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Main Article

Is intralesional cidofovir worthwhile in juvenile recurrent respiratory papillomatosis?

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Abstract

Objective: To investigate the efficacy of intralesional cidofovir in the treatment of recurrent respiratory papillomatosis (RRP) in children.

Methods: Prospective observational study of four consecutive children with RRP treated at an academic tertiary children's hospital. Laryngo-bronchoscopy was performed at three- to five-weekly intervals. Photodocumentation was obtained and disease severity assessed using an anatomical RRP severity score. Surgical debulking of large papillomas was then performed, and cidofovir (5 mg/ml) injected into any remaining papillomas as well as submucosally at the sites of resected papillomas. The efficacy of cidofovir was assessed by the change in papilloma severity score over the course of the treatment.

Results: Complete disease remission was obtained in one patient, with a partial response seen in two others. One patient showed no significant response. The greatest beneficial effect was seen after the fourth cidofovir injection; however, two patients demonstrated a deterioration in severity scores after treatment was withheld at this point. Both responded well to further cidofovir injections. However, a clear plateau in the response to cidofovir was seen in all patients by the eighth injection.

Conclusion: Intralesional cidofovir may help control papilloma regrowth and reduce disease severity in many children with RRP. In most cases, cidofovir would appear to be less efficacious in causing disease eradication. There appears to be little evidence to support prolonged treatment regimes (i.e. more than eight treatments).

Key words: Larynx; Papilloma; Child; Human Papilloma Virus; Cidofovir

Introduction

Recurrent respiratory papillomatosis (RRP) is the most common benign tumour of the larynx in children.[1] It is caused by infection with human papilloma virus (HPV) subtypes 6 and 11.[2] Clinical symptoms, which include hoarseness and stridor, depend on the site and extent of the lesions. On rare occasions, death may occur due to airway obstruction or diffuse pulmonary papillomatosis.[3]

The traditional mainstay of RRP treatment has been surgical excision of the papillomatous lesions using CO_2 laser.[1,3] More recently, the efficacy of microdebrider excision of laryngeal and tracheal papillomata has been reported.[4] However, in children, early recurrence of papillomatosis is an expected outcome, necessitating the performance of repeat procedures, which may be associated with increased patient and parental anxiety and an increased risk of long-term morbidity.[1,3] One of the reasons suggested for this high recurrence rate is the presence of dormant HPV in neighbouring, apparently normal mucosal cells.[5]

The high recurrence rate of RRP in children has led to much interest in the development of adjuvant therapies which may alter the natural course of the disease, particularly in children with recalcitrant papillomatosis. To date, several different therapies have been tried, with variable results, including interferon-α2a,[6] photodynamic therapy,[7] retinoic acid,[8] and indole-3-carbinol.[9] In addition, significant adverse effects have been reported with some of these therapies. A recent study has reported the use of cidofovir (1-[(S)-3-hydroxy-2-(phosphononomethoxy)-propyl]cystosine), a cytosine nucleotide analogue with potent *in vitro* and *in vivo* activity against HPV, administered by local injection into papillomata in children with RRP.[1] The results of a small number of cohort studies of children with severe and/or recalcitrant RRP have shown mixed results for cidofovir.[10–15] The purpose of the present study was to investigate whether intralesional cidofovir was of any benefit as an adjuvant treatment in children with RRP.

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Methods

The present report comprised a prospective study of four consecutive children who presented to our institution with new cases of RRP. In all cases, the diagnosis of RRP was confirmed by histological examination of excised laryngeal papillomata. Informed consent for the use of cidofovir was obtained from the parents of all children.

Procedures were performed under general anaesthesia, with spontaneous ventilation. The site and extent of papillomas were first assessed using rigid telescopes (Karl Storz, Tuttlingen, Germany) under suspension laryngoscopy. Photodocumentation was obtained using the advanced image and data archiving (AIDA) compact system (Karl Storz). The severity of RRP was graded according to the anatomical staging system described by Derkay *et al.*[10] Surgical excision of large papillomata was then performed. At the time of the commencement of the study, this was achieved using the CO_2 laser at a setting of 5 W in repeat mode. However, during the study period, this equipment was replaced by a powered rotary laryngeal microdebrider at a setting of 300 rpm, used for the same purpose.

After removal of the large papillomata, injection with cidofovir (Pharmacia-Upjohn, Pfizer, Cork, Ireland) was performed using a Brunner syringe. The concentration of cidofovir used was 5 mg/ml. Submucosal injection was performed at sites from which papillomata had been surgically removed and at neighbouring sites, as well as directly into any remaining papillomata. The mean amount of cidofovir injected per procedure, not accounting for leakage into the airway, was 3.9 ml (range, 2–6 ml). Patients stayed in hospital the night following the procedure and were monitored for signs of airway compromise. They were generally scheduled to return for a repeat procedure three to five weeks later.

Statistical analysis of changes in the papilloma severity score, comparing the initial score (before first cidofovir injection) to the last score recorded, was performed using a matched-pair Wilcoxon signed rank testing, calculated using WinStat for Microsoft Excel (version 2001.1) software.

Results

Details of the patients are shown in Table I. All patients were female. Two had extensive papillomatosis causing airway obstruction prior to cidofovir treatment. A mean of 3.0 (range, 1–6) surgical procedures had been performed prior to the first cidofovir injection. None of the patients had previously received any other form of adjunctive medical therapy for RRP. During the study, patients underwent a mean of 10.5 (range, 8–18) cidofovir injections, over a mean period of 10.5 months (range, 7–16 months).

Anatomic papilloma grading scores for each patient throughout the duration of cidofovir treatment are shown in Figures 1 to 4. Complete disease remission was obtained in one patient (patient 1) after eight injections. This patient remained disease free over a follow-up period of 12 months. Two others (patients 2 and 3) demonstrated significant improvements in papilloma grading scores; however, low-grade disease persisted in both. One patient (patient 4) showed no significant response to cidofovir after a total of 18 injections.

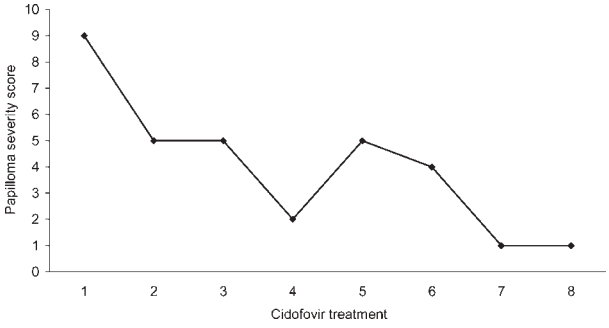

FIG. 1

Response of anatomic papilloma severity score to intralesional cidofovir in patient 1.

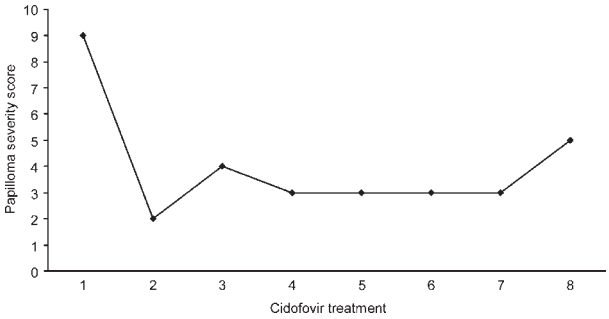

FIG. 2

Response of anatomic papilloma severity score to intralesional cidofovir in patient 2.

TABLE I

DETAILS OF PATIENTS, INTRALESIONAL CIDOFOVIR TREATMENT AND RESPONSE

Patient	Age at diagnosis (years)	Surgical procedures prior to 1st cidofovir injection (*n*)	Time between 1st diagnosis and 1st cidofovir treatment (months)	Papilloma score before 1st cidofovir injection	Cidofovir injections (*n*)	Duration of cidofovir treatment (months)	Most recent papilloma score
1	6	6	30	9	8	10	1
2	3	1	1	9	8	7	5
3	6	2	1.5	18	8	9	7
4	16	3	7	9	18	16	6

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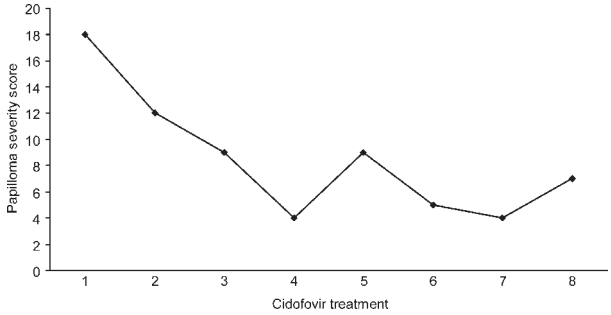

FIG. 3
Response of anatomic papilloma severity score to intralesional cidofovir in patient 3.

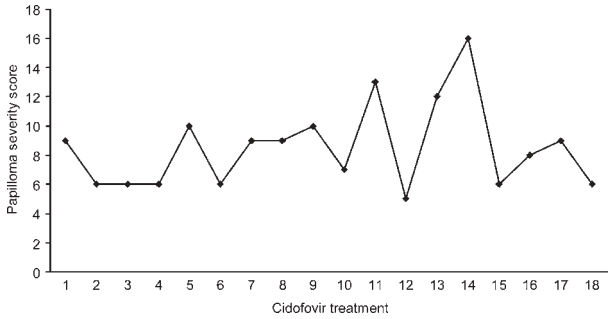

FIG. 4
Response of anatomic papilloma severity score to intralesional cidofovir in patient 4.

The final anatomic papilloma grading scores in every patient were less than those observed prior to first cidofovir injection; however, the small number of patients precluded achievement of statistical significance ($p = 0.07$).

In the three patients who responded to cidofovir, the greatest benefit appeared to occur after the fourth treatment. After this, a clear plateau in severity scores was seen. It is notable that patients 1 and 3 demonstrated a worsening of papilloma staging scores during the period of treatment. In both cases, this occurred after four cidofovir treatments had produced a good response, following which both patients were left for a ten-week interval before the next laryngoscopy. This suggests that, while the greatest part of the beneficial effects of cidofovir are obtained in the first four treatments, this number of treatments alone may not be adequate. Both patients subsequently had a good response to further cidofovir injections.

Discussion

The results of the present prospective study suggest that intralesional cidofovir may be of benefit in decreasing disease severity in children with RRP. In some cases, cidofovir may lead to disease remission. However, some patients may show no significant response to cidofovir, even after prolonged treatment, while, in others, cidofovir may fail to eradicate disease despite improvement in disease burden.

The main shortcoming of the present study was the lack of a control group. Thus, although impressive reductions in anatomic staging scores were seen in three of the four patients during the study period, it is not possible to define how much of this reduction was due to cidofovir as opposed to the surgical treatment administered. The lack of a control group is a problem which also applies to most other studies investigating the efficacy of cidofovir in RRP.[11–15]

The results of the present study would appear to be largely consistent with those of previous studies, which have also reported mixed results. Disease-free status was achieved in five of 10 children in the series of Pransky *et al.*[11] and in six of 11 children in the series of Akst *et al.*[12] Chhetri and Shapiro reported that four of five children with RRP achieved disease-free status in their study; however, this was maintained by only two patients.[13] Mandell *et al.* compared four children with RRP who received cidofovir with three children, treated by a different surgeon, who did not receive cidofovir; they found significantly lower papilloma grading scores among children in the cidofovir group.[16] Conversely, Shirley and Wiatrak reported that cidofovir was ineffective in six of 11 children with RRP and only partially effective in two others,[14] while Milczuk reported cidofovir to be effective in only one of four children with RRP.[15]

One of the more disappointing findings in the present study was the inability of cidofovir to eradicate disease after eight injections in two patients who had shown a good initial response. On the other hand, despite the presence of extensive papillomatosis causing airway obstruction prior to cidofovir treatment in two patients, no patient in the present series demonstrated rapid papilloma growth leading to airway compromise once cidofovir treatment had been commenced. Thus, while it would appear that the effectiveness of cidofovir in causing disease eradication in children is unsatisfactory, it may have some benefit in containing extensive papilloma regrowth and in preventing the development of airway obstruction. These effects may be related to the presumed mechanism of action of cidofovir. Cidofovir is a cytosine analogue that becomes incorporated into the genome of deoxyribonucleic acid (DNA) viruses. Programmed cell death occurs in epithelial cells infected by replicating papilloma viruses that incorporate cidofovir into the viral genome. However, this does not occur in cells infected with dormant DNA virus.[12,17,18] Our experience with cidofovir is echoed by Pransky *et al.*, who also believed that the greatest utility for cidofovir is its ability to rapidly control extensive papilloma growth, but that it could not be advocated as a potential 'cure'.[11]

The number of cidofovir injections that should be administered is controversial. Akst *et al.* reported complete resolution of disease in six of 11 children with RRP after four injections of cidofovir 5 mg/ml. The other five patients proceeded to undergo treatment with cidofovir at increased concentration (10 mg/ml); however, the results of this were mixed.[12] In Milczuk's series, two of four patients

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undergoing cidofovir injections at six- to eight-weekly intervals experienced a rebound in papilloma growth after the fourth injection, which did not respond to further injections.[15] These data would suggest that the major benefit of cidofovir is obtained within the first four injections. On the other hand, Pransky *et al*. reported that only one of five patients treated with four cidofovir injections achieved long-term control, while the mean number of injections in five patients who were rendered disease free was 9.8, suggesting that four treatments may not be adequate.[11] In the present study, the greatest beneficial effects of cidofovir were seen within the first four treatments. However, it is notable that two patients experienced a worsening of papilloma scores after being left for a prolonged interval after the fourth cidofovir treatment, but they subsequently responded well to further injections, with complete disease remission being obtained in one patient. This would suggest that four cidofovir treatments may not be adequate to obtain maximum disease control. On the other hand, a plateau in the effect of cidofovir on disease severity was clearly evident in all patients by the time they had received eight injections, suggesting that cidofovir is likely to confer little further benefit beyond this number of injections.

The scheduling of injections is another area of controversy. Chhetri and Shapiro recommended that injections be performed initially at two-week intervals.[13] Milczuk suggested that the poor results for cidofovir in his series may have been related to the relatively long interval (six to eight weeks) between treatments,[15] although Mandell *et al*. reported good results with two-monthly treatment schedules.[16] In the present study, treatments were scheduled at three- to four-week intervals. When treatments were delayed for five to six weeks, it was our impression that a greater than expected regrowth of papillomas occurred; however, examination of the data showed that this was a rather inconsistent phenomenon. It was notable, however, that when two of the patients were left for a prolonged interval (10 weeks), significant papilloma regrowth occurred.

In the present study, it was notable that intralesional cidofovir injection did not lead to stridor, respiratory distress or any other adverse effects. This is also consistent with the results for previous series.[11] Nevertheless, it continues to be our policy to monitor children overnight, so that any case of sudden airway obstruction can be swiftly dealt with. Another major concern which has previously been expressed regarding the use of cidofovir for RRP is its potential for carcinogenesis. To date, there has been no substantiation of such a risk, although there are few long-term data available.[14–17]

The use of intralesional cidofovir as first line adjunctive treatment in children with RRP continues to be an area of controversy. Our experience would suggest that a variable proportion of children are likely to experience a reduction in disease severity after a small number of injections, with a low risk of adverse effects. The main benefit of this may be the controlling of rapid papilloma regrowth causing airway obstruction. However, with further treatments, the initial response to cidofovir would appear to taper off, with persistence of low-grade disease commonly seen. Continued treatment with intralesional cidofovir at this stage necessitates consideration of the substantial expense (approximately €1000) of each treatment as well as the potential for long-term adverse effects with prolonged treatment. On the basis of our data, we would suggest that children with severe RRP be offered a course of four to eight treatments with intralesional cidofovir, administered at one-monthly intervals. However, regardless of the response, it would appear that there is little evidence to justify further treatments beyond this.

- **Cidofovir, a cytosine nucleotide analogue, has potent *in vitro* and *in vivo* activity against human papilloma virus**
- **This prospective study investigated the use of intralesional cidofovir in paediatric recurrent respiratory papillomatosis (RRP), in four children being followed by regular laryngo-bronchoscopy**
- **Complete remission of papillomatosis was seen in one patient, with a partial response in two others**
- **Although this study suffered from small numbers and the lack of a control group, there was some evidence that cidofovir may reduce the severity of RRP**

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Mr P Sheahan takes responsibility for the integrity of the content of the paper.
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