International Journal of Pediatric Otorhinolaryngology 73 (2009) 681–684

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Intralesional injection of cidofovir for recurrent respiratory papillomatosis in children

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ARTICLE INFO

Article history:
Received 21 September 2008
Received in revised form 28 December 2008
Accepted 2 January 2009
Available online 3 February 2009

Keywords:
Cidofovir
Recurrent Respiratory Papillomatosis
Children

SUMMARY

Introduction: Papillomatosis of the larynx appears as the result of an infection by the human papilloma virus (HPV). In children, the disease produces benign lesions, which grow rapidly and show a marked tendency to recur once removed. The course of the disease is unpredictable. Some patients can achieve spontaneous remission; however, in other cases the disease progresses violently and requires multiple operations. There is currently no effective therapy for recurrent respiratory papillomatosis (RRP). The basic goal of treatment is to preserve the patency of air passages while simultaneously preserving the phonatory and anatomical functioning of the larynx. Over the last 10 years, the possibility of a pharmacological treatment has been continually explored: in particular, the administration of locally passed cidofovir (first reported in a 1999 study by Pransky) to the larynx with papillomas is under current scrutiny.

Goal of study: The goal of the following study is to estimate the effectiveness of locally administered cidofovir for treatment of papillomas of the larynx in children.

Patients and methods: From 2005 to 2007, 10 patients (seven boys and three girls) between the ages of 1–18 years were treated. Operations were executed using microlaryngoscopy (Karl-Storz endoscopy) with general anesthesia. Cidofovir was passed intralesionally with concentration 5–10 mg/ml in quantity from 1 to 5 mg/kg in a 4-week interval.

Results: Seven of the 10 patients achieved total remission 6 months after the completion of treatment, scoring 0 points on Derkay's scale. These patients underwent therapy with cidofovir from 6 to 13 months. Three months after the completion of treatment, three children suffered a recurrence of papillomas. Two of them are estimated at 3 points on Derkay's scale, while the third is estimated at 5 points.

Conclusions: The results of the study indicate that intralesional injections of cidofovir can be an effective method of treatment for recurrent respiratory papillomatosis in children.

1. Introduction

Recurrent respiratory papillomatosis (RRP) appears as the result of an infection by the human papilloma virus (HPV). Children develop benign lesions, marked by frequent recurrence with large aggressiveness and susceptibility. The clinical course is unpredictable. Some patients come to spontaneous remission, particularly during the maturation period; however, in other cases the disease progresses violently and requires frequent surgical procedures.

In 1982, human papillomavirus type 6 was detected in papillomas of the larynx [1]. The virus has a circular shape, with a double chain of DNA. Actually, there are about 100 well-known subtypes of these viruses. In children, subtypes 6 and 11 appear most often. The disease appears in 70–80% of cases up until the fifth year of life [1,2]. The frequency of RRP occurrence in children is 1–4/100,000 [3]. Regression of the disease during puberty is often observed and, in children, very rarely leads to malignancy [1].

In adults, papillomavirus subtypes 6, 11, and 18 are most often observed [4]. It is confirmed at the rate of 1.8–3.9/100,000 persons [5]. Adults usually have solitary, slow-growing papillomas lesions. Papillomatosis of the larynx in adults can degenerate and become malignant [1,2,4].

As RRP is most often located in the larynx, the most typical symptom is hoarseness and, in more advanced cases, increasing inspiratory stridor and dyspnea [1,2]. Diagnosis of the disease involves subjective examination, flexible and rigid endoscopy of the air passages with realization of photographic records, histopathologic investigation, and PCR [2,4,7,8].

Currently there are many treatment modalities; none can be predictive of cure. The basic aim of treatment is patency of the air

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doi:10.1016/j.ijporl.2009.01.002

passages while preserving correct phonatory function and anatomy of the larynx [2]. Treatment procedures include classic microsurgery, laser (CO_2, argon, Nd-YAG), microdebrider, and fotodynamic therapy [1,2,6]. Numerous pharmacological treatments of RRP have also been attempted, including interferon, acyklovir, rybaviryne, izoprinosine, podophyllin, hormone, metotreksat and recently passed intralesional injections of cidofovir [1,2,6].

Cidofovir is a cytosine nucleotide analog, which inhibits cytomegalovirus DNA polymerase [9–11]. Cidofovir shows potential antiviral activity against a broad spectrum of herpes viruses, including the Epstein–Barr virus, cytomegalovirus, herpes simplex types 1 and 2, and varicella zoster, as well as HPV and adenovirus. Cidofovir is currently approved by The Food and Drug Administration to treat cytomegalovirus retinitis in patients with HIV [6,7,8]. The first reported use of cidofovir for adult's laryngeal papillomatosis was published by Van Custem in 1995 and Snoeck [11], and in children by Pransky [9,10].

2. Goal of study

The goal of the following study is to estimate the effectiveness of the local use of cidofovir for recurrent respiratory papillomatosis in children.

3. Patients and methods

Between February 2005 and June 2007, 10 patients with RRP underwent treatment (seven boys and three girls, ages from 1 to 18 years, with an average age of 10.6). Before treatment, each patient's parents or legal guardians were informed of the potential side effects of cidofovir and were required to sign a waiver agreement acknowledging said information before the start of treatment.

Papillomatosis severity scores were estimated according to the Derkay scale [12]. This instrument grades each affected sub-site using a 4-point scale: 0 – indicating none, 1 – minimal, 2 – moderate, and 3 – severe (Fig. 1). Each sub-site is scored separately. All sub-site scores are added and a cumulative score is obtained for each patient under treatment.

The clinical course of the disease and the results of treatment were estimated using the following scale: 0 points – total retreat of the disease; 1–5 points – moderate improvement; 6–15 points – medium exacerbation of disease; and above 15 points – severe progression of the disease [12]. A complete blood chemistry profile, including blood cell count, was obtained for all patients before the start of treatment as well as in a 1-month interval before every injection of cidofovir.

larynx					
	epiglottis	lingual		laryngeal	
	Aryepiglottic Folds	right		left	
	False Vocal Cords	right		left	
	True Vocal Cords	right		left	
	Anterior commissure				
	Posterior commissure				
trachea					
	upper	anterior		posterior	
	middle	anterior		posterior	
	lower	Anterior		posterior	
	bronchi	right		left	
	tracheostoma				
other					
	nose			palate	
	pharynx			esophagus	
	lungs				
total	For each site score as: 0= none, 1=surface lesion, 2= raised lesion, 3= bulky lesion				

Fig. 1. Papillomatosis staging sheet [12].

Surgical procedures were executed using microlaryngoscopy (Karl-Storz endoscopy), with general anesthesia by spontaneous ventilation. In cases with severe dyspnea, intubation was applied during the operation using the smallest possible intubation tube. Papillomas were removed by microsurgical methods. In all cases, histopathological examinations of the removed papillomas were made. Cidofovir was injected intralesional to the areas infested with the papillomas and also in surrounding mucosa, using a laryngeal needle (Karl-Storz endoscopy). During endoscopic operations all patients were documented with photographic records. All patients were then hospitalized for 24 h post operation. During this time patients were observed for any difficulties in breathing. Cidofovir was passed submucosal at a concentration of 5–10 mg/ml in dose 1–5 mg/kg, every 4 weeks.

Concentration of the drug was increased above 5 mg/ml in children with very advanced clinical courses (above 15 points by Derkay's scale), as well as in cases where there is no significant improvement after three injections. The volume of medicine passed submucosal to the vocal folds should not be larger than 0.5 ml. Treatment of cidofovir continued until two consecutive endoscopies showed no macroscopic papillomas. All patients received follow-up endoscopic examinations in conditions of operates theatre, using rigid endoscopes 0° (Karl-Storz endoscopy) with general anesthesia or in older children using flexible nasofiberoscope with local anesthesia.

At the conclusion of therapy each patient was given a follow-up examination once a month. For all patients, it was necessary to apply anti-gastroesophageal reflux drugs during the cidofovir therapy.

4. Results

Ten patients (seven boys and three girls, ages from 1 to 18 years, with an average age of 10.6) received intralesional cidofovir along with surgical excision between February 2005 and June 2007. Papillomatosis was diagnosed at a mean age of 6.0 years (range 1–16 years). Children with papillomatosis before cidofovir therapy were treated at a mean age of 4.65 years (range 0–11 years). Seven patients (patient nos. 1, 2, 3, 5, 6, 9, and 10) had been previously treated by surgical excision from 2 to 21 times (average 6.8 the times, see Table 1). Within this group, five patients (1, 2, 5, 6, and 10) had CO_2 laser therapy from 1 to 5 times (mean 1.6, see Table 1). One patient (no. 10) at the age of 6 had been treated by interferon for 3 month. In three patients (nos. 4, 7, and 8) cidofovir was applied despite the fact they had not received any other method of therapy previously: this decision was made due to the severe clinical course of the disease in their cases, from 12 to 17 points on Derkay's scale (see Table 2).

In six patients (nos. 1, 2, 3, 4, 5, and 8) papillomas were affirmed in supraglottis and glottis, in one patient (no. 7) in subglottis and glottis, and in three patients (nos. 6, 9, and 10) lesions were present in three sub-sites of the larynx. Patient no. 4 also had papillomas in the hypopharynx (see Table 1).

Six patients (nos. 2, 5, 6, 7, 9, and 10) showed severity scores from 16 to 29 points, and four patients (no. 1, 3, 4, and 8) had 9–15 points (see Table 2).

Two patients (nos. 6 and 9) had tracheostomy by reason of severe airway obstruction. Two patients (nos. 2 and 8) before treatment of cidofovir had total aphonia. Patient no. 7, in spite of having been recognized with papillomatosis of the larynx at age 6 years, for 3 years had been not treated (see Table 1).

Patients received from 6 to 14 doses of cidofovir (average 8.8 doses); three patients received two injections after the appearance of complete remission.