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Use of intralesional cidofovir in the recurrent respiratory papillomatosis: a review of the literature

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Abstract. – OBJECTIVE: Recurrent respiratory papillomatosis (RRP) is characterized by exophytic, benign, and papillary lesions infected by the virus in the epithelium of the upper aerodigestive tract. RRP is caused by persistent infection of the respiratory epithelium by human papillomavirus (HPV) HPV6 and-11. The clinical course of RRP is unpredictable, frequently relapsing, and may be lifelong. The aim of this study is to evaluate the efficacy and safety of the use of intralesional Cidofovir in the treatment of RRP.

PATIENTS AND METHODS: We have selected articles on the use of cidofovir as adjuvant therapy in laryngeal papillomatosis. We reviewed 20 reports that enrolled 185 patients with "adult onset recurrent respiratory papillomatosis" (AORRP) and 85 patients with "juvenile onset recurrent respiratory papillomatosis" (JORRP). We evaluated concentration of cidofovir, number of injections, injection interval, therapeutic response, side effects, and progression to dysplasia.

RESULTS: The mean concentration of cidofovir was 7.5 mg/ml at injection. The mean number of injections per patient is 6 with 26 days between injections. The percentage of patients with dysplasia after use of cidofovir is 1.48%. The AORRP response to cidofovir is better with a 74% complete response rate, compared to 56.5% of the JORRP.

CONCLUSIONS: Intralesion use of cidofovir has a good adjuvant action in RRP increasing the complete remission of the disease. The treatment does not increase the risk of laryngeal dysplasia.

Key Words:
Cidofovir, Recurrent respiratory papillomatosis, Laser Co2, HPV, Larynx.

Introduction

Recurrent respiratory papillomatosis (RRP) is a condition predominantly affecting the larynx and trachea (and occasionally bronchi and lung parenchyma)[1-5]. RRP may cause life-threatening airway obstruction or voice change. It is a potentially devastating disease with significant morbidity although it is rarely fatal. Although RRP is considered a benign condition, the lesions are capable of undergoing a malignant transformation in 3% to 5% of patients[6-10]. RRP has a bimodal age distribution, presenting commonly in children younger than five years or in adults between 20 and 30 years. The primary causative agent is human papilloma virus (HPV). Two subtypes are thought to cause the majority of RRP cases in patients, namely HPV-6 and HPV-11[11-15]. In juvenile-onset RRP (JORRP), the transmission may be secondary to direct contact with papilloma virus in an infected birth canal from maternal cervical human papilloma virus infection. In the case of adult-onset RRP (AORRP), the modes of disease transmission have not been well established[16-20]. The common symptoms of RRP include progressive hoarseness, stridor, and respiratory distress[21]. Diagnosis is made by visualization with flexible nasolaryngoscopy or direct laryngo-bronchoscopy. Biopsy of the lesions is useful for histologic confirmation of RRP and to exclude malignant transformation[22-24].

Treatment involves surgical removal of the epithelial lesion in order to maintain airway patency and phonation. CO_2 laser is convenient and precise and represents one of the best op-

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tions in the management of RRP. Lasers offer surgeons the advantage of unobstructed vision of the surgical field with minimal tissue manipulation and a longer working distance. The potential benefits of laser surgery are decreased risk of postoperative bleeding, increased sterility, minimal surrounding tissue damage, better intraoperative hemostasis, fewer surgeries, and complications, such as tracheostomy. However, microdebriders with cold instruments are still in use[25-28]. The most used adjuvant drugs are interferon, various virostatics (acyclovir, valacyclovir, and cidofovir), and indole-3-carbinol[21]. Cidofovir is an antiviral agent indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Since 1998, cidofovir has been used to treat patients with RRP. Its mechanism of action involves decreasing the efficiency of DNA transcription following incorporation into the growing DNA chain. Usually the drug is injected after surgery in microlaryngoscopy under general anesthesia. Cidofovir is used at an intralesional level at a concentration ranging from 2.5 to 37.5 mg/ml, to an amount that varies according to the extent of papillomatosis (on average 3 ml in each region involved). The frequency depends on the number of relapses and the speed in which they occur (on average it is administered 3 times with intervals of 3-4 weeks), trying not to exceed the dose expected by the pharmaceutical company of 3 mg/pro kg. The aim of this study is to evaluate the efficacy and safety of the use of intralesional cidofovir in the treatment of RRP[29].

Patients and Methods

We have selected articles on the use of cidofovir as adjuvant therapy in laryngeal papillomatosis treated with CO_2 laser or cold instruments, with a minimum number of 4 cases. All articles were found on PubMed and Scopus using the keywords "recurrent respiratory papillomatosis" and "cidofovir". The data of this systematic investigation observed the Preferred Reporting Items for Systematic Review accordingly with the (PRISMA) statement (Figure 1). We reviewed 20 reports that enrolled a total of 185 patients with "adult onset recurrent respiratory papillomatosis" (AORRP) and 85 patients under 12 years of age with "juvenile onset recurrent respiratory papillomatosis" (JORRP). Our review evaluated the following evaluation parameters: concentration of infiltrated

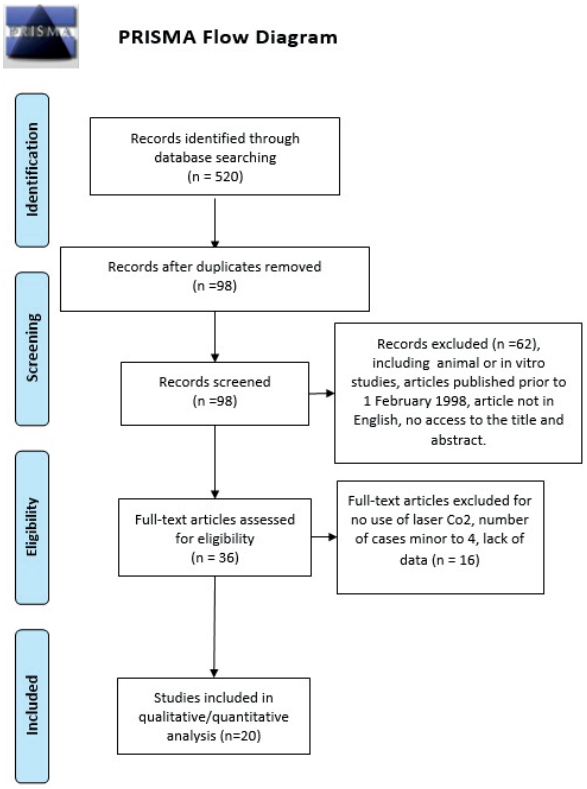

Figure 1. PRISMA flow chart for the selection of the articles in the literature to be included in the review.

cidofovir (mg/ml), number of injections, injection interval, therapeutic response (CR: complete response, PR: partial response, NR: no response), side effects, and progression to dysplasia.

We use Darkey[26] and Pontes scores[9] to evaluate the response to the drug. CR = Score 0 after treatment; PR = Score after treatment minor compared to initial score; NR = Score after treatment major or equal compared to the initial score (Table I).

Results

The concentration of cidofovir ranges from 2.5 to 15 mg/ml, with a mean of 7.5 mg/ml at injection. The mean number of injections per patient is 6 with a minimum of 2 and a maximum of 13 doses. The injection interval varies from a minimum of 2 to a maximum of 8 weeks, with a mean of 26 days between injections. The percentage of patients with dysplasia after use of cidofovir is 1.48%.

Between the concentration of cidofovir and the percentage of complete response, there is a linear correlation with a Pearson correlation index (r) of

Table I. Data collection e analysis.

Author	AORRP/ JORRP	Cidofovir concentration	Response	N° injections	Side effects	Injections interval	Dysplasia
Wierzbicka et al[1] (2011)	26 AORRP 6 JORRP total = 32	5 mg/ml	CR = 56.25% (18 = 2 JORRP + 16 AORRP); PR = 40.6% (13 = 3 JORRP + 10 AORRP); NR = 3,12% (1 JORRP)	2.5 3.7	3 patients None	4-6 weeks 4-6 weeks	None None
Graupp et al[2] (2013)	26 AORRP 8 JORRP total = 34	7.5-15 mg/ml	CR = 79.6% (27 = 7 JORRP and 20 AORRP); PR = 20,4% (6 AORRP + 1 JORRP)				
Naiman et al[3] (2006)	16 JORRP	From 5 mg/ml to 7.5 mg/ml	CR = 75% (12 JORRP); PR = 25% (4 JORRP)	9	None	2-4 weeks	None
Pudszuhn et al[4] (2007)	7 AORRP 3JORRP total=10	5 mg/ml	CR = 60% (6 = 5 AORRP + 1 JORRP); PR = 20% (2 JORRP); 2 AORRP stopped therapy	4.3	None	4 weeks	1 carcinoma in situ
Dikkers[5] (2006)	9 AORRP	2.5 mg/ml	CR = 77.7% (7 AORRP); PR = 22,3% (2 AORRP)	9	None	6 weeks	1 dysplasia
Snoeck et al[6] (1998)	14 AORRP 3 JORRP total = 17	2.5 mg/ml	CR = 82,3% (14 = 2 JORRP + 12 AORRP); PR = 11,7% (2 = 1 JORRP + 1 AORRP); 1 AORRP lost in follow-up	7	None	2-4 weeks	Not specified
Murono et al[7] (2016)	10 AORRP	7.5 mg/ml	CR (1) 10% PR (9) 90%	3	None	2 weeks	1 squamous cell carcinoma
Grasso et al[8] (2014)	31 AORRP	7.5 mg/ml	CR (26) 83,9% PR (5) 16,1%	4	None	Only if (recidiva) continuing	6 dysplasia, relapse 5 solved therapy
Pontes et al[9] (2006)	10 AORRP	6 mg/ml	CR (7) 70% 20% NR (1) 10% PR (2)	4.2	None	Only if relapse (recidiva)	None
Peyton et al[10] (2004)	11 JORRP	5 mg/ml	CR (3) 27% 18% NR (6) 55%	6 PR (2)	None	2 weeks	None
Chung et al[11] (2003)	11 JORRP	5-10 mg/ml	CR (6) 55% PR (5) 45%	6	None	4 weeks	None
Bielamowicz et al[12] (2002)	13 AORR	4.17-6.25 mg/ml	CR (13) 100%	6	None	4 weeks	None
Chhetri et al[13] (2003)	5 JORRP	5 mg/ml	CR (4) 80% PR (1) 20%	13	None	2-4 weeks	None
Chhetri et al[14] (2002)	5 AORRP	37.5 mg/ml (percutaneous)	CR (4) 80% PR (1) 20%	7	None	2-4 weeks	None

Table continued

Table I *(Continued)*. Data collection e analysis.

Author	AORRP/ JORRP	Cidofovir concentration	Response	N° injections	Side effects	Injections interval	Dysplasia
Co et al[15] (2004)	5 AORRP	7.5 mg/ml	CR (1) 20% PR (4) 80%	4.4	None	4 weeks	None
Lee et al[16] (2004)	10 AORRP 3 JORRP = 13	7.5 mg/ml	CR (8A+2J) PR (2A) 15% NR (1J) 7%	3.5 78%	3 patients with vocal fold scarring	3 weeks	None
Sheahan et al[20] (2006)	4 JORRP	5 mg/ml	CR (1) 25% PR (2) 50% NR (1) 25%	10.5	None	3-5 weeks	None
Mandell et al[17] (2004)	4 JORRP	5 mg/ml	CR (3) 75% PR (1) 25%	4	None	8 weeks	None
Naiman et al[18] 2006	19 AORRP	5-7.5 mg/ml	CR (17) 90% PR (2) 10%	4.5	None	2-4 weeks	None
Pransky et al[19] (2003)	11 JORRP	2.5-5 mg/ml	CR (5) 45% PR (5) 45%	9	None	2-4 weeks	None

AORRP = adult onset recurrent respiratory papillomatosis; JORRP = juvenile onset recurrent respiratory papillomatosis; CR = complete response; PR = partial response; NR = no response; N° = number.

0.125. A "r" $\geq$ 0.7 is considered significant. In this case, Pearson correlation index in not statistically significant.

We have analyzed the cidofovir adjuvant therapy in the treated patients, according to the AORRP or JORRP division (Table II). The AORRP response to cidofovir is better with a 74% complete response rate, compared to 56.5% of the JORRP. The review shows the usefulness of post-surgical adjuvant therapy, in fact, the response to cidofovir was null only in one case of AORRP (0.6%) and in 10 cases of JORRP (11.7%). The results obtained show that the prognosis of the disease, after the use of cidofovir is better in adults than in children. In both cases, a post-surgical adjuvant therapy decreases the percentage of relapse, increasing the complete response.

Discussion

A recent international retrospective study of 635 patients with RRP, which includes 275 treated with cidofovir in 16 hospitals in 11 countries of the world, shows no statistically significant differences in the occurrence of neutropenia, renal dysfunction or an increase in the malignant transformation of the upper respiratory tract epithelium after cidofovir use[29].

In all twenty studies reported in our review, where there was an off-label use of cidofovir, no side effects occurred. In the study of Wierzbika et al[1] a patient had asthenia and diarrhea for 4 days, but suffered from Gilbert's syndrome, while two patients had a slight increase in transaminases (AST and ALT) but returned to range after 6 weeks of balanced diet to not overload the liver. In Murono et al[7], the values of creatinine, neutrophils, and total leukocytes were evaluated in the 10 patients studied before and after the use of cidofovir. The results show that there are no statistically significant changes in the values obtained. Only one article in literature treated the vocal outcomes before and after treatment but did not meet the inclusion criteria for the review.

The results and side effects of excessive therapeutic doses of cidofovir in patients with RRP and HPV is one of the most discussed topics in the European Society of Laryngology (ELS) and

Table II. Results of cidofovir adjuvant therapy.

	AORRP	JORRP
Complete Response	137 (74%)	48 (56.5%)
Partial Response	44 (23.8%)	27 (31.8%)
No Response	1 (0.6%)	10 (11.7%)
Stopped Therapy	3 (1.6%)	
Total	185	85

AORRP = adult onset recurrent respiratory papillomatosis; JORRP = juvenile onset recurrent respiratory.

has prompted a multicentric retrospective study to provide reliable data on the safety and efficacy of cidofovir in RRP[30].

Several studies[31,32] have reported that HPV-11 and HPV-6 may promote bronchial carcinoma and squamous cell larynx. The purpose of the review is to confirm the low probability that RRP lesions treated with cidofovir-infiltration evolve to injury dysplastic. Only 4 patients developed dysplasia during therapy. In Murono et al[7], one patient developed a squamous cell carcinoma 3 years after the last administration of the drug, but *in situ* hybridization for HPV was negative and the patient was a regular smoker. In the study of Grasso et al[8] one patient developed dysplasia that became carcinoma *in situ* after 6 treatments. In the same study another 5 patients developed dysplasia during the treatment, but the pathology completely regressed continuing the use of cidofovir. The review data confirm that cidofovir does not seem to induce dysplastic changes in patients infected with HPV in the laryngeal epithelium, in fact, the percentage of patients with dysplasia after use of cidofovir is 1.48%, less than percentage of patients who develop RRP malignant disease by HPV 6 and 11 spontaneously (2-3%)[33-40].

Conclusions

Based on the review data, intralesion use of cidofovir has a good adjuvant action in RRP. The drug shows a high efficiency by increasing the complete remission of the disease. Cidofovir has no side effects even after high cumulative doses. Treatment with intralesional cidofovir seems to be safe and does not increase the risk of laryngeal dysplasia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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