Cidofovir Injection for Recurrent Laryngeal Papillomatosis

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Background: Recurrent laryngeal papillomatosis is caused by the human papilloma virus and characterized by multiple exophytic lesions of the vocal tract; it is a benign disease, but one that tends to recur after removal of growths. Due to the nature of the disease, alternative treatment strategies have focused on antiviral injection at lesion sites that eliminate repeated surgical procedures. The purpose of this study was to evaluate the efficacy of cidofovir injection following initial papilloma excision with a microdebrider.

Methods: Cidofovir injections (at a concentration of 7.5 mg/mL) were conducted in 5 patients (1 child; 4 adults). The injection number per patient varied from 2 mL to 6 mL. Repeated cidofovir injections were indicated only if recurrent or newly grown lesions were found in any of 3-week follow-up visits.

Results: Short-term complete remission was observed with different duration, from 11 to 21 weeks, following initial 2 to 3 cidofovir injections. All patients relapsed eventually, and their recurrent lesions were not successfully eradicated by repeated cidofovir injection. One patient's prognosis was complicated by scarring of both vocal cords.

Conclusion: Surgical excision combined with cidofovir injection failed to prevent relapsing laryngeal papillomatosis. Once lesions recurred, repeated cidofovir injections alone were not able to achieve complete remission, although these procedures might be helpful in lessening the severity of the clinical course. Further studies in determining the dosage, duration of injection, and more long-term follow-up are required to clarify the efficacy of cidofovir for the treatment of recurrent laryngeal papillomatosis. [*J Chin Med Assoc* 2008;71(3):143–146]

Key Words: cidofovir, larynx, papilloma, surgery

Introduction

Recurrent respiratory papillomatosis is commonly associated with human papilloma virus type 6 (HPV-6) or HPV-11. It is seen in both children and adults. The most commonly involved site is the larynx. Extralaryngeal spread to the lower airway is relatively uncommon.[1] The mainstay of treatment is surgery to maintain a patent airway and improve voice quality. However, recurrence after surgery is common for most pediatric patients and for a portion of adults. Because repeated surgical procedures are required and accompanied by high morbidity, such as scarring and stenosis,[2] adjuvant therapies, including interferon-α2a, retinoic acid, indole-3-carbinol, photodynamic therapy, and antiviral agents, have been applied to decrease the need for surgery.[3] The criteria most practitioners have used for initiation of adjuvant treatment are: (1) patient undergoes more than 4 surgical procedures in 1 year; (2) distal spread of disease; or (3) rapid regrowth with airway compromise.[2] Among the adjuvant agents, cidofovir is the most frequently used. Cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine; Vistide®, formerly known as HPMPC] is an antiviral drug approved by the US Food and Drug Administration for systemic use in the treatment of cytomegalovirus retinitis among HIV/AIDS patients.[4] Several studies on cidofovir injection for treatment of recurrent laryngeal papillomatosis (RLP), using different regimens, failed to achieve therapeutic agreement.[5–9] In our clinic, we conducted

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the first cidofovir-injection treatment to assess its efficacy in Taiwanese patients with RLP following excision of lesions by a microdebrider.

Methods

Beginning from May 2005, 5 patients (2 males; 3 females), 1 of whom was an 8-year-old girl, were enrolled into our study; they signed informed consent forms and the use of cidofovir was approved by the Bureau of Pharmaceutical Affairs, Department of Health, Taiwan, R.O.C. All patients had a history of RLP determined by pathology studies. The average duration of their disease was 71.6 months (range, 9–135 months); they had previously undergone multiple surgical procedures, either by CO_2 laser or other surgical techniques. The median number of surgical treatments was 9.4 (range, 4–22).

Videolaryngoscopy was used to record the laryngeal lesions. The staging/severity of the disease and post-cidofovir treatment status were assessed and scored according to the anatomic staging system developed by Derkay and colleagues.[10] Surgical excision and intralaryngeal injection procedures were performed with patients under general anesthesia and direct laryngoscopy.

These procedures were performed by one of the authors (Y.S. Lin). While the papilloma lesions were being removed with a microdebrider (2.9-mm Skimmer Angle-Tip; XOMED, Jacksonville, FL, USA), cidofovir 7.5 mg/mL was directly injected into the lesion bed. The injected volume depended on lesion extension and ranged from 2 mL to 6 mL. Renal and liver functions were monitored before and during the treatment period by blood-biochemical parameters to prevent nephro- and hepatotoxic potentials of cidofovir.

Patients were discharged on the day of surgery and followed-up every 3 weeks thereafter. At every follow-up, videolaryngoscopy was performed. Remissions were defined by the absence of gross disease seen in the office by videolaryngoscopy. Once recurrent or new growth lesions were detected in the office, a repeated intralesional cidofovir injection under general anesthesia was indicated. No further surgical excision was performed.

Results

Among the 5 patients, the age at diagnosis of RLP ranged from 7 to 51 years (Table 1). The pretreatment severity score was 10 ± 3, and the mean follow-up period was 34.4 weeks (Table 2). The first cidofovir

Table 1. Patient characteristics

Patient	Gender	Age, yr	Age at diagnosis, yr	Prior surgeries, *n*	Severity score before cidofovir treatment		
					Total	Supraglottis	Glottis
1	F	8	7	4	13	4	9
2	F	19	10	22	10	5	5
3	F	44	39	6	5	0	5
4	M	48	44	10	11	5	6
5	M	63	51	5	11	4	7

Table 2. Treatment and follow-up data

Patient	Cidofovir injections, *n* (Total/CR)*	Severity score after last injection†			Duration of CR, wk	Duration of F/U, wk‡
		Total	Supraglottis	Glottis		
1	6/2	4	1	3	14	35
2	5/3	4	0	4	21	39
3	4/2	2	0	2	21	36
4	6/3	6	3	3	11	32
5	5/3	3	1	2	12	30

**Number of total cidofovir injections vs. number of cidofovir injections to complete remission; †score 3 weeks after the first procedure; ‡weeks after the first procedure. CR = complete remission; F/U = follow-up.*

injection was combined with microdebrider excision. Three weeks after the first injection, all patients presented with recurrent lesions, and additional cidofovir injections were then applied at 3-week intervals until the patients were lesion-free. Following 2–3 repeated injections, all patients achieved complete remission ranging from 11 to 21 weeks.

During the follow-up period, patients experienced different degrees of improvement of their severity scores; however, none was lesion-free at their last visit. Patient 4 (male, 48 years old) relapsed 11 weeks after the first 3 injections, and, subsequently, an additional 3 injections were conducted over a 9-week treatment period. Unfortunately, the complication of partial scar formation over bilateral vocal folds was noted during his last visit.

Discussion

RLP has been recognized as one of the most challenging and frustrating disease for both the patients it afflicts and the physicians who care for them. Although spontaneous resolution at puberty has been reported in some children,[11] the unpredictability of the illness is the typical clinical course with RLP affecting both children and adults. However, the childhood-onset form is believed to be more aggressive than the adult form.[2] This was the case with Patient 1, who presented the most severe score before cidofovir treatment.

Until now, the underlying pathophysiology of HPV infection of the respiratory tract, especially in the larynx and vocal cords, is not well understood. The nature of the variability of RLP may explain why certain individuals require only a few therapeutic procedures, whereas others require many. Hence, numerous adjuvant medical therapies have been developed. Cidofovir has demonstrated the most potential for disease control;[12] however, more research is required to determine efficacy and safety. In this study, we focused on cidofovir, based on an elucidated pathogenesis of HPV infection.

Cidofovir is a cytosine nucleotide analog that can selectively inhibit viral DNA polymerases during viral replication. In 1998, the first successful use of local cidofovir injection alone for the treatment of severe laryngeal papillomatosis was reported.[13] Several studies investigating the efficacy of cidofovir in the management of recurrent respiratory papillomatosis have presented encouraging preliminary results,[5–8] while Peyton Shirley and Wiatrak[9] and this present study have not come to a general agreement. Variations among these surveys consist of inclusion criteria, sample sizes, affected areas, adjuvant therapy prior to cidofovir, cidofovir dosage, injection interval, and follow-up period. All of these make the description of cidofovir effect difficult. Although no general agreement exists on the curative efficacy of cidofovir, cidofovir injection did have a significant palliative effect in our patients. All the patients had decreased severity scores during treatment and by the end of treatment, which was consistent with previous reports.

Regarding the concomitant efficacy of cidofovir and surgical excision, this study showed that 2 or 3 cidofovir injections associated with 1-time microdebrider excision could attain a varied duration of complete remission in all of these patients; however, repeated cidofovir injections even more than 2 times, as in a recurrent follow-up period, was not observed to regress the lesion completely. This observation would support the previous work of Naiman and colleagues[6] that surgical excision associated with cidofovir injections might remain necessary in persistent papillomatosis after cidofovir treatment.

Finally, Patient 4 developed a complication in the form of scar formation over bilateral vocal folds. In the literature, vocal-fold scarring that complicated excision with a microdebrider was never reported. Lee and Rosen found vocal-fold scarring in 3 patients after recurrent respiratory papillomatosis was controlled by cidofovir treatment.[8] The present study hardly clarified the issue of whether the local complication was related to cidofovir injection, excision with the microdebrider, or both. Undoubtedly, the combined treatment can increase the possibility of scarring.

In conclusion, RLP defied surgical excision and adjuvant cidofovir injection. The combined treatment failed to prevent relapse in the case of RLP. Once lesions recurred, repeated cidofovir injections alone were not able to achieve complete remission, although these procedures might have lessened the severity of this disease. Larger studies and more long-term follow-up are required to clarify the efficacy of cidofovir.

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