Original Article

LOCAL APPLICATION OF CIDOFOVIR AS AN ADJUVANT THERAPY FOR RECURRENT LARYNGEAL PAPILLOMATOSIS IN CHILDREN

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This study was conducted in the Pediatric Otolaryngology Discipline – Department of Otolaryngology and Head and Neck Surgery of Universidade Federal de São Paulo – UNIFESP, São Paulo, SP, Brazil.

ABSTRACT

OBJECTIVE. To evaluate the efficacy of local application of cidofovir in association with surgical treatment of recurrent laryngeal papillomatosis (RLP) in children. Study design: Prospective.

METHODS. Fourteen patients, with a mean age of 4.7 years and with two or more relapses after surgical treatment, were submitted to papilloma resection and injection of 22.5 mg cidofovir (7.5 mg/mL) in the region of excision. After 2- to 3-week intervals, the same dose of cidofovir was repeated two or three times. In the case of relapse, a new cycle of surgery followed by local applications of cidofovir was restarted. HPV-6 was found in five children and HPV-11 in other five children; in four cases HPV typing was not performed.

RESULTS. Before the beginning of the study, patients were submitted, on average, to two surgical procedures per year for relapse control. After treatment with cidofovir, annual surgery rates dropped to 1.1 ($p = 0.013$). The mean interval time between relapses before the beginning of the study was 1.6 months; at the end of the study, interval time reached 4.4 months ($p = 0.014$). Patients with HPV-6 did not show any significant changes in interval time between relapses after treatment with cidofovir, whereas 60% of the children with HPV-11 became disease-free at the end of the study.

CONCLUSION. Cidofovir is an efficient adjuvant in the treatment of RLP in children when used by means of local applications in association with surgical resection of lesions. HPV-11 may be more susceptible to the beneficial effects of cidofovir.

KEYWORDS: Papilloma. Tumor virus infections. Larynx. Child. Antiviral agents.

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INTRODUCTION

Recurrent laryngeal papillomatosis (RLP) is a disease characterized by the widespread formation of often multiple papillomas in the respiratory tract, with a trend toward recurrence. The larynx is the most commonly affected site, especially the vocal folds, epiglottis and vestibular folds.[1,2] In approximately 30% of the cases, RLP affects extralaryngeal sites, in particular, the oral cavity and trachea.[1,3]

This disease may affect individuals across all age groups and show a diverse clinical course. The earlier the initial manifestation, the more aggressive RLP tends to be.[2,4] Children diagnosed before the age of 3 years are 3.6 times more likely to require more than four surgical procedures per year and to have more than one anatomical site involved.[1]

RLP is caused by human papillomavirus (HPV), usually HPV-types 6 and 11.[4,5] Infection with HPV-11 is associated with more aggressive disease and a poor prognosis for remission.[4]

The annual incidence of RLP in children aged less than 14 years is approximately 4/100,000[3] and disease distribution is similar among boys and girls.[1,2]

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In most children, initial manifestation of disease occurs between 2 and 4 years of age, voice changes being the most common symptom.[1,2] A progressive increase in lesion size may result in dyspnea and stridor, and, in rare cases, the disease can lead to death due to severe airway obstruction, bronchopulmonary spread, or malignant transformation.[3,5]

Treatment of RLP is based on the excision of papilloma in order to maintain airway patency and improve voice quality. Lesions are resected by microlaryngeal surgery, using cold microtweezers, laser or microdebrider. However, even after all lesions are resected, the virus may persist in the tissue and the disease tends to relapse. On average, children are submitted to five surgical procedures per year for relapse control.[1,2]

Relapse control requires excessive manipulation of the larynx, which may result in sequelae such as synechia, stenosis and granulation tissue.[6]

In order to reduce or eliminate the need for future surgical procedures, several adjuvant therapies have been proposed. Between 12.6 and 47.6% of children with RLP receive adjuvant interventions,[2,7,8] which are recommended in cases of aggressive disease, when relapse is frequent or there is distal airway compromise.[5] Interferon and cidofovir are the most common adjuvant drugs currently used; however, as well as other adjuvant drug strategies already utilized, such as photodynamic therapy, indole-3-carbinol, cimetidine, acyclovir, retinoids, ribavirin, and mumps vaccine, they have shown controversial results and none have gained wide acceptance so far.[9,10]

Cidofovir is a nucleotide analog of cytosine and a potent inhibitor of virus replication, including adenovirus, cytomegalovirus, herpes simplex, varicella-zoster, Epstein-Barr, and papilloma viruses. It has been approved by the Food and Drug Administration (FDA) only for the treatment of cytomegalovirus-retinitis in patients with acquired immunodeficiency syndrome, administered intravenously. Among the reported side effects of cidofovir, nephrotoxicity is the main and most significant; other adverse effects include neutropenia, weakness, nausea, and diarrhea. In addition, the FDA takes into consideration the potential carcinogenicity of cidofovir in humans, since it has been reported to cause mammary adenocarcinoma in rats.[11,12]

Cidofovir has been used as an adjuvant in the treatment of RLP in adults and children since 1998, from different administration and dosage regimens, reporting controversial results. Doses between 2.5 and 30 mg of cidofovir are reported in the literature, injected intralesionally or in the region of papilloma excision. Some studies have demonstrated favorable results, that is, remission or decreased severity of disease in most patients treated with cidofovir,[13-20] whereas other studies have not observed a significant improvement.[21,22]

Objective

To evaluate the efficacy of local application of cidofovir in association with surgical treatment of RLP in children.

Methods

This study was approved by the Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP), protocol no. 1185/02.

All patients with RLP followed up at UNIFESP Pediatric Otolaryngology Outpatient Clinic, with two or more relapses after surgical treatment, were invited to participate in the study. The child's guardian was informed about the use of cidofovir and its potential complications and, after reading and signing the written consent form, the patient was included in the study.

Patients with papillomas involving sites outside the larynx, with history of renal or hepatic disease, receiving any other adjuvant treatment, or with evidence of atypia in lesions resected in previous surgical procedures were excluded from the study.

Between January 2002 and April 2006, 14 children met the criteria for inclusion in the study. Age ranged from 1 to 10 years (mean = 4.7 years), and patients did not show any other health problems. The sample was composed of seven females and seven males. All patients had been previously submitted to 2-11 (mean = 4) surgical procedures. The follow-up period ranged from 1.5 to 3.9 years (mean = 2.9 years).

At first, the study patients were submitted to papilloma resection by microlaryngeal surgery, using conventional instruments (cold microtweezers), followed by injection of 22.5 mg diluted cidofovir (7.5 mg/mL distilled water) in the region of excision. After 2- to 3-week intervals, the same dose of cidofovir was repeated two or three times. A surgical procedure associated with three or four local applications of cidofovir was considered as a "cycle". In the second, third and fourth applications, when relapses or residual lesions were observed, lesions were then resected, followed by injection of cidofovir.

Surgical excisions and cidofovir applications were performed via suspension laryngoscopy, under general anesthesia and mechanical ventilation. The number of applications per cycle and the interval time between applications varied, since, occasionally, the patients could not attend the scheduled appointments or the procedure was canceled by the anesthesia team.

After completing a cycle, the patient was followed up monthly and assessed by fiber-optic nasolaryngoscopy. When a relapse was detected, a new cycle was restarted.

Patients underwent blood test and examination of the hepatic and renal function after each cidofovir application, as well as histopathological evaluation of the resected material.

PCR-based virus typing was performed, and HPV-6 was found in five children and HPV-11 in other five children. In four cases, typing could not be performed due to loss of specimens (Table 1).

Lesions were staged according to the topographic classification proposed by Avelino et al.[23] (Chart 1). In the beginning of the study, disease stage ranged between II and IV (Table 1).

Chart 1 – Staging of recurrent laryngeal papillomatosis proposed by Avelino et al.[23]

S (Supraglote)	G (Glote)	I (Infraglote)	
S1 Focal lesion < 1/3 of extension of the lumen	G1 Focal lesion on the vocal fold or commissure < 1/3 of extension of the vocal fold G1a One vocal fold G1b Both vocal folds	I1 Focal lesion < 1/3 of extension of the lumen	Stage I: • 1 or 2 degree 1 levels
			Stage II: • 3 degree 1 levels • 1 or 2 degree 2 levels • 1 degree 3 level, with others at degree 0 or 1
S2 One or more focal lesions < 2/3 of extension of the lumen	G2 One or more focal lesions < 2/3 of extension of the vocal fold G2a One vocal fold G2b Both vocal folds	I2 One or more focal lesions < 2/3 of extension of the lumen	
S3 Lesion > 2/3 of extension of the lumen	G3 Lesion > 2/3 of extension of the vocal fold G3a One vocal fold G3b Both vocal folds	I3 Lesion > 2/3 of extension of the lumen	Stage III: • 3 degree 2 levels • 1 degree 3 level, with others at degree 2 or 3
S4 Obstructive lesion or tracheotomy	G4 Obstructive lesion or tracheotomy	I4 Obstructive lesion or tracheotomy	Stage IV: • Any degree 4 level

Table 1 – HPV typing, stage of the disease in the beginning of the study, number of cycles of cidofovir per patient, intervals between relapses before and after treatment with cidofovir, number of surgeries before and after treatment with cidofovir.

Patient	HPV	Initial stage	Number of cycles	Interval between relapses (months)		Total surgeries		Surgeries/year	
				Pre-cidofovir	Post-cidofovir	Pre-cidofovir	Post-cidofovir	Pre-cidofovir	Post-cidofovir
1	6	II	2	4	3	2	3	1.3	1.2
2	--	II	1	0.5	--	11	1	2	0.7
3	6	II	2	1.6	0.5	2	4	1.3	1.1
4	11	III	2	0.5	4	3	4	0.7	1.3
5	11	IV	3	1	--	8	3	2.3	0.8
6	--	II	3	1.1	3	4	4	1.6	0.8
7	6	II	1	1.1	9	3	4	3.3	1
8	11	II	2	1.4	--	4	2	4.4	1.1
9	--	II	1	0.2	6	3	4	1.2	2.6
10	6	II	2	1	5	2	3	2	1.2
11	11	IV	3	5	--	5	3	2.6	0.8
12	11	II	1	0.5	7	2	1	2.2	0.6
13	--	II	1	4	5.5	5	2	1.5	0.7
14	6	II	3	0.2	1	3	4	2	1.7
Mean				1.6	4.4	4	3	2	1.1
p				0.014		0.239		0.013	

The interval time between relapses and the number of surgical procedures required for relapse control after treatment with cidofovir was compared to the pre-treatment period (control period) using the paired Student *t* test, with a significance level of 5%.

Results

All patients were submitted to the first cidofovir cycle. After the first cycle, 13 patients showed disease recurrence, which occurred, on average, after 4.2 months. Prior to the beginning of our study, the mean interval time between relapses was 1.6 months. This increase in interval time between relapses was statistically significant (p = 0.016) and one patient (patient number 2) no longer had relapses until completion of the study (Table 2).

Of the 13 patients who showed disease recurrence after the first cidofovir cycle, nine started a second cycle immediately after detection of recurrence. Four patients (patients number 7, 9, 12, and 13) could not undergo the second cidofovir cycle, at the time of relapse, because cidofovir was not available. After the second cycle, one patient (number 8) became disease-free until the end of the study, and the remaining patients showed disease recurrence, which occurred, on average, after 3.8 months (p = 0.051). Although not significant, the value of p, in this case, was close to 0.05, which might indicate some degree of improvement in the interval time between relapses after the second cidofovir cycle (Table 2).

Of the eight patients who showed disease recurrence after the second cidofovir cycle, four were submitted to a third cycle of applications and two patients (number 5 and 11) became disease-free until the end of the study. Four patients (number 1, 3, 4, and 10) could not undergo the third cidofovir cycle, since cidofovir was not available at the time of relapse. In this case, the statistical analysis could not be carried out due to the limited number of patients (Table 2).

The patients who showed disease recurrence after treatment with cidofovir, but could not undergo a new cycle because cidofovir was not available at the time of relapse, continued to attend follow-up appointments monthly and were submitted to microlaryngeal surgery for papilloma resection according to each child's need. These patients did not receive additional applications of cidofovir.

The interval time between relapses that occurred prior to the beginning of the study and after cidofovir cycles, as well as the number of cycles to which each patient was submitted are shown in Table 1. A statistically significant increase could be observed in the mean interval time between relapses after treatment with cidofovir (p = 0.014).

Before the beginning of the study, patients had been submitted to 2-11 (mean = 4) surgical procedures. During the study period, the number of surgical procedures ranged between 1 and 4 (mean = 3), as described in Table 1.

Table 2 – Intervals between relapses before and after the cidofovir cycles and patients who were disease-free for one year or longer at the end of the study

Patient	Interval between relapses (months)				Period without relapse at the end of the study (years)
	Pre-cidofovir	After 1st cycle	After 2nd cycle	After 3rd cycle	
1	4	0.6	3	--	--
2	0.5	--	--	--	1
3	1.6	2	0.5	--	--
4	0.5	7	4	--	--
5	1	0.7	4	--	2.5
6	1.1	1	2	3	--
7	1.1	9	--	--	--
8	1.4	6	--	--	1
9	0.2	6	--	--	--
10	1	3.5	5	--	--
11	5	5	11	--	2.6
12	0.5	7	--	--	--
13	4	5.5	--	--	--
14	0.2	2.5	1.5	1	--
Mean	1.6	4.2	3.8	2	--
	p	0.016	0.051	--	--

This table also indicates annual surgery rates (number of surgeries per year) before and after the beginning of cidofovir therapy. Before the beginning of the study, patients were submitted, on average, to two surgical procedures per year. After treatment with cidofovir, annual surgery rates dropped to 1.1. The difference in the total number of surgeries was not statistically significant ($p = 0.239$), but there was a significant reduction in annual surgery rates ($p = 0.013$).

At the end of the study, patients 2, 5, 8, and 11 had been disease-free for one or more years. Table 2 shows for how long these patients were disease-free until the end of the study. HPV-11 was found in three of these patients, and in one of them HPV typing was not performed. Similarly, among the five patients with HPV-11, three (60%) were disease-free at the end of the study (patients 5, 8, and 11) and two (patients 4 and 12) showed a significant increase in interval time between relapses after treatment with cidofovir (Table 1).

None of the children with HPV-6 became disease-free at the end of the study. In addition, there was no significant difference in interval time between relapses before (1.6 months) and after (3.7 months) treatment with cidofovir ($p = 0.248$) (Table 1).

None of the patients showed adverse affects during the study, changes in laboratory tests, or evidence of carcinoma in the histopathological examination.

Discussion

RLP remains a challenge for patients, their families and otolaryngologists. Despite being rare and benign, the disease results in significant morbidity due to the sites affected and frequent recurrence of lesions. In general, recurrences persist until adulthood and, depending on the extension and recurrence of disease, the several surgical procedures required by these patients may increase the risk of complications and interfere with the quality of life of the patient.

Microlaryngeal surgery for papilloma resection is the standard treatment for RLP. A number of adjuvant therapies have been proposed; however, in most cases, a cure is not achieved, only palliation. Cidofovir is one of the most common adjuvant drugs currently used in the treatment of RLP[5] and, despite the favorable results demonstrated in most studies,[13-20] administration and dosage regimens, as well as safety of cidofovir, are yet to be established in the treatment of this disease.

In the present study, the use of cidofovir increased interval time between relapses and reduced the number of surgical procedures required per year for relapse control. Furthermore, at the end of the study, four patients became disease-free.

The number of cidofovir applications per patient apparently did not affect disease progression, that is, persistence or remission of disease. Both the patients who showed disease recurrence and the patients who showed no more lesions were submitted to 1-3 cycles of cidofovir application.

However, disease remission was often higher among patients with HPV-11. On the other hand, none of the patients with HPV-6 became disease-free at the end of the study. Despite the small sample size and incomplete virus typing, this result might suggest a difference in the susceptibility to cidofovir according to HPV subtype.

None of the patients showed changes in laboratory tests or drug-related adverse affects, confirming the apparent safety of the drug in pediatric patients when used by means of local application.

Moreover, there is great concern with the potential carcinogenicity of cidofovir in the treatment of RLP. In 2005, Wemer et al.[24] reported a case of RLP that progressed to severe dysplasia during treatment with cidofovir. A recent review of articles on the use of cidofovir as an adjuvant therapy in RLP reported only five cases (2.7%) of dysplasia among 188 patients, an acceptable number within the percentage expected for spontaneous malignant degeneration, which may occur during disease progression and is observed in 2-3% of the cases.[25] Among the children investigated, there were no signs of malignant transformation during the follow-up period.

Despite the encouraging results, randomized controlled studies should be conducted to further evaluate the use of cidofovir.

Conclusion

Cidofovir is an efficient adjuvant in the treatment of RLP in children when used by means of local applications in association with surgical resection of lesions. HPV-11 may be more susceptible to the beneficial effects of cidofovir.

No conflicts of interest declared concerning the publication of this article.

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