









Systemic Use of Bevacizumab for Recurrent Respiratory Papillomatosis: Who, What, Where, When, and Why?

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BACKGROUND

Recurrent respiratory papillomatosis (RRP) is a potentially lethal disease caused by the human papillomavirus (HPV) and characterized by recurrent papillomas in the aerodigestive tract. Cases of RRP are expected to be significantly reduced with increased acceptance of the HPV-9 vaccine. Currently, the mainstay of RRP treatment is via surgical intervention, with a minority of patients requiring adjuvant medical therapies during their disease.

Several adjuvant therapies have been administered, with little consensus on which treatments are most effective and the timing of their administration. In the past, systemic Interferon- α was used for severe RRP, and evidence showed it could prolong surgical intervals. However, the use of interferon- α for JORRP treatment has been curtailed due to serious side effects, including neurologic disorders, leukopenia, and thrombocytopenia. Thus far, systemic bevacizumab has a superior safety profile with hypertension, epistaxis,

proteinuria, and impaired wound healing the most common side effects reported. To achieve a lasting remission with a serviceable voice and patent airway, providers must consider how and when to approach intervention with adjuvants to limit the risks and damage from frequent airway surgeries.

Bevacizumab (Avastin[®], Genentech) is a monoclonal antibody that binds to and inhibits vascular endothelial growth factor (VEGF) expressed on papilloma epithelium. Preliminary results from intravenous bevacizumab initiated for “salvage” and then continued as a maintenance medical treatment in patients with severe laryngeal, tracheal, and pulmonary RRP have demonstrated dramatic clinical responses.

The question arises of whether to embark on a paradigm shift from traditional repeated surgical treatments to early initiation of medical management utilizing bevacizumab as a primary treatment modality.

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LITERATURE REVIEW

Compared to normal laryngeal mucosal tissue, RRP tissue samples have been found to have increased expression of VEGF. Bevacizumab binds to VEGF, preventing angiogenesis and subsequent papilloma growth. Systemic infusions of bevacizumab as an adjuvant treatment of RRP have demonstrated dramatic successes.¹ After the publication of initial reports showing modest success in treating laryngeal papillomas in adults and children with intralésional bevacizumab, Mohr described five patients who experienced a striking reduction in the surgical interval after initiation with systemic bevacizumab.² Since this initial report, Zur reported success in a child whose disease had been recalcitrant to treatment with multiple other adjuvants. Worldwide interest in the systemic use of bevacizumab has grown amongst providers treating adults and children with RRP with multiple published case series.

Most of the early adopters offer systemic bevacizumab when the patient does not respond to frequent surgical intervention while also having failed at least one other

adjuvant therapy. Best surveyed nine centers that regularly treat patients with RRP on their experiences with intravenous bevacizumab. Even in a cohort that comprised patients with severe disease, including tracheal and pulmonary papilloma, with many prior adjuvant treatments, the surgical interval was significantly lengthened after systemic bevacizumab in all patients. In some cases, surgery was no longer necessary.³ The largest single-center cohort also documents dramatic responses in a group of severe adult RRP patients, though patients were found to require maintenance therapy or their disease will recur.⁴

In a systematic review, Ryan identified 20 patients with juvenile-onset RRP (JoRRP) treated with systemic bevacizumab.¹ The mean patient age was 12.8 years, and they received initial dosing of 5–10 mg/kg bevacizumab followed by re-dosing at a mean of 3-week intervals. All patients had a clinically significant disease reduction, with 11/20 requiring no further surgery after initiating treatment. All patients had severe disease based on needing frequent surgeries, tracheostomy, and/or tracheal or lung parenchyma involvement—80% of these patients had already failed 1–6 medical adjuvants.¹

These early results with systemic bevacizumab have led us to consider a paradigm shift in RRP care: should RRP no longer be considered a surgical disease but primarily managed with IV bevacizumab? Given the inevitable deleterious consequences of repeated surgery on vocal function, the goal of this approach would be to cause less permanent scarring and long-term dysphonia by immediately transitioning to non-surgical management. An additional potential goal would be to theoretically reduce the chance of the spread of disease into the trachea and lungs. Another consideration when comparing treatment modalities is the inherent health risks and QOL impact of repetitive anesthetics and surgery, the financial burden and significant emotional turmoil of repetitive surgery, and the societal cost of missed work/school.

The argument against this approach, especially in those with JoRRP, is recognizing that many patients demonstrate gradual slowing of papilloma growth over time, while the long-term side effects of indefinite bevacizumab are unknown. In addition, the endpoint of treatment is unknown as recurrence of disease is common after discontinuation of treatment. Some insight may be drawn from NF2, where long-term bevacizumab is used to control tumor growth in those with bilateral vestibular schwannomas.

Ideal dosing protocols for initiation and long-term maintenance have not been universally adopted. The authors' currently recommended protocol is intravenous infusions at a 10 mg/kg concentration, obtaining blood chemistries to establish baseline renal and hepatic

function, and documenting disease severity via the Derkay staging scale and CT imaging of the lungs. Engaging with medical colleagues familiar with bevacizumab while utilizing an infusion center with multi-disciplinary expertise can help reduce complications and improve the patient experience.

These 10 mg/kg infusions are initially spaced out at 3–4 week intervals until there is no disease requiring debridement. Infusion intervals can then be gradually increased to 2–4 months, and dosing lowered to 5 mg/kg. Decisions to change dosing intervals are informed by monitoring through in-office laryngoscopies, bronchoscopies under anesthesia for those pediatric patients with the more distal disease, vocal function, and pulmonary imaging. It appears that those who achieve remission but experience regrowth of papillomas when the infusion intervals get longer will respond again if intervals are shortened.⁴

Based on the Delphi survey methodology, Sidell's international consensus statement supported treatment in cases with severe disease burden or disease in locations difficult to treat with standard interventions, the use of a staging system to describe the RRP burden prior to initiation of systemic treatment, the engagement of medical colleagues and utilization of well-equipped infusion centers.⁵

Some centers have now been using intravenous bevacizumab as a first-line of therapy in pediatric patients with good success and with minimal to no morbidity.

BEST PRACTICE SUMMARY

Administration of systemic bevacizumab earlier in the RRP disease process may provide the benefit of decreased disease progression in addition to minimizing surgical sequelae. Although additional controlled studies are needed, a paradigm shift toward medical management of this vexing disease should be considered.

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