

Cidofovir effects on recurrent laryngeal papillomatosis in children: preliminary report

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Key words: laryngeal papillomatosis, cidofovir, HPV virus.

Summary

Aim: To demonstrate the effects of local application of Cidofovir in children with recurrent laryngeal papillomatosis (RLP), according to our 2002 institutional protocol for RLP management. Study Design: Preliminary/clinical prospective. Material and Method: Our series included 5 RLP pediatric patients assisted at the otolaryngology pediatric clinic at the Federal University of Sao Paulo. They were all submitted to local application of Cidofovir and had up to a one-year follow-up. Before starting the treatment with Cidofovir, these patients had been submitted to at least three surgical procedures with histopathological exams confirming the diagnosis of papillomatosis (inclusion criteria); with no clinical evidence of nephropathy or hepatic disorders (exclusion criteria). The protocol consisted of surgical removal of the lesions, followed by local application of 3 ml of Cidofovir (7.5mg/ml). The treatment cycle included minimum of 3 applications, and at any sign of recurrence, another cycle of application would begin. Results: We observed that before the use of Cidofovir, recurrences in all 5 children had shorter intervals (one each three months). After Cidofovir application, the evolution of the illness changed dramatically and the 5 patients did not need any debulking for more than one year. No children presented laboratorial exams alteration, local or systemic collateral effects with local injection of Cidofovir. Based on our preliminary results we observed that local application of Cidofovir in children promotes good short-term control of RLP recurrences.

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Article submitted on July 08, 2004. Article accepted on November 10, 2004.

INTRODUCTION

Recurrent laryngeal papillomatosis (RLP) is a disease whose main characteristic is the presence of verruciform epithelial lesions that may be pedicle or sessile, single or multiple, but which are, usually, recurrent lesions¹. This clinical entity leads to high morbidity because these lesions are confluent and develop into dysphonia (voice disorders) and dyspnea (changes in the respiratory pattern), both progressive conditions. The lesions may trigger respiratory failure due to airway obstruction and can even cause death. Recurrences have frustrated ENT doctors for several decades. In the specialty, this disease is considered as one of the most difficult conditions to control. The lesions affect mainly the larynx but may also affect the mouth, nose, pharynx, esophagus and the whole tracheobronchial tree. In the larynx, the most affect sites are the vocal folds, the epiglottis and the vestibular folds. Other common sites are: the nasal vestibular lumen, nasopharyngeal surface of the soft palate, carina and the bronchi².

This epithelial proliferation, considered a benign neoplasia, is caused by human papillomavirus (HPV) infection, a multiple type DNA virus. HPV-6 and HPV-11 types are the most common in laryngeal papillomatosis, but we may also see HPV-16 and HPV-18 types,^{3,6} which may have malignancy potential. Fortunately, we seldom find HPV-16 and HPV-18 types in children with RLP⁶, but one must always request HPV typing and, whenever these two types are present, one must consider higher malignancy potential.

Although this is a benign disease, its clinical evolution implies frequent hoarseness and upper airway obstruction relapses. Thus, patients are often submitted to multiple surgeries. Children usually have more aggressive relapses and poorer prognosis. Doyle, in 1994⁷, while studying patients with severe recurrent laryngeal papillomatosis showed, in his series, that although no adults had to be submitted to tracheotomy, 60% of children were submitted to tracheotomy.

Relapse control requires excessive larynx manipulations, which may lead to permanent sequelae such as stenosis, formation of anterior and posterior membranes, vocal fold lesions, formation of granulation tissue, among other disorders.^{4,7,8}

Different therapeutic approaches have been developed for treating recurrent laryngeal papillomatosis: larynx microsurgery with mechanical removal or CO₂ laser removal; the use of anti-metabolites, hormones, podophyllin, alpha interferon, indol-3-carbinol, photodynamic therapy and antiviral agents. The antiviral agents that have already been used in RLP are Acyclovir, Ribavirin and Cidofovir. As Acyclovir and Ribavirin have shown poor results, the most used antiviral agent has been Cidofovir.

Cidofovir [(S)-1-(3-Hydroxy-2-Phosphonyimethoxypropyl) Cytosine, HPMPC, Vistide[®]] is an antiviral that has been proven

quite effective in the inhibition of virus replication such as herpes, adenovirus, cytomegalovirus and papillomavirus¹⁴⁻¹⁶. This drug has been approved by the FDA (Food and Drug Administration) to be used in retinitis caused by cytomegalovirus in patients with AIDS. The first reports on the use of Cidofovir were published in 1993, by Kurtzman et al.¹⁴, showing the outcomes in animals. Snoeck et al.¹⁷, 1995 were the first researchers to use Cidofovir in humans with anal lesions caused by HPV. They used a gel formulation in three patients with good outcomes. Its use in RLP was first reported by Snoeck in 1998¹⁶. Since then, several authors have been showing positive outcomes with the use of this medication in RLP treatments.¹⁸⁻²⁵ If administered by IV it may cause hepatotoxicity and nephrotoxicity but, when used as local applications, there has been no report of any type of local or systemic side effects.

The use of Cidofovir as treatment for recurrent laryngeal papillomatosis is quite recent. Nevertheless, the studies that have been published are unanimous about its absolute efficacy although there are some differences regarding the standardization of its use in controlling the relapses and its proper administration. For this reason, we must carry out more standardized and controlled studies with the drug so that we may assess cure expectations or relapses control.

The objective of this study is to show, by means of this preliminary report, the effects of Cidofovir in children with RLP, complying with a protocol adopted in our services since 2002.

MATERIAL AND METHOD

In this trial we have included 5 children who have been followed up for at least one year as outpatients, follow-up in our pediatric laryngology clinic and who have complied with a protocol for Cidofovir use. They all have agreed to sign a Free Informed Consent Form, as determined by the standards of the Ethics and Research Committee, Medical School, Federal University of Sao Paulo.

In order to be included in this protocol, the patients had to comply with some inclusion and exclusion criteria:

A. Inclusion Criteria:

1. Diagnosis confirmed by clinical pathology analysis.
2. At least two relapses after surgical procedure.
3. Material collection for HPV typing.

B. Exclusion Criteria:

1. Chronic use of hepatotoxicity drugs.
2. Liver disorders.
3. Kidney disorders.

After inclusion and exclusion criteria were met, the protocol consisted of surgical treatment with suspension

laryngoscopy with cold steel removal of papillomatosis lesions and local injection of Cidofovir (concentration and dose of 7.5mg/ml) up to 3 ml. These children were submitted to a cycle at least for 3 applications within intervals of 2-3 weeks, when no lesions occurred. In case there were signs of lesion relapse, the lesion was removed and a new cycle of applications began.

When tracheal site was affected, the same dose was used after the removal of the lesions, via bronchoscopy with the use of a 0° and 4 mm non-flexible endoscope and with cup forceps.

All the lesions removed in the procedure were sent to clinical pathology analysis. Part of the lesion was removed before starting the use of Cidofovir and sent to a Molecular Biology laboratory to check HPV typing. The proposed typing test was done by PCR (Polymerase Chain Reaction).

After each application, we requested new laboratorial exams such as blood count, alkaline phosphatase, gamma-GT, TGO, TGP, urea and creatinine.

These children were followed up every 2 weeks with video nasofibroscopy and video laryngoscopy (whenever possible). At any sign of relapse, they were submitted to debulking and a new cycle of 3 applications began, as recommended. After a 2-month relapse-free period, they were submitted to monthly follow-up consisting of video nasofibroscopy and video laryngoscopy for early detection of any sign of relapse.

We have adopted the protocol described above to observe the patients response to the adopted therapy in a standardized way.

OUTCOMES

In this preliminary trial, we have included 5 children who had been followed up for more than one year: 3 were males and 2 females, ages ranging from 3 to 9 years of age, mean age: 5.2 years. Among these children, only one had tracheotomy and had the disease spread to the lower airways.

Child number 1, male, 6 years, born and coming from Aracaju, who had already undergone 5 previous surgeries in intervals of approximately 2 months between each procedure. He was included in the protocol and submitted to total of 9 applications of Cidofovir. After 6 applications, he had no relapses for a 11-month period, after which he showed a small lesion focus in the left vocal fold (asymptomatic); he was, then, submitted to a new 3-application cycle and has now been followed up for 1 year and 2 months with no signs of relapse. His typing for HPV detected HPV-11.

Child number 2, male, 5 years, born and coming from Rio de Janeiro, had already been submitted to 10 previous surgeries and had been, by that time, tracheotomized for one year. The disease had spread through the whole trachea to the carina. The interval between

procedures was approximately of 2-3 months. After his inclusion in our protocol, he was submitted to 9 applications of Cidofovir in the larynx and in the trachea. After the 5th Cidofovir application, he was decannulated. Currently, he has been followed up for 1 year and 3 months. It was not possible to have his HPV typing but the material is stored in the Molecular Biology laboratory, in perfect conditions to preserve the virus structure.

Child number 3, male, 3 years, born and living in Sao Paulo, had already undergone 4 previous surgeries with 1-2 months intervals between procedures. After his inclusion in the protocol, he was submitted to 10 Cidofovir applications. Currently, in a follow-up of 1 year and 3 months, he shows no signs of relapse. The HPV type responsible for RLP in this patient was type HPV-6.

Child number 4, female, 3 years, born and coming from Maranhão, had already been submitted to 3 surgeries in intervals of 3 months, approximately. After her inclusion in the protocol, she received 5 applications of Cidofovir. Recurrences were controlled for 11 months when a small lesion focus appeared in the vestibular fold. As Cidofovir was not available at the moment, we decided to wait and see. She has been followed up every month for the past 5 months and the lesion focus showed discreet growth in size but it is still asymptomatic. The child has had no symptoms for 1 year and 4 months. The material for performing the typing test is also stored at the Molecular Biology laboratory.

Child number 5, female, 9 years, born and living in Sao Paulo, had already undergone 3 previous surgeries in intervals of 3 months between procedures. After her inclusion in the protocol, she received 5 applications of Cidofovir and remained free of recurrences for 12 months. Later, she showed a small lesion in the vestibular face of the right vocal fold. Then, we started a new 3-application cycle. However, as the patient did not show up for the third application, she only received two. At the same time, as she did not regularly comply with follow-up schedules, she has been excluded from the protocol. She remained in the follow-up program as an outpatient and has had no recurrence for a whole year. Currently, she showed a small lesion in the right vocal fold, which is still asymptomatic. The material collected for HPV typing is also stored in the Molecular Biology laboratory.

In all five children, we had good control of recurrent lesions when we compared the intervals between surgeries before and after the use of the medication.

No child showed any type of change in the laboratorial exams and no local or systemic side effect with the local injection of Cidofovir.

DISCUSSION

Several authors have demonstrated positive results with the use of Cidofovir in RLP patients. Pransky et al. in 1999 and 2000^{20,21} were the first researchers to demonstrate

results in pediatric patients. In their first study, they had a series of 5 children and used Cidofovir in an initial concentration of 2.5mg/ml with maximum dosage of 1mg/kg. During the study, they increased the concentration to 5mg/ml, in applications of 1 to 2 ml, and the total dosage they used ranged from 2.5 to 10 mg, in intervals of 2-3 weeks. In their second study, they added 5 more children in their series and maintained the same concentration (5mg/ml), but they administered 2 to 4 ml per application and performed at least 4 applications in intervals of 2 weeks. They also recommended previous debulking. Snoeck¹⁶ and Willian²², on the other hand, presented different methodologies: they performed local application of Cidofovir without any debulking (lesion removal). Snoeck, who was a pioneer in the use of Cidofovir for RLP, recommended a concentration of 2.5mg/ml and applied the medication until the lesions disappeared, but he only studied the adult population.

Although there are some studies with the use of Cidofovir, the methodology published in the literature varies a lot and there is no consensus regarding the ideal dose to be used, the number of applications and the interval between applications. Besides, some authors favor local application only on the lesions, whereas other authors associate the lesions exeresis with local application of the medication.

In our series, we have been using Cidofovir for almost 4 years and have had excellent results in adults²⁵. In these patients the procedure was to perform surgical removal of the lesions and administer 18mg of Cidofovir, and new applications only when lesion relapses occurred.

When we started using the medication in children, we observed that the results were not as positive as the results previously observed in adults. Then, we started to use a protocol based on the one used by Pransky, in which we applied Cidofovir at least 4 times in intervals of 2 weeks. But the concentration and the doses we used (7.5mg/ml up to 3 ml) were higher than those recommended in the literature. We agreed with Pransky methodology regarding the association of lesions removal with Cidofovir application, especially in the pediatric population where the diameter of the upper airways is smaller, thus, with higher risk of obstruction.

In our outcomes with these 5 children we have observed good recurrence control when we compared the intervals between surgeries before starting the treatment and after the use of the medication. Before the applications of Cidofovir, these 5 children had recurrences in shorter intervals (1 to 3 months), which required surgical procedures. After their inclusion in the protocol, there was a change in the disease evolution in the 5 children, as they remained free of recurrences during at least one year. Moreover, the recurrences in patients numbers 4 and 5 could only be noticed due to our strict follow-up because

these patients remained asymptomatic. Milczuk, in 2003²³, also had positive outcomes in 4 children who were treated with Cidofovir.

Nevertheless, we observed that we had to have several applications to obtain good response and patients 1, 2 and 3 – who have received 9 to 10 Cidofovir applications, achieved better outcomes and were free of disease for more than 14 months.

We believe that these children – maybe because they have a more aggressive type of recurrent laryngeal papillomatosis – need heavier doses and higher number of Cidofovir applications than adults do. The dosage used in our protocol is a little higher than the doses described in literature up to now^{20,21,23,24}. These patients needed more than one 3-application cycle to achieve good control of recurrences. However, these children did not have any type of changes in their laboratorial exams, clinical pathology analysis and also did not show any local or systemic side effect, as in accordance to other cases in the literature^{15,16,20,21,26}. The only study described in the literature that reports side effects with local use of Cidofovir was published by Bienvenu²⁷ in 2002. This was the report of a case study with an immunodepressed patient, with previous chronic renal failure who developed an extensive acuminate condyloma and who was, then, submitted to local application of Cidofovir in gel 4% for 12 continuous days. Although there was lesion involution, on the 19th day the patient developed acute renal failure. The author underlined that the patient had received a higher dose than those described by other authors and had genital excoriations during treatment and, in addition, suffered from chronic renal failure. Considering all previous conditions affecting this patient, we do not believe that this case should be relevant when analyzing the side effects in the local use of Cidofovir.

Although HPV typing by Molecular Biology (PCR) is part of the protocol, due to budget limitations, we were only able to obtain the typing for patients 1 and 3. The material from the other patients has been collected and is stored for further typing as soon as possible.

Based on the preliminary outcomes, we consider Cidofovir as a promising therapy to control recurrent laryngeal papillomatosis in children with aggressive form of the disease. The protocol in use allowed us to standardize the dose, to choose the proper moment to perform new applications, and also to have close observation to check possible recurrences. Nevertheless, our follow-up is not long enough to report any cure. This is a new therapy (little bit more than 5 years); thus, we must have strict follow-up of these patients and develop study protocols with larger number of patients and longer follow-up periods. Bearing in mind this purpose, we continue to develop this protocol in our service and to include new patients.

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