ORIGINAL ARTICLE

Adult Intralesional Cidofovir Therapy for Laryngeal Papilloma

A 10-Year Perspective

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Objective: To assess the long-term efficacy of intralesional cidofovir therapy in a previously reported cohort of adult subjects with laryngeal papilloma.

Design: Retrospective review.

Setting: Tertiary care medical center.

Patients: We previously reported on the favorable clinical response to intralesional cidofovir therapy in 13 adult subjects. The subjects were enrolled in an open-trial prospective study (1997-2001) and completed the injection-only treatment protocol, and all subjects achieved a disease remission after a mean of 6 injections. In the present study, we review the clinical course of these subjects during an extended observational period (2001-2006).

Intervention: Patients with documented relapse of disease underwent additional intralesional cidofovir injections.

Main Outcome Measures: Additional interventions, disease severity, and adverse outcomes are reported.

Results: Following the original cidofovir protocol, 6 patients (46%) received no further interventions. The remaining 7 patients (54%) required further treatment for disease relapse, with a mean duration of remission before relapse of 1.05 years. Of the 7 patients who experienced disease relapse, 2 continued to have stable disease with regular injections, 2 were lost to follow-up during relapse treatment, and 3 achieved disease remission again. For this latter cohort, the mean number of injections per year necessary to achieve a second remission was 3.82. This compares with a mean of 1.77 injections per year that these patients received on an as-needed basis prior to the original study.

Conclusion: Intralesional cidofovir injections have been shown to be an effective therapy for adult laryngeal papilloma and should be considered in those patients who experience disease relapse.

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RECURRENT RESPIRATORY PAPILLOMATOSIS (RRP) is a relatively uncommon disease process caused by the human papillomavirus (HPV). The disease has a bimodal age distribution and manifests as benign growths of epithelial tissue in the respiratory tract, primarily in the larynx.[1,2] Laryngeal papillomatosis is a cause for significant morbidity owing to its ability to affect vocal fold function and, when aggressive, can compromise a patent airway.[3] The mode of transmission of laryngeal papilloma is unknown, the clinical behavior is unpredictable, and recurrence is common.[4]

Historically, the treatment for laryngeal papilloma has involved a surgical approach. Repetitive surgical ablation with the carbon dioxide laser and the microdebrider blade have both been described and are commonly used in practice.[2,4,5] Nonsurgical management has included the use of multiple pharmacologic agents, including subcutaneous injection of indole-3-carbinol or interferon alfa. Each method of treatment carries its own risks, and effectiveness is variable.[4-6] A third pharmacologic agent that has received a significant amount of attention since its first reported use to treat RRP in 1995 is the cytosine nucleotide analogue cidofovir. Since its introduction, cidofovir has been both touted for its efficacy in achieving disease remission and questioned regarding its off-label use and the potential to cause malignant degeneration in laboratory animals.[2,4,7,8] In 2002, the senior author (S.A.B.) described 13 subjects who had completed a cidofovir injection protocol (1997-2001) designed to evaluate the efficacy and local adverse effects of cidofovir as treatment for laryngeal papilloma.[4] In the present study, we review the initial 13 subjects over an extended observational period (2001-2006) and discuss ad-

ditional interventions, disease severity, and adverse outcomes as they relate to this cohort.

METHODS

A retrospective review of 13 adult subjects with biopsy-proven laryngeal papilloma was performed. Subjects were previously enrolled in a strict open-trial prospective study (1997-2001). During this study period, they received and completed an intralesional cidofovir injection–only treatment protocol. Before the protocol, patients were receiving interventions on an as-needed basis. Following the protocol, all subjects achieved disease remission.

In the present study, the clinical course of these 13 original subjects was followed. During this extended observational period (2001-2006), the patients received interventions on an as-needed basis. Flexible or 70° rigid endoscopic laryngeal video examination was used for office-based evaluation. In addition, videostroboscopy was performed on all patients. Patients with documented relapse of disease underwent additional intralesional cidofovir injections.

Injections were performed in the operating room. A 5.5- or 6.0-mm endotracheal tube was used for general endotracheal anesthesia. Suspension microlaryngoscopy was performed with a Pilling-Dedo laryngoscope. For cidofovir treatments, infiltration of papilloma lesions was performed with a tuberculin syringe connected to a 25-gauge bayonet laryngeal injection needle. Medication was injected until the lesion and surrounding mucosa blanched. Medication retention during the injection was aided by grasping each affected region of the larynx with a Bouchayer forceps before needle placement. This pinching technique stabilized the lesions, resulting in maximum medication retention within the lesion as evidenced by minimal spillage of medication into the airway and excellent blanching of the affected tissue. The cidofovir concentration that was used was the same in all patients and below the current US Food and Drug Administration (FDA)-approved maximum dose. All patients who underwent surgery were discharged home the same day of surgery.

Medical records were reviewed for disease relapse and any necessary interventions.[9] Complications of interventions or adverse events were noted.

RESULTS

Thirteen patients (9 male and 4 female subjects) completed the original protocol (1997-2001). At the onset of the original study, the mean (range) age of the subjects was 48 years (18-85 years). By the conclusion of the protocol, all subjects had achieved clinical remission with no visibly detectable papilloma. On average, lesion remission was achieved after 6 injections. Prior to entrance into the original protocol (pre-1997), disease duration ranged from 1 to 30 years, with a mean duration of 7 years. During this time, the subjects had a mean number of 16 injections, yielding a mean number of 2.15 injections per year.

Since the termination of the protocol (2001), patients have returned on an as-needed basis. Of the 13 subjects, 6 (46%) received no further interventions. The remaining 7 patients (54%) required further treatment for disease relapse. For this "relapse" cohort, the mean time from disease remission in 2001 to recurrence was 1 year. The mean duration of disease prior to entrance into the original protocol for these patients was 11 years, compared with 3 years for the remission group.

Following relapse, all 7 patients required surgical intervention. For 6 patients, this entailed the sole use of intralesional cidofovir therapy. The seventh patient required concomitant cold steel papilloma excision with cidofovir injection for bulky disease. By the conclusion of this study (2006), of the 7 patients who experienced relapse, 2 continued to have stable disease with regular injections, 2 were lost to follow-up during relapse treatment, and 3 had achieved disease remission again. For this latter cohort, the mean time from original remission to relapse was 13 months, and the mean time from relapse to achieve a second remission was 8 months. The mean number of injections per year necessary to achieve this second remission was 3.82, and all of the treatments were solely intralesional cidofovir injections. Before enrolling in the original study, these 3 patients were receiving a mean number of 1.77 injections per year.

No adverse events or complications, including vocal fold scarring, from interventions were noted. The **Table** summarizes the results for all 13 subjects.

COMMENT

Recurrent respiratory papillomatosis is a disease process that manifests as benign growths of epithelial tissue in the respiratory tract. This disease is relatively uncommon, developing in 3 to 5 per 100 000 individuals and affecting both adults and children. Although RRP presents more frequently during childhood, the onset may occur at any age, and no distinct histological differences have been reported.[1,2,4]

Laryngeal papilloma is caused by HPV, a DNA virus that results in the proliferation of epithelium. Of the many HPV viral subtypes, HPV-6 and HPV-11 are the predominant types found in RRP.[3,5] The mechanism of transmission of RRP is largely unknown. The exposure of the upper airway to HPV-6 and HPV-11 has been suggested to be a common occurrence, with reported detection rates as high as 25% in the airways of unaffected individuals.[5] This suggests that RRP is somewhat ubiquitous and the development of laryngeal papilloma may be related to a defect in the immunity of the affected patient. One mechanism of infection described in the literature includes the transmission of cervical HPV with subsequent development of RRP in infants following vaginal delivery. Activation of quiescent HPV in an adult host acquired at birth has also been suggested, although triggers for reactivation remain unknown.[3]

Recurrent respiratory papillomatosis predominantly affects the larynx, although any level of the airway can become involved.[1] Symptoms and disease course are highly variable, ranging from minimal involvement of laryngeal structures to progressive obstruction of the airways and life-threatening respiratory distress.[3] In certain severe circumstances, tracheotomy may be necessary to maintain airway patency. Tracheotomy has been noted to cause disease progression to the bronchi, bronchioli, and alveoli, when conventional treatment methods may be rendered useless.[3,5]

Although variation exists with regard to disease severity, laryngeal papilloma frequently follows a recurrent course, legitimizing the search for curative interven-

Table. Summary of Data for 13 Adult Subjects Who Received Intralesional Cidofovir Therapy

Patient No./ Sex/Age, y	Symptom Duration Before Original Protocol, y	Surgical Procedures Before Original Protocol, No.	Procedures per Year Before Original Protocol, Mean No.	Time From Remission at Protocol End to Relapse, y	Cidofovir Treatments Following Relapse, No.	Time From Relapse to Second Remission, y	Postrelapse Procedures per Year, No.
Patients with remission							
1/F/18	5.01	1	0.20				
2/M/28	3.67	3	0.82				
3/M/35	1.25	5	4.00				
4/M/38	9.33	48	5.14				
5/M/66	0.92	2	2.17				
6/M/44	1.08	1	0.93				
Mean value	3.54	10	2.21				
Patients with relapse							
7/M/37	5.00	10	2.00	1.08	3	1.08	2.77
8/F/49	26.02	40	1.54	1.67	1	Lost to follow-up	
9/M/52	10.01	12	1.20	1.58	3	Lost to follow-up	
10/F/85	1.50	4	2.67	2.17	1	0.67	1.50
11/F/71	3.09	2	0.65	0.08	3	0.42	7.20
12/M/72	30.02	65	2.17	0.33	15	Active	
13/M/30	4.00	18	4.50	0.42	18	Active	
Mean value	11.38	21.57	2.10	1.05	6.29	0.72	3.82
Total mean value	7.76	16.23	2.15				

tions.[2] To date, the predominant mode of treatment for RRP worldwide involves a surgical approach. Repetitive surgical ablation with a carbon dioxide laser has been used for the removal of papilloma while simultaneously controlling hemorrhage in the surgical field.[5] Carbon dioxide laser ablation, however, is not without complications. Operating cost is significantly higher than with other surgical approaches, and the risk of thermal airway injury and airway fire further limit its utility. Lee and Smith[5] describe the use of the microdebrider blade as an alternative to the carbon dioxide laser. This technique offers superior operative results and minimizes the risk of collateral thermal injury to the airway, which can be seen with carbon dioxide laser ablation.[2,5] Regardless of technique, the surgical ablation or resection of laryngeal papilloma commonly results in a high rate of recurrence and carries with it the risk of additional scarring of the affected area.[2,4]

Nonsurgical management of RRP has included the use of subcutaneous injection of interferon alfa as well as the use of indole-3-carbinol; however, results have been variable. Interferon alfa has been reported to decrease papilloma growth with subcutaneous injection on alternating days over a 6-month period. Unfortunately, adverse effects of interferon alfa are common and limit the utility of the drug. Neurological impairment, decreased renal function, and hepatocellular damage have been reported with prolonged use of interferon alfa, and cessation of the drug frequently results in the regeneration of laryngeal papilloma.[5,6]

A third pharmacologic agent used to treat RRP is cidofovir, a cytosine nucleotide analogue approved by the FDA to treat cytomegalovirus retinitis, a once-common infection of the eye in patients with AIDS. Cidofovir functions to combat HPV by incorporating itself into the DNA chain of the virus, selectively inhibiting viral DNA polymerase and thus DNA synthesis in the HPV virus. Without successful DNA synthesis, the virus is unable to replicate and propagate within the host.

Cidofovir has been shown to be a strong agent in the clinical armamentarium against RRP. Snoeck et al[3] demonstrated the complete disappearance of papilloma in 14 of the 17 patients with RRP with the use of intralesional injections of cidofovir in 1998. The mean duration of remission was 13.6 months for these patients, who required 3 to 15 injections, with cidofovir volumes ranging from 4 to 8 mL per injection. In 1999, Pransky et al[6] demonstrated beneficial responses to adjuvant intralesional cidofovir injections in conjunction with surgical debulking in 5 pediatric patients with severe RRP. In this study, each of the 5 patients had a history of multiple surgical ablation procedures before the cidofovir injections. Of the 5 patients, 4 showed significant improvement in airway status and a marked reduction in the severity of their papilloma. This study also demonstrated a reduction in necessary operative intervention intervals from every 2 weeks to every 3 months on average. One patient in the study remained entirely free of disease at the time of writing. This study was updated by Pransky et al[10] in 2000, with the addition of 5 new patients with severe RRP, who were treated under a revised injection protocol. Of these 5 new patients, 4 demonstrated marked improvement in disease status, with decreased severity of papilloma as well as a reduced interval of necessary intervention. Of the 5 original patients, all continued to demonstrate marked improvement in disease status. None of the 5 patients showed evidence of adverse effects from cidofovir therapy.

In 2000, Wilson et al[2] reported complete resolution of disease in 3 adults with RRP with the use of intralesional cidofovir injections at The George Washington University Medical Center, Washington, DC. In this study, multiple prior treatment methods before cidofovir injection was attempted had failed in each of the 3 patients. Treatment resulted in the complete resolution of disease in all 3 patients; however, each experienced minor recurrence of papilloma after 18 months, 3 months, and 6 months, respectively. All areas of recurrent disease re-

sponded well to reinjection with cidofovir, and the patients were again disease free.

In 2002, the senior author reported the clinical results of 13 adult subjects who had completed the cidofovir injection protocol for RRP at The George Washington University Medical Center.[4] In this study, each of the 13 patients achieved clinical remission after a mean number of 6 injections, with the longest remission duration at the time of writing reaching 3 years. Preprotocol disease duration and anatomical staging were correlated positively with the number of injections required to achieve disease remission. Other independent variables such as clinical papilloma staging, preprotocol excision treatment frequency, and subject age at the time of protocol entrance were statistically nonsignificant variables regarding the number of treatments required for remission in this cohort.

Since this study in 2002, the senior author has continued to treat the original cohort of subjects with intralesional cidofovir injections. This treatment group has allowed for the long-term evaluation of cidofovir. During this study (2001-2006), 6 patients (46%) required no additional treatments. As such, the efficacy of cidofovir can be evaluated as long-term disease remission occurring in about half the patients.

Evaluating the course of the "relapse" group of 7 patients can help determine the clinical behavior of the disease to intralesional cidofovir treatments. Of the 7 patients, 3 achieved a second remission with the sole use of cidofovir injections. The mean number of injections per year to achieve this second remission (3.82) was higher than what these 3 patients were receiving on an as-needed basis prior to this study (1.77). However, the 3.82-injections-per-year mean resulted in disease remission, while 1.77-injections-per-year mean did not. In addition, the former procedures were solely cidofovir injections and the latter were not.

In addition to showing efficacy in terms of disease remission, cidofovir has been demonstrated to be effective in maintaining stable disease without surgical excision. Given the adversities (ie, recurrence and scarring) associated with excision therapies, cidofovir should be favored by many clinicians for the treatment of RRP.

Of final note, while under the care of the senior author, none of the 13 subjects developed clinical evidence of malignancy. This is an important observation, since many of the patients have been followed for 10 years (1997-2006). Possibly, the most criticized feature of cidofovir as a treatment for laryngeal papilloma is the black box warning that it carries: "Cidofovir should be considered to be a carcinogen in rats as well as a potential carcinogen in humans."[11(p834)] The argument exists that regardless of the route by which the drug is administered, all cells in the patient's body are exposed to levels of cidofovir comparable to those achieved in the animal studies.[12] Findings from animal studies demonstrated the induction of adenocarcinoma in laboratory rats. Despite the number of patients who have achieved remission through the use of cidofovir, only a single case of dysplasia has been reported in conjunction with the use of the agent in humans. This case, reported by Wemer et al[12] in 2005, describes the development of moderate and severe dysplasia within laryngeal papillomas, which were treated with intralesional cidofovir injections over a 27-month period.[12] However, no cases of adenocarcinoma have developed in patients receiving cidofovir treatment. The case report by Wemer et al[12] highlights the unclear potential of cidofovir to induce "cancerous or precancerous changes in humans affected with RRP"[11(p834)] and rightfully identifies the necessary inclusion of this potential in the process of informed consent.

In conclusion, the present study objectively confirms the safety and efficacy of intralesional cidofovir in the management of laryngeal papilloma. Intralesional cidofovir injections have been shown to be an effective therapy for adult laryngeal papilloma and should be considered in patients who experience disease relapse.

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