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REVIEW ARTICLE

Outcomes of bevacizumab and cidofovir treatment in HPV-associated recurrent respiratory papillomatosis – review of the literature

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Joanna Jackowska[1ABDEF], Hanna Klimza[1ADEF], Krzysztof Piersiala[2BDE], Małgorzata Wierzbicka[1ADF]

[1]Poznan University of Medical Sciences, Department of Otolaryngology and Laryngological Oncology, Poznan, Poland, Head: Prof. dr hab. n. med. Małgorzata Wierzbicka
[2]Student Research Group at the Department of Otolaryngology, Department of Head and Neck Surgery, Poznan University of Medical Sciences, Poznan, Poland, Head: Prof. dr hab. n. med. Małgorzata Wierzbicka

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ABSTRACT:

Objective: Recurrent respiratory papillomatosis (RRP) is caused by types 6 and 11 human papilloma virus and occurs in both children and adults. It is characterized by proliferation of benign squamous cell papillomas within the aerodigestive tract. The problem with recurrent respiratory papillomatosis treatment is high recurrence of papilloma growth following surgical removal.

Method: A literature review was carried out via surveys based on electronic data in public domains: MedLine (USA National Library of Medicine), PubMed and SciELO, using keywords such as: recurrent respiratory papillomatosis, adjuvant treatment, cidofovir, and bevacizumab. All types of papers written in English were included (cross-sectional, prospective and retrospective clinical trials, review papers, and case reports).

Results: In the recent literature, several types of treatment such as surgery with mechanical debulking or laser and adjuvant therapies are mentioned. Intralesional bevacizumab and cidofovir treatment may increase the interval between surgical procedures and decrease the number of procedures per year.

Conclusions: There is still an ongoing discussion within the European Laryngological Society regarding the balance between effectiveness and side effects of RRP adjuvant treatment, however, recent results show promising long-term effects. Bevacizumab and cidofovir in aggressive RRP give hope for improved treatment outcomes.

KEYWORDS: recurrent respiratory papillomatosis, cidofovir, bevacizumab, adjuvant treatment

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a chronic disease, that occurs in both children and adults and is characterized by proliferation of benign squamous cell papillomas within the aerodigestive tract. RRP usually involves the larynx, but it may spread to the lung and undergo malignant conversion [1]. It is caused by the human papilloma virus (HPV) types 6 and 11. HPV is a member of the Papillomaviridae family [2].

The HPV genome consists of six early (E1, E2, E4, E5, E6 and E7) and two late (L1 and L2) open reading frames and a noncoding region, which codes for oncoproteins and capsid proteins [3]. HPV infections have an underhanded and insidious character and can manifest as persistent latent or active forms, with an unpredictable course. Infections may remain subclinical or be active, with rapid progress or spontaneous regress.

There are significant differences in the juvenile (JO RRP) and adult onset (AO RRP) forms of the disease (Table 1), mostly concerning the acquisition of infection, the course of disease

and prognosis [4,5,6]. In JO RRP, vertical transmission, i.e., the infection from an HPV-positive mother to her newborn, is presumed to be the major mode of transmitting HPV; this can cause subclinical or clinical infections. The risk of child infection can be reduced by cesarean birth, however, the risk of transmission via the placenta persists [7]. The route of viral acquisition in AORRP is by sexual contact [8]. HPV-DNA has been found in 5-25% normal larynx mucosa, which is not synonymous with an active disease [9]. HPV has also been identified in the healthy mucosa of patients with AO-RRP. It has been shown, that patients with RRP have an increased propensity to harbor HPV in the oral cavity [10]. However, knowledge about this link between acquisition and pathogenesis is lacking [11]. A deficient host immune system is thought to be the reason why only some individuals develop RRP [12]. Possibly, the most intriguing element of AO--RRP pathogenesis relates to the factors that predispose an individual to develop the disease. RRP patients do not seem to mount the expected cell-mediated immune response and develop a tolerance to the virus and are thus unable to clear the infection [13,14,15,16,17,18]

There are differences in the course and prognosis of the disease in HPV 6 or 11 infection (Table 2) [11, 19, 20, 21]. Also, in 0-20% of RRP patients, other HPV types are detected [22, 23]; of these, 2-14% are double HPV 6/11 infected patients.

At present, there is no cure and furthermore, no single treatment can eradicate RRP. The current standard of care is surgical therapy with the goal of complete removal of papillomas and preservation of normal structures. Clinical severity of RRP is defined in numerous ways, but the most common is frequency of surgeries necessary to maintain patency of the airway. Aggressive RRP requires 10 or more surgical procedures, with three or more procedures within the period of one year, and an additional feature of distal involvement reaching the subglottic area [24]. Disease severity can be also defined as the need for tracheotomy and malignant transformation. There have been no differences in disease eradication found between surgical techniques [25]. Regardless of the approach and instruments used, the virus remains latent even after careful resection. Therefore, it is prudent to leave residual papillomas when their removal might damage normal tissue and produce excessive laryngeal scarring [26].

Adjuvant therapy is required in up to 20% of cases, i.e., when rapid re-growth of papillomas compromises the airway or when distal multisite spread of the disease is observed [26]. The aim of this review is to present the current perspectives in newer adjuvant therapies in aggressive RRP growth.

METHOD

A literature review was carried out via a survey based on electronic data in public domains: MedLine (USA National Library of Medicine), PubMed and SciELO, using keywords such as: recurrent respiratory papillomatosis, adjuvant treatment, cidofovir, and bevacizumab. All types of papers written in English were included (cross-sectional, prospective and retrospective clinical trials, revive papers, and case reports).

RESULTS

In this literature review, all 24 papers devoted to cidofovir and bevacizumab for RRP treatment were included. Although the small number of studies and methods used for analysis does not allow to draw firm conclusions, these appear to be promising chemotherapeutics.

Cidofovir CA [(S)- 1- (3)- hydroxy-2-phosphonylomethoxypropyl) cytosine or HPMPC] is a cytosine nucleotide analog, known to have considerable antiviral activity against a variety of herpes viruses. It inhibits viral replication. The antiviral drug Vistide (Gilead Sciences, Inc. Foster City, CA) was approved by the US FDA for use in those infected with HIV who also have cytomegalovirus infection. Even though it has not been approved for topical or intralesional use, cidofovir has also been used to treat several cutaneous and mucosal viral lesions. Its first used as adjuvant treatment for severe RRP was presented in 1995 by Van Cutsem et al. [27]. In 1998, Snoeck et al. [28] published a case series that included adult patients and Pransky et al. [29] analyzed the introduction of this drug to the pediatric population. The standards of care were published by Derkay in 2005 [30] and later, in a systemic review by Chadha and James in 2007 [31]. Cidofovir provided durable remission in all described patient samples presented between 1998-2011 (Table 3) [28, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]. Cidofovir is the most widely described injectable adjuvant treatment in the current literature. In 2011, a general warning to physicians against off-label use was published by Gilead, although the company did not specify the severity and type of off-label complications. In 2012, the use of cidofovir was re-evaluated by Derkay et al. [46]. Cross-sectional studies among 82 surgeons who treated 801 adults and 447 children reported serious side effects in 24 children and 36 adults; among this number, malignant transformation and kidney failure occurred in 1.7% and 1% of patients, respectively [46]. More often, cutaneous rash, headache, a local inflammatory response, vocal cord scarring, compromised airway and hematologic disorders were described [47]. Also, an association was found between the use of cidofovir and dysplastic mucosa changes [48] and

Tab. I. Differences between juvenile onset and adult onset RRP [4,5,6].

	JUVENILE ONSET JO-RRP	ADULT ONSET AO-RRP
Predominance of HPV type	HPV 11	HPV 6
Age at diagnosis	Usually lower than 12	Usually above 12
Incidence in USA	0.17- 4.3 per 100,000 children	0.54-1.8 per 100.00 adults
Transmission	Vertical	Sexual
Risk factors	Maternal, correlated with clinical triad: young, teenage mother, firstborn, delivered vaginally	Increased numbers of lifetime sexual partners Mouth-to-mouth contact (instead of orogenital contact in HR HPV).
Clinical course	More aggressive form High risk of tracheotomy 13%-21% Higher morbidity and mortality	Less aggressive form Risk of tracheotomy 4%-6% Co morbidities: asthma, GERD Can worsen the clinical course
Extralaryngeal spread	30% of cases	16% of cases

a single case of squamous cell carcinoma arising from a squamous papilloma was reported [49]. FDA considers cidofovir as possibly carcinogenic because it increased the incidence of breast adenocarcinoma in rats. Broekmema [47] reported malignant degeneration in RRP patients but ruled out an association between cidofovir and malignancy [50]. However, the induction of alterations in gene expression associated with malignant transformation has not been confirmed [51]. There is an ongoing discussion within the European Laryngological Society about the balance between the effectiveness and side effects of cidofovir, but until now, the results have shown promising long-term effects [43].

Bevacizumab (Avastin; Genentech, San Francisco, CA) is a human monoclonal antibody that binds to and neutralizes the biologic activities of the vascular endothelial growth factor (VEGF) isoforms and blocks the interaction with their receptors [52]. Vascularization is a crucial factor that determines how rapidly papillomas reappear, thus supporting use of an angiogenesis inhibitor, i.e., an anti-VEGF antibody. Rahbar et al. showed [53] strong expression of VEGF-A in the epithelium from papillomas in patients with RRP as well as expression of VEGFR-1 and 2 mRNA in underlying vascular endothelial cells. Histological analysis revealed regression of perivascular edema and normalization of the vascular structure after intra--epithelial bevacizumab injection [54]. There are a few papers in the current literature describing the results of intralesional and systemic application of bevacizumab (Table 4) [53, 54, 55, 56, 57, 58, 59, 60, 61].

DISCUSSION

The retrospective character of most studies, the limited number of patients, lack of initial patient staging, and variety of RRP treatments used encompassing numerous surgical options (cold instruments, CO2 or angiolytic lasers, and microdebriders) make unification of observations difficult. For cidofovir, there is growing single-arm experience across several centers [44] with well-documented efficacy, however, doctors still observe treatment failure. Recently, 18 statements of consensus were approved by the RRP Task Force to inform the current practice of cidofovir adjuvant treatment in adults and children [43]. Importantly, intralesional injections are still considered off-label use, requiring extraordinary treatment precautions, a strict treatment regimen with regular biopsies and the need for a general status follow-up after the procedure.

Tab. II. Main differences between types 6 and 11 human papilloma virus [11, 19, 20, 21].

HPV 6	HPV 11
Above 12 years of age	Age at diagnosis lower than 12
Less aggressive form	More aggressive form
Extralaryngeal spread - 16%	Extralaryngeal spread - 30%
Malignant progression - 2%	Malignant progression - 33%
No differences in Dikkers scale, designed for clinical use with therapeutic intent	RRP at more anatomic sites and more extensive per site (higher Derkay/Coltera score)
	Higher expected surgical frequency

Bevacizumab is a most recent method of the adjuvant therapy in the most aggressive RRP cases. Treatment with monoclonal antibodies until now dedicated to malignant tumors in RRP is considered to be off-label use. Patients who wish for the treatment must provide signed consent, informing them about experimental aspects of the therapy. Adjuvant therapy with bevacizumab is an attractive treatment modality, but

Tab. III. Results of RRP treatment with Cidofovir presented by multiple investigators.

	YEAR	NO. OF PTS	DOSE OF CIDOFOVIR	METHOD OF ADMINISTRATION	RESULTS LOCAL IMPROVEMENT
Snoeck et al. [29]	1998	14	2.5 mg/mL	IEI*	+
Chhetri et al. [33]	2002	5	N/A	IEI	+
Co et al. [35]	2004	5	7.5 mg/mL	IEI	+
Lee et al. [36]	2004	13	5 mg/mL	IEI	+
Pontes et al. [34]	2006	10	N/A	IEI	+
Naiman et al. [37]	2006	19	5-7.5 mg/mL	IEI	+
Dikkers et al. [38]	2006	9	2.5 mg/mL	IEI	+
Podszuhn et al. [40]	2007	8	5 mg/mL	IEI	+
Tanna et al. [32]	2008	13	N/A	IEI	+
McMurray et al. [39]	2008	14	N/A	IEI	+
Wierzbicka et al. [42]	2011	26	5 mg/mL	IEI	+
Mikolajczak et al. [41]	2012	8	6.5 mg/mL	IEI	+
Graupp et al. [44]	2013	26	average 79.7 mg/cycle	IEI	+
Grasso et al. [43]	2014	31	75 mg/mL	IEI	+
Murono et al. [45]	2017	10	7.5 mg/mL	IEI	+

* IEI – Intraepithelial injection.

Tab. IV. Experiences in using Bevacizumab in RRP.

	YEAR	NO. OF PTS	DOSE OF BEVACIZUMAB	METHOD OF ADMINISTRATION	RESULTS LOCAL IMPROVEMENT
Rahbar R. et al. [53]	2005	12	N/A	IEI	+
Nagel et al. [58]	2009	1	10 mg/ml	systemic	+
Maturo et al. [59]	2010	3	1.25 mg/ml	IEI	+
Zeitels et al. [55]	2011	20	7,5–12,5 mg/ml	IEI, 4 times, 6 week intervals	+ (in 95% pts)
Best et al. [57]	2012	43	15–88 mg/ml	IEI	+
Rogers et al. [60]	2013	10	2,5 mg/ml	3 IEI, 5-9 weeks interval	+
Sidell et al. [56]	2014	9	kolejno 5 mg/ml	IEI 5 times, 6 week intervals	+
Mohre et al. [54]	2014	5	5–40 mg/ml	systemic	+
Bedoya et al. [61]	2017	2	5–15 mg/ml	systemic	+

* IEI – Intraepithelial injection.

there exists limited data concerning the optimal dosage, efficacy and safety of the drug. The paucity of randomized trials, small study groups, and lack of detail regarding surgical and medical treatment data between institutions are obstacles in creating the recommendations for routine use.

To conclude, both antiviral and anti-vascular endothelial growth factor antibody adjuvant therapies in aggressive RRP give hope for improved treatment outcomes. Multicenter longitudinal trials would help to clarify the safety and efficacy of these therapies and finally establish a treatment paradigm.

REFERENCES

1. Derkay C.S., Wiatrak B.: Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008; 118 (7): 1236–1247.
2. de Villiers E.M., Fauquet C., Broker T.R., Bernard H.U., zur Hausen H.: Classification of papillomaviruses. Virology. 2004; 324 (1): 17–27. doi:10.1016/j.virol.2004.03.033.
3. Seedat R.Y., Combrinck C.E., Burt F.J.: HPV associated with recurrent respiratory papillomatosis. Future Virol. 2013; 8 (5): 477–492. doi:10.2217/fvl.13.31.
4. Ruiz R., Achlatis S., Verma A., Born H., Kapadia F., Fang Y. et al.: Risk factors for adult-onset recurrent respiratory papillomatosis. Laryngoscope. 2014; 124 (10): 2338–2344.
5. Omland T., Lie K.A., Akre H., Sandlie L.E., Jebsen P., Sandvik L. et al.: Recurrent respiratory papillomatosis: HPV genotypes and risk of high-grade laryngeal neoplasia. PLoS One. 2014; 9 (6): e99114.
6. McKenna M., Brodsky L.: Extraesophageal acid reflux and recurrent respiratory papilloma in children. International Journal of Pediatric Otorhinolaryngology. 2005; 69 (5): 597–605.
7. Mammas I.N., Sourvinos G., Spandidos D.A.: The paediatric story of human papillomavirus (Review). Oncology Letters. 2014; 8 (2): 502–506.
8. Ruiz R., Achlatis S., Verma A., Born H., Kapadia F., Fang Y., Pitman M., Sulica L., Branski R.C., Amin M.R.: Risk factors for adult-onset recurrent respiratory papillomatosis. Laryngoscope. 2014; 124: 2338–2344. doi:10.1002/lary.24730.
9. Gillison M.L., Broutian T., Pickard R.K., Tong Z.Y., Xiao W., Kahle L. et al.: Prevalence of oral HPV infection in the United States, 2009–2010. Journal of the American Medical Association. 2012; 307 (7): 693–703.
10. Born H., Ruiz R., Verma A., Taliercio S., Achlatis S., Pitman M. et al.: Concurrent oral human papilloma virus infection in patients with recurrent respiratory papillomatosis: A preliminary study. Laryngoscope. 2014; 124 (12): 2785–2790.
11. Tjon Pian Gi R.E., San Giorgi M.R., Slagter-Menkema L., van Hemel B.M., van der Laan B.F., van den Heuvel E.R. et al.: Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck. 2014 Jun 23.
12. Bonagura V.R., Vambutas A., DeVoti J.A., Rosenthal D.W., Steinberg B.M., Abramson A.L., Shikowitz M.J., Gjertson D.W., Reed E.F.: HLA alleles, IFN-gamma responses to HPV-11 E6, and disease severity in patients with recurrent respiratory papillomatosis. Human Immunology. 2004; 65 (8): 773–782.
13. Rosenthal D.W., DeVoti J.A., Steinberg B.M., Abramson A.L., Bonagura V.R.: T(H)2-like chemokine patterns correlate with disease severity in patients with recurrent respiratory papillomatosis. Molecular Medicine. 2012; 18: 1338–1345.
14. Bonagura V.R., Vambutas A., DeVoti J.A., Rosenthal D.W., Steinberg B.M., Abramson A.L., Shikowitz M.J., Gjertson D.W., Reed E.F.: HLA alleles, IFN-gamma responses to HPV-11 E6, and disease severity in patients with recurrent respiratory papillomatosis. Human Immunology. 2004; 65 (8): 773–782.
15. Gelder C.M., Williams O.M., Hart K.W., Wall S., Williams G., Ingrams D. et al.: HLA class II polymorphisms and susceptibility to recurrent respiratory papillomatosis. Journal of Virology. 2003; 77 (3): 1927–1939.
16. DeVoti J., Hatam L., Lucs A., Afzal A., Abramson A., Steinberg B. et al.: Decreased Langerhans cell responses to IL-36γ: altered innate immunity in patients with recurrent respiratory papillomatosis. Molecular Medicine. 2014; 20: 372–380.
17. Venkatesan N.N., Pine H.S., Underbrink M.P.: Recurrent respiratory papillomatosis. Otolaryngologic Clinics of North America. 2012; 45 (3): 671–694, viii–ix.
18. Rodman R., Mutasa S., Dupuis C., Spratt H., Underbrink M.: Genetic dysregulation in recurrent respiratory papillomatosis. Laryngoscope. 2014; 124 (8): E320–325.
19. Lee L.A., Cheng A.J., Fang T.J., Huang C.G., Liao C.T., Chang J.T. et al.: High incidence of malignant transformation of laryngeal papilloma in Taiwan. Laryngoscope. 2008; 118 (1): 50–55.
20. Rabah R., Lancaster W.D., Thomas R., Gregoire L.: Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatric and Developmental Pathology. 2001; 4 (1): 68–72.
21. Ruiz R., Achlatis S., Verma A., Born H., Kapadia F., Fang Y. et al.: Risk factors for adult-onset recurrent respiratory papillomatosis. Laryngoscope. 2014;124(10):2338–2344.
22. Sanchez G.I., Jaramillo R., Cuello G., Quintero K., Baena A., O'Byrne A. et al.: Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head and Neck. 2013; 35 (2): 229–234.
23. Draganov P., Todorov S., Todorov I., Karchev T., Kalvatchev Z.: Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green real-time PCR. International Journal of Pediatric Otorhinolaryngology. 2006; 70(3): 469–473.
24. Doyle D.J. , Gianoli G.J., Espinola T., Miller R.H.: Recurrent respiratory papillomatosis: juvenile versus adult forms. Laryngoscope. 1994; 104: 523–527.
25. Campisi P., Hawkes M., Simpson K.: Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope. 2010; 120 (6): 1233–1245.
26. Derkay C.S., Wiatrak B.: Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008; 118 (7): 1236–1247.
27. Van Cutsem E., Snoeck R., Van Ranst M., Fiten P., Opdenakker G., Geboes K. et al.: Successful treatment of a squamous papilloma of the hypopharynx-esophagus by local injections of (S)-1-(3-hydroxy-2 phosphonylmethoxypropyl)cytosine. Journal of Medical Virology. 1995; 45 (2): 230–235.
28. Snoeck R., Wellens W., Desloovere C., Van Ranst M., Naesens L., De Clercq E. et al.: Treatment of severe laryngeal papillomatosis with intralesional injections of cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine]. Journal of Medical Virology. 1998; 54 (3): 219–225.
29. Pransky S.M., Albright J.T., Magit A.E.: Long-term follow-up of pediatric recurrent respiratory papillomatosis managed with intralesional cidofovir. Laryngoscope. 2003; 113 (9): 1583–1587.

30. Derkay C.S., Smith R.J., McClay J., van Burik J.A., Wiatrak B.J., Arnold J., Berger B., Neefe J.R.: HspE7 treatment of pediatric recurrent respiratory papillomatosis: final results of an open-label trial. Annals of Otology, Rhinology & Laryngology. 2005; 114 (9): 730–737.
31. Chadha N.K., James A.L.: Antiviral agents for the treatment of recurrent respiratory papillomatosis: a systematic review of the English-language literature. Otolaryngology–Head and Neck Surgery. 2007; 136 (6): 863–869.
32. Tanna N., Sidell D., Joshi A.S., Bielamowicz S.A.: Adult Intralesional Cidofovir Therapy for Laryngeal Papilloma, Arch. Otolaryngol. Neck Surg. 2008; 134: 497. doi:10.1001/archotol.134.5.497.
33. Chhetri D.K., Blumin J.H., Shapiro N.L., Berke G.S.: (2002) Office-based treatment of laryngeal papillomatosis with percutaneous injection of cidofovir. Otolaryngol Head Neck Surg. 126: 642–648.
34. Pontes P., Avelino M., Pignatari S., Weckx L.L.M.: Effect of Local Application of Cidofovir on the Control of Recurrences in Recurrent Laryngeal Papillomatosis, Otolaryngol. Neck Surg. 2006; 135: 22–27. doi:10.1016/j.otohns.2005.10.060.
35. Co J., Woo P.: Serial Office-Based Intralesional Injection of Cidofovir in Adult-Onset Recurrent Respiratory Papillomatosis, Ann. Otol. Rhinol. Laryngol. 2004; 113: 859–862. doi:10.1177/000348940411301102.
36. Lee A.S., Rosen C.A.: Efficacy of cidofovir injection for the treatment of recurrent respiratory papillomatosis. Journal of Voice. 2004; 18 (4): 551–556.
37. Naiman A.N., Abedipour D., Ayari S., Fresnel E., Coulombeau B., Bour J.B., Froehlich P.: Natural history of adult-onset laryngeal papillomatosis following multiple cidofovir injections. Annals of Otology, Rhinology & Laryngology. 2006; 115 (3): 175–181.
38. Dikkers F.G.: Treatment of recurrent respiratory papillomatosis with microsurgery in combination with intralesional cidofovir – a prospective study. European Archives of Oto-Rhino-Laryngology. 2006; 263 (5): 440–443.
39. McMurray J.S., Connor N., Ford C.N.: Cidofovir Efficacy in Recurrent Respiratory Papillomatosis: A Randomized, Double-Blind, Placebo-Controlled Study, Ann. Otol. Rhinol. Laryngol. 2008; 117: 477–483. doi:10.1177/000348940811700702.
40. Pudszuhn A., Welzel C., Bloching M., Neumann K.: Intralesional cidofovir application in recurrent laryngeal papillomatosis. European Archives of Oto-Rhino-Laryngology. 2007; 264 (1): 63–70.
41. Mikolajczak S., Quante G., Weissenborn S., Wafaisade A., Wieland U., Lüers J.C., Klussmann J.P., Beutner D.: The impact of cidofovir treatment on viral loads in adult recurrent respiratory papillomatosis, Eur. Arch. Oto-Rhino-Laryngology. 2012; 269: 2543–2548. doi:10.1007/s00405-012-2103-7.
42. Wierzbicka M., Jackowska J., Bartochowska A., Józefiak A., Szyfter W., Kędzia W.: Effectiveness of cidofovir intralesional treatment in recurrent respiratory papillomatosis. European Archives of Oto-Rhino-Laryngology. 2011; 268 (9): 1305–1311.
43. Grasso M., Remacle M., Bachy V., Van Der Vorst S., Lawson G.: Use of cidofovir in HPV patients with recurrent respiratory papillomatosis. European Archives of Oto-Rhino-Laryngology. 2014; 271 (11): 2983–2990.
44. Graupp M., Gugatschka M., Kiesler K., Reckenzaun E., Hammer G., Friedrich G. Erratum to: Experience of 11 years use of cidofovir in recurrent respiratory papillomatosis, Eur. Arch. Oto-Rhino-Laryngology. 2013; 270: 2785–2785. doi:10.1007/s00405-013-2569-y.
45. Murono S., Nakanishi Y., Tsuji A., Endo K., Kondo S., Wakisaka N., Yoshizaki T.: Intralesional cidofovir injection for recurrent respiratory papillomatosis in Japan, Auris Nasus Larynx. 2016; 43: 541–545. doi:10.1016/j.anl.2016.01.005.
46. Derkay C.S., Volsky P.G., Rosen C.A., Pransky S.M., McMurray J.S., Chadha N.K. et al.: Current use of intralesional cidofovir for recurrent respiratory papillomatosis. Laryngoscope. 2013; 123 (3): 705–12.
47. Broekema F.I., Dikkers F.G.: Side-effects of cidofovir in the treatment of recurrent respiratory papillomatosis. European Archives of Oto-Rhino-Laryngology. 2008; 265 (8): 871–879.
48. Sajan J.A., Kerschner J.E., Merati A.L., Osipov V., Szabo S., Blumin J.H. Prevalence of dysplasia in juvenile-onset recurrent respiratory papillomatosis. Archives of Otolaryngology – Head and Neck Surgery. 2010; 136 (1): 7–11.
49. Lott D.G., Krakovitz P.R.: Squamous cell carcinoma associated with intralesional injection of cidofovir for recurrent respiratory papillomatosis. Laryngoscope. 2009; 119 (3): 567–570.
50. Avelino M.A., Zaiden T.C., Gomes R.O.: Surgical treatment and adjuvant therapies of recurrent respiratory papillomatosis. Brazilian Journal of Otorhinolaryngology. 2013; 79 (5): 636–642.
51. Donne A.J., Rothera M.P., Homer J.J.: Scientific and clinical aspects of the use of cidofovir in recurrent respiratory papillomatosis. International Journal of Pediatric Otorhinolaryngology. 2008; 72 (7): 939–944.
52. Maturo S., Hartnick C.J.: Use of 532-nm pulsed potassium titanyl phosphate laser and adjuvant mintralesional bevacizumab for aggressive respiratory papillomatosis in children: initial experience. Archives of Otolaryngology – Head and Neck Surgery. 2010; 136 (6): 561–565.
53. Rahbar R., Vargas S.O., Folkman J., McGill T.J., Healy G.B., Tan X. et al.: Role of vascular endothelial growth factor-A in recurrent respiratory papillomatosis. Annals of Otology, Rhinology & Laryngology. 2005; 114 (4): 289–295.
54. Mohre M., Schliemann C., Biermann C., Schmidt L.H., Kessler T., Schmidt J. et al.: Rapid response to systemic bevacizumab therapy in recurrent respiratory papillomatosis. Oncology Letters. 2014; 8 (5): 1912–1918.
55. Zeitels S.M., Barbu A.M., Landau-Zemer T., Lopez-Guerra G., Burns J.A., Friedman A.D. et al.: Local injection of bevacizumab (Avastin) and angiolytic KTP laser treatment of recurrent respiratory papillomatosis of the vocal folds: a prospective study. Annals of Otology, Rhinology & Laryngology. 2011; 120 (10): 627–634
56. Sidell D.R., Nassar M., Cotton R.T., Zeitels S.M., de Alarcon A.: High-dose sublesional bevacizumab (avastin) for pediatric recurrent respiratory papillomatosis. Annals of Otology, Rhinology & Laryngology. 2014; 123 (3): 214–221.
57. Best S.R., Friedman A.D., Landau-Zemer T., Barbu A.M., Burns J.A., Freeman M.W.: Safety and dosing of bevacizumab (avastin) for the treatment of recurrent respiratory papillomatosis. Annals of Otology, Rhinology & Laryngology. 2012; 121 (9): 587–593.

58. Nagel S., Busch C., Blankenburg T., Schütte W.: Treatment of respiratory papillomatosis – a case report on systemic treatment with bevacizumab. Pneumologie. 2009; 63 (7): 387–389.

59. Maturo S., Hartnick C.J.: Use of 532-nm pulsed potassium titanyl phosphate laser and adjuvant mintralesional bevacizumab for aggressive respiratory papillomatosis in children: initial experience. Archives of Otolaryngology – Head and Neck Surgery. 2010; 136 (6): 561–565.

60. Rogers D.J., Ojha S., Maurer R., Hartnick C.J.: Use of adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children. JAMA Otolaryngology—Head & Neck Surgery. 2013; 139 (5): 496–501.

61. Bedoya A., Glisinski K., Clarke J., Lind R.N., Buckley C.E., Shofer S.: Systemic Bevacizumab for Recurrent Respiratory Papillomatosis: A Single Center Experience of Two Cases. Am. J. Case Rep. 2017; 18: 842–846.

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Corresponding author: Joanna Jackowska, e-mail: drjackowska@gmail.com

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