectable adjuvant treatment in the current literature. Cidofovir is a cytosine nucleotide analog known to have considerable antiviral activity against a variety of herpes viruses.14 The US Food and Drug Administration (FDA) has approved cidofovir for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency disease. The first use of cidofovir for the treatment of RRP was described by Snoeck et al15; in their study, 8 of 11 mostly adult patients showed excellent responses. Pransky et al16 followed 11 children with RRP treated with intralesional cidofovir over 6 years and found that 5 patients decreased their mean severity scores from 17.8 to 4.0 and no longer required cidofovir. Pransky et al16 also reported remarkable decreases in the total number of surgical procedures per year and increases in the interval between procedures for children with RRP treated with cidofovir.17 The current standard of care was derived from a systematic review by Chadha and James,18 which estimated the median intralesional cidofovir treatment protocol to be a concentration of 2.5 mg/mL to 5 mg/mL, every 2 to 4 weeks for a year. Injecting cidofovir in this manner is believed to limit malignant change and provide durable remission by preventing an increase of HPV type E6,19,20

Derkay and the Multidisciplinary Taskforce on Recurrent Respiratory Papillomas20 have published guidelines for clinicians interested in using cidofovir to treat RRP because of potential carcinogenic effects in animal studies22 and case reports showing malignant conversion23 or progressive dysplasia in patients with RRP receiving intralesional cidofovir.24 With the growth of patient and family websites and web resources (http://www.rerp.org), many families come in with concerns and are looking for alternative treatments. They often ask about bevacizumab, and a paucity of long-term outcomes data exists, especially in the pediatric population.

Bevacizumab (Avastin) is a human monoclonal antibody that binds to and neutralizes the biologic activities of vascular endothelial growth factor (VEGF) isoforms, blocking the interaction with their receptors.24 Rahbar et al25 showed strong expression of VEGF-A in the epithelium from papillomas in patients with RRP as well as expression of VEGFR-1 and VEGFR-2 messenger RNAs in underlying vascular endothelial cells. In a pilot study and a prospective investigation thereafter, Zeitels et al26,27 showed good results using bevacizumab with 532-nm pulsed KTP laser in adult patients. However, no standardized grading system was used to assess the visual appearance of the larynx, such as Derkay scores. Because of the favorable results in our previous study28 and in the studies by Zeitels et al26,27 we sought to further investigate the use of bevacizumab as adjuvant therapy in children with RRP. The goal of this study was to describe our experience with intralesional bevacizumab in children with aggressive RRP by comparing the median number of surgical procedures per year, median duration of time between procedures, Derkay staging, and voice quality of life (QOL) before and after bevacizumab treatment. One must remember that this is a small case series, which should be used as motivation for a blinded, randomized controlled trial in the future.

| Table 1. Demographics of Children Treated With Intralesional Bevacizumab |
|-----------------|-----------|-----------------|-----------------|
| Patient No./Sex/Age at First Bevacizumab Injection | HPV Type | Prior Cidofovir Injections, No. |
| Treatment/Age at First RRP Treatment | | |
| 1/F/4 y/2 mo | 11 | 4 |
| 2/F/13 y/8 y | 6 | 3 |
| 3/M/22 mo/10 mo | 6 | 0 |
| 4/F/18 mo/9 mo | 11 | 0 |
| 5/F/8 y/2 y | 6 | 0 |
| 6/M/20 y/16 y | 11 | 2 |
| 7/M/8 y/3 y | 6 | 0 |
| 8/M/6 y/2 y | 6 | 6 |
| 9/F/2 y/9 mo | 6 | 0 |
| 10/F/16 y/2 y | 11 | Unknown |

Abbreviations: HPV, human papilloma virus; RRP, recurrent respiratory papillomatosis.

**METHODS**

**PATIENTS**

The Massachusetts Eye and Ear Infirmary institutional review board approved this study. Ten children aged 18 months to 18 years at first bevacizumab treatment were included in this study (Table 1). Children met inclusion criteria if they had under-
started 1 year prior to the first bevacizumab injection and ended papillomas. Each patient underwent a series of 3 bevacizumab concentration of 2.5 mg/mL into the areas most affected by the ryngeal needle to inject a total of 0.5 mL of bevacizumab at a standard surgical therapy or start bevacizumab adjuvant therapy. They were provided literature on bevacizumab28 were not included in this study. The age at first RRP treatment ranged from 2 months to 16 years. Six of the patients were female, and 4 were male. Six of the patients had papillomas positive for HPV type 6, and 4 were positive for HPV type 11. Four of the patients had failed treatment with anything from 2 to 6 cidofovir injections.

The families were thoroughly counseled regarding various adjuvant therapies. They were provided literature on bevacizumab. A special informed consent form was developed with the aid of the pharmacists at the Massachusetts Eye and Ear Infirmary disclosing the off-label use of bevacizumab, including risks and benefits. Families chose to either continue standard surgical therapy or start bevacizumab adjuvant therapy after reading the consent form. Parents or legal guardians had to sign both the expanded bevacizumab consent form and standard consent form before bevacizumab was used in the children.

SURGICAL TECHNIQUE
Suspension microlaryngoscopy with microdebrider removal of bulky disease followed by 532-nm pulsed KTP laser treatment of sessile papillomas involving the anterior commissure, true vocal folds, or ventricles represented standard surgical treatment (as defined by the senior author, C.J.H.). Once this standard surgical treatment was complete, we performed bevacizumab injections. Pransky et al16 used a 2-week interval between cidofovir injections because they found greater than expected papilloma regrowth when the interval was more than 2 weeks and because of data from several prior studies.15–18,29 Our technique for adjuvant bevacizumab injections involved using a laryngeal needle to inject a total of 0.5 mL of bevacizumab at a concentration of 2.5 mg/mL into the areas most affected by the papillomas. Each patient underwent a series of 3 bevacizumab injections approximately 2 to 3 weeks apart. Our time points started 1 year prior to the first bevacizumab injection and ended 1 year following the third injection.

STATISTICAL ANALYSIS
The duration of time between surgical procedures, number of procedures per year, Derkay staging, total PVRQOL (pediatric voice-related QOL) score, Emotional PVRQOL score, and Physical PVRQOL score were compared with those from the year before the first bevacizumab injection and compared with those from the year before the first bevacizumab injection. The median duration of time between surgical procedures increased by 5.9 weeks after bevacizumab (95% CI, 3.7–10.2; P = .002). The median number of procedures per year decreased by 4 (95% CI, −6.5 to −2.5; P = .002). Derkay staging decreased by 6 (95% CI, −12.0 to −2.3; P = .03). If the 3 surgical procedures in which bevacizumab was injected are included, the median number of procedures the year after the first bevacizumab injection was 7.

The voice outcomes also improved after bevacizumab treatment. The median total PVRQOL score increased by 25.5 (95% CI, −0.6 to 39.1; P = .02). When broken down into separate parameters, the Emotional PVRQOL score increased by 11.3 (95% CI, −0.1 to 16; P = .047), and the Physical PVRQOL score increased by 14.3 (95% CI, −0.5 to 23.1; P = .047).

RESULTS

All 10 patients completed the aforementioned protocol. The median duration of time between surgical procedures, number of procedures per year, Derkay staging, total PVRQOL score, Emotional PVRQOL score, and Physical PVRQOL score were compared with those from the year before the first bevacizumab injection (Table 2). The median duration of time between surgical procedures increased by 5.9 weeks after bevacizumab (95% CI, 3.7–10.2; P = .002). The median number of procedures per year decreased by 4 (95% CI, −6.5 to −2.5; P = .002). Derkay staging decreased by 6 (95% CI, −12.0 to −2.3; P = .03). If the 3 surgical procedures in which bevacizumab was injected are included, the median number of procedures the year after the first bevacizumab injection was 7.

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DISCUSSION

Pediatric RRP remains an extremely challenging disease to treat. Ideally, medical treatment will eventually be developed in the future to treat RRP without the need for multiple surgical procedures. Since maintaining an adequate airway is an absolute necessity, repeated procedures are performed at the expense of scarring and potentially permanent voice disturbance. Adjuvant therapy, such as cidofovir, is considered by surgeons to ensure the longest time possible between surgical interven-
Adjuvant therapy is an attractive treatment modality in children with aggressive RRP, but limited data exist concerning the optimal dosage, efficacy, and possible adverse effects. Most studies involve small numbers of patients and/or lack consistent surgical and medical treatment of these patients between institutions. Despite some solid evidence showing efficacy of cidofovir in pediatric RRP, it not all children experience such remarkable responses. Cidofovir use is also not without risk. Because of potential carcinogenic effects in animal studies and case reports of malignant conversion and progressive dysplasia in patients with RRP receiving intralesional cidofovir, the Multidisciplinary Task Force on Recurrent Respiratory Papillomas has published guidelines for clinicians interested in using cidofovir to treat RRP. Since cidofovir is not effective in all cases and may be associated with a risk of malignant disease, parents of children with aggressive RRP desire other adjuvant treatments that are safe and beneficial.

Bevacizumab is a human monoclonal antibody that binds to and neutralizes the biologic activities of VEGF isoforms, blocking the interaction with their receptors. In 1994, the FDA approved bevacizumab for the treatment of metastatic colorectal cancer largely owing to the pioneering work by Folkman. Bevacizumab has been used in treatment of diabetic retinopathy, macular degeneration, and other ophthalmologic conditions. Potential risks from intravenous bevacizumab administration include, but are not limited to, bleeding, blood clotting, high blood pressure, and hypothyroidism. No adverse effects have resulted from intraocular injections of bevacizumab at a dose 100 to 400 times lower than the intravenous dose.

After the study by Rahbar et al showing high levels of VEGF-A in pediatric papilloma specimens and the work by Zeitels et al using bevacizumab in adult patients with RRP, it seemed logical to assess the efficacy of bevacizumab in children with aggressive RRP. The initial bevacizumab dose used in adults ranged from 5 to 12.5 mg at a concentration of 25 mg/mL. We used an initial concentration of 2.5 mg/mL, which had been used safely in pediatric ophthalmology. The concentrations were formulated by our institutional pharmacy. The patients' parents were thoroughly counseled and given handouts regarding bevacizumab and various adjuvant therapies before initiating bevacizumab therapy, as outlined in our prior work. Extrapolating from the data presented by Chadha and James in their systematic review of intralesional cidofovir, we chose to perform 3 intralesional bevacizumab injections at a concentration of 2.5 mg/mL every 2 to 3 weeks. One must also consider the overall dose injected, especially in the pediatric population. We injected approximately 0.5 mL at each session.

In our study, children who were treated with intralesional bevacizumab injections required 4 fewer surgical procedures per year and showed an increase in the duration of time between procedures by 5.9 weeks. In addition, the Derkay staging decreased by 6 points. While these results may not be as dramatic as those with cidofovir presented by Pransky et al, they show that intralesional bevacizumab may make a remarkable impact on the patients and their families. Fewer surgical procedures and more time between procedures will hopefully lead to less scarring and fewer general anesthetics for these patients. For 50% or more of the patients, 1 or 2 additional procedures resulted because of the decision to use bevacizumab and thus may be associated with a significant cost and burden. We have devised a potential algorithm for the use of adjuvant intralesional bevacizumab in our pattern of practice (Figure). Our definition of cidofovir and bevacizumab failure is defined as requiring the same number of procedures or more the year after treatment with cidofovir or bevacizumab compared with those required the year before cidofovir or bevacizumab treatment. For those children who fail treatment with the initial bevacizumab injections, we have begun treating them with a series of 3 injections at a concentration of 5 mg/mL every 2 to 3 weeks. These data will be reported in the future.

The voice outcomes also improved after bevacizumab when comparing the total PVRQOL scores as well as the Emotional PVRQOL and Physical PVRQOL scores separately. Parents felt that their children's QOL was noticeably improved. These results compared favorably with those presented by Zeitels et al even though our dose of bevacizumab was considerably lower. Whether these improved voice outcomes were directly due to bevacizumab or merely a result of fewer procedures remains to be elucidated. However, cidofovir has been reported to stiffen the vocal cords through scarring and fibrosis, which we have not found to occur with the use of bevacizumab.

Our study had a few limitations. Our sample population was small, and we were unable to assess the effect of age, HPV type, and sex in patients treated with bevacizumab. Also, all surgical procedures were performed according to the senior author's technique. Multicenter trials would likely help investigate different surgical techniques. The dose of bevacizumab was merely an estimation based on the use of this medication in pediatric ophthalmology, and the time interval between injections was

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**Figure.** Proposed algorithm for adjuvant use of intralesional bevacizumab in recurrent respiratory papillomatosis.
deduced from prior cidofovir data. The amount injected into the papillomas was not exactly the same for every patient and varied based on the severity of disease. Larger longitudinal trials may better assess the effect of age of first RRP treatment, HPV type, sex, dose and time interval of bevacizumab, potential scarring, and histopathologic changes over time. Using the difference in the median number of surgical procedures per year before and after intralesional bevacizumab and placebo would need 38 patients (19 in the bevacizumab group and 19 in the placebo group) to show a significant difference in the number of procedures per year (power = 90%; α = .05; Mann-Whitney test).

In conclusion, our pilot study suggests that bevacizumab may indeed limit the number of surgical procedures required per year and increase the duration between procedures in patients with aggressive RRP, while simultaneously improving voice outcomes. Physicians should consider bevacizumab as an adjuvant therapy in this unique subset of patients. While we are hopeful of bevacizumab’s efficacy, we are aware that our data would be compatible with other explanations: disease variability with regression to the mean; the generally favorable natural history of RRP; bias (even subconsciously). It is possible that bevacizumab is not efficacious. One should note that this study is a small case series. A larger, blinded, randomized controlled, multicenter study would answer the question.

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Correspondence: Christopher J. Hartnick, MD, MS Epi, Department of Pediatric Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114 (Christopher_Hartnick@meei.harvard.edu).

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