ISSN: 2053-3578 I.F. 9.1

SYSTEMIC BEVACIZUMAB (AVASTIN) FOR JUVENILE-ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS: A SYSTEMATIC REVIEW

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Annotation: The article devoted to open the theme systemic bevacizumab (avastin) for juvenile-onset recurrent respiratory papillomatosis: a systematic review. Moreover, it deals with the important data about cause and treatment of the illness.

Key words: *pediatric population, histopathological specimen, laryngeal models, potential treatment modality, adjuvant treatments, Local injections, lesional injection.*

Recurrent respiratory papillomatosis (RRP) is a stubborn disease. Despite volumes of researches done for a definite cause and management, the scientific community offers only theories for causation and options for treatments. Bevacizumab has emerged as a promising solution to the fear of sufferers of RRP of undergoing repeated surgeries. The patients who received bevacizumab, either systemically or intralesionally, show decreased need for surgeries mostly and even remission in a few. Till date there are limited studies of use of bevacizumab, in adults, but only reports of its use in pediatric population. This is a report of two cases of juvenile onset RRP with use of systemic bevacizumab infusion in a child and intralesional injection in an adult. After discovery of evidence for increased angiogenic activity in the excised RRP histopathological specimen, bevacizumab, a biological agent, an antagonist of vascular endothelial growth factor (VEGF), was identified as a potential treatment modality [1]. Local bevacizumab injections, has shown promising results in porcine laryngeal models, and shown satisfactory results as an adjuvant treatment in adult onset RRP. But there have only been few case reports of its use in paediatric age group.

Caused mostly by HPV 6 and 11, RRP can be life threatening both in its benign form by narrowing the airway by mass effect, as well as in its pre-malignant potential. The classical modality of treatment is surgical debridement using cold instrumentation, carbon dioxide laser or microdebrider. The adjuvant treatments are advocated in those cases where multiple surgeries, generally more than 6 in a year, are required with decreased interval between two surgeries, or in cases with pulmonary involvement. Cidofovir (both intralesional and systemic administration) has been the most widely used adjuvant therapy for the disease, off-label [2]. Nonetheless, no specific treatment is very promising. Bevacizumab, a VEGF antagonist, is an anti-angiogenic agent which

was first considered a modality of adjuvant therapy when evidence of strong expression of VEGF-A messenger RNA was found on the epithelium of laryngeal papilloma on in situ hybridisation, along with increased expression of VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) in underlying vascular endothelial cells.

Local injections of bevacizumab have been postulated to increase the concentration of anti-VEGF to act locally. Prior use of systemic infusions of treatment of other malignancies as colon, breast and gliomas, laid basis for trying it in cases of refractory RRP. However, both routes of administration of bevacizumab, have shown beneficial effect in increasing the interval between surgeries and in a few patients, as well as resolution of the lesions. It has improved the voice outcome of the patient as well. But the studies have been conducted on adult onset RRP and adults with juvenile onset RRP [3]. While local injections are not reported to have any systemic complications, systemic infusions of the drug is known to cause self-limiting proteinuria, haemoptysis, hypertension, joint pain and lethargy which mostly improve with cessation of therapy or by increasing duration between doses. Other life threatening but relatively rare complications include intracranial haemorrhages, thromboembolism, hypertensive crisis and gastrointestinal perforations have also been reported, but more in adults than children. Other available options for adjuvant therapy are indole-3-carbinol and interferon-α2a, celecoxib, and vaccination for HPV. Although the use of bevacizumab for RRP has increased but, lack of strong evidence in literature requires larger multicentric trials to assess efficacy of systemic and intralesional bevacizumab administration in both paediatric and adult population, and prospective studies for studying the long-term effects of bevacizumab.

Juvenile-onset recurrent respiratory papillomatosis is benign, but troublesome disease due to its propensity for recurrence and need for multiple surgical procedures. To reduce recurrences the patient is started on adjuvant therapy. Many agents have been tried for adjuvant therapy. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). Studies have shown strong expression of VEGF-A mRNA was noted in the squamous epithelium of papillomas and VEGFR-1 and VEGFR-2 were noted in the endothelial cells of the underlying vessels [4].

In a Prospective observational study by Mohr et al. [5], immediate and sustained response was seen after systemically administering bevacizumab was observed in five patients with progressive JORRP who underwent multiple local procedures. Another significant observation was that 4 out of 5 patients did not require any further surgical intervention. One patient underwent

laryngectomy due to malignant transformation. They recorded the response of the lesion to treatment during the administration of the drug and those patients who showed relapse on discontinuation of the drug showed a response on retreatment. Sidell et al. [6] demonstrated a median 58% improvement in 5 patients who underwent sub epithelial injections of bevacizumab along with KTP LASER ablation. Another study by Zeitel et al. [7] combining sub lesional bevacizumab with KTP laser found that there was a significant response to the disease. Out of 20 patients who received 4 injections, 3 had no discernible disease, 16 patients had a partial response and 1 patient had increased disease. 7 of the patients did not require any further laser coagulation. In a prospective case series by Roger et al. [8], intra lesional injection of bevacizumab alone produced an average increase of 5.9 weeks in the time interval between the injections, the median number of surgical interventions were decreased by 4, physical pediatric voice-related quality of life was increased by 14.3 and median emotional pediatric voice-related quality of life was increased by 11.3. In another study by Maturo et al. [9], after treating the patient with microdebrider pulsed KTP laser and intralesional bevacizumab, all children showed increased time interval between prodecures.

To sum up all given facts above it should be noted that Our case report suggests that systemic bevacizumab may be a useful adjuvant treatment option to consider for young children with RRP. While serial microdebridements remains the gold standard for treatment of aggressive juvenile RRP, patients requiring more than 4 microdebridements per year can benefit greatly from systemic bevacizumab infusions. This benefit can be most appreciated in younger children who have been shown to exhibit more severe disease and can benefit greatly from early infusion therapy.

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