Review

Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir

Papillomatosi respiratoria ricorrente da HPV: revisione della letteratura e aggiornamento sull'uso del cidofovir

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SUMMARY

Recurrent respiratory papillomatosis is a viral induced disease characterised by exophytic epithelial lesions affecting the larynx. The problem with its treatment is the high recurrence of papilloma growth after surgical removal. The aim of our review is to analyse the actual use of cidofovir, an agent used in adjuvant therapy. We have reviewed 6 manuscripts that included a total of 118 patients. The parameters taken into account were: concentration of infiltrated cidofovir (mg/ml), therapeutic response, relapse-free time (months), side effects, genotypes (HPV-6/11/18) and evolution of dysplasia. Cidofovir was injected at concentrations from 2.5 to 15 mg/ml, therapeutic response was from 56.25% to 82.3% and relapse-free time was from 10.05 to 49 months. There were 2 cases of dysplasia during therapy. Ten patients had been infected by HPV-6, 4 patients by HPV-11 and 10 patients by HPV-6 and HPV-11. The purposes of our review include the following: to stress that the juvenile form is more aggressive than other forms, to demonstrate than the drug has good adjuvant action although it does not significantly change the final response to the disease, to show that side effects are modest and, finally, to disprove the hypothesis that cidofovir may promote evolution towards dysplasia. In conclusion, combination of surgical removal and injection of cidofovir is associated with good response in recurrent respiratory papillomatosis.

KEY WORDS: Cidofovir • Recurrent respiratory papillomatosis • Larynx

RIASSUNTO

La papillomatosi respiratoria ricorrente è una malattia di origine virale caratterizzata da lesione esofitiche della laringe. Il problema del trattamento è l'alta frequenza con cui si riforma la lesione dopo l'asportazione chirurgica. Lo scopo della nostra review è valutare l'efficacia del cidofovir attualmente utilizzato come terapia adiuvante. Abbiamo analizzato 6 manoscritti, per un totale 118 pazienti. Sono stati considerati i seguenti parametri di valutazione: concentrazione cidofovir infiltrato (mg/ml); risposta terapeutica; tempo libero da ricadute (mesi); effetti indesiderati; genotipo (HPV-16,-18/HPV-6,-11) e evoluzione displasia. L'infiltrazione del cidofovir è variata da 2,5 mg/ml a 15 mg/ml, con una risposta terapeutica tra il 56,25% e l'82,3% e un tempo libero da ricadute dai 10,05 ai 49 mesi. In corso di terapia si sono avuti due casi di displasia. 10 pazienti erano stati infettati da HPV-6, 4 da HPV-11, 10 da entrambi i genotipi HPV-6 e 11. Dai nostri dati è emersa la conferma che la forma giovanile è maggiormente aggressiva, il farmaco ha una buona azione adiuvante ma non incide in modo significativo sulla risposta finale alla malattia, modesti sono gli effetti collaterali ed infine si smentisce l'ipotesi che il cidofovir possa favorire l'evoluzione verso la displasia. In conclusione la combinazione dell'ablazione chirurgica e cidofovir ha una buona azione adiuvante nella papillomatosi respiratoria ricorrente.

PAROLE CHIAVE: *Cidofovir • Papillomatosi respiratoria ricorrente • Laringe*

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Introduction

Recurrent respiratory papillomatosis (RRP) is primarily caused by human papilloma virus (HPV). It is a benign and rare disease of the larynx, but rarely involves an extra laryngeal extension especially in childhood forms, with tracheal and bronchial involvement that is life-threatening [1 2]. Treatment includes surgical removal of the epithelial lesion in order to maintain airway patency and phonation. Occasionally, surgical therapy is not sufficient and specific antiviral medical therapy is ineffective. One of the most important types of adjuvant therapy is the injection of intralesional cidofovir (Vistide) [3]. Herein, we review published studies that enrolled patients with RRP. All patients were treated by surgically removing laryngeal papillomas in combination with laryngeal injections of cidofovir.

Aetiology, epidemiology, clinical presentation and pathophysiology

Aetiology

HPV is a small non-enveloped virus, approximately 55 nm in diameter that belongs to the papillomaviridae family and has 72 capsomers. Its DNA genome is a double-stranded circular structure and encodes 8-10 genes. The mechanism involved infection of the host cell is unclear. Analysis of HPV has revealed more than 180 different genotypes. In the larynx affected by mucosal HPV, viral types are classified as low risk (HPV-6, HPV-11 responsible for approximately 90% of patients with RRP) [4] and high risk (HPV-16, HPV-18) in reference to the potential malignant transformation that occurs in less than 1% of cases [5 6].

The virus initially infects the basal layer of epithelia through minor abrasions. In the upper layers of squamous epithelia virions are produced, which are freed through normal desquamation processes, causing inflammation. E6 and E7 proteins, expressed by the virus, inactivate interferon regulatory factor allowing HPV infection to remain persistent and asymptomatic. Viral genomes can replicate in an episomal or integrated manner. When viral genomes replicate episomally, they show relatively low levels of E6 and E7 gene expression, and, in most cases, resolve spontaneously by an effective immune response. However, when viral DNA is introduced into the host genome, in most cases, it often displays a strong expression of E6 and E7 genes. In these cases, carcinogenic transformation progresses rapidly. The E7 protein promotes cell division by binding pRb, while virus protein E6 binds and inhibits p53 protein which is active in repressing the cell cycle in case of DNA damage. E6 protein also activates cellular telomerase that synthesise telomere repeat sequences. HPV types 6 and 11 replicate episomally, and as such are not usually carcinogenic.

Epidemiology

HPV tends to induce widespread latent infection due to the interference with host immune function. The anogenital site is the primary reservoir of HPV. It is widely accepted that HPV may be transmitted from the mother's anogenital site to the infant's respiratory tract during and even before delivery through infected placenta and amniotic fluid, resulting in juvenile-onset RRP after months or years, while in adults it may be transmitted through oral-genital sexual contact. Approximately 0.7% of infants, with maternal anogenital warts during pregnancy, have a 231-fold higher risk of illness than others. These facts suggest maternal anogenital warts during pregnancy may be a primary risk factor for the juvenile-onset of RRP. In adults, RRP may be caused by high risk factors such as sexual activity and/or oral sex with multiple partners. Additionally, extra-oesophageal acid reflux disease is a high risk factor for RRP. Iatrogenic transmission also deserves attention since HPV can survive on cryoprobe, in liquid nitrogen and in the plume generated by laser ablation or electrocautery [7].

Rabah et al. found that HPV-11 infection confers a more aggressive course to RRP than HPV-6. HPV-11 is more common among the Afro-American patients than among Caucasians. Patients with HPV-11 are diagnosed at a younger age (36.2 *vs.* 48.2 months) and are more likely to have active disease. They tend to have longer periods of disease activity (8 years *vs.* 5 years), require more surgical procedures (42 procedures/patient *vs.* 13.6), and more procedures per patient per year (2.9 *vs.* 5.3). Three patients infected with HPV-11 developed invasive papillomatosis and bronchogenic squamous cell carcinoma, and 2 of these died of disease [8]. The most reliable data regarding the Norwegian population where the incidence is 0.17 per 100,000 individuals in young people with an average age of 4 years, and 0.54 per 100,000 person-years in adults with an average age of 34 years; disease is more frequent in men.

RRP may arise anywhere in the respiratory tract with a preference for the so-called transformation area where squamous epithelia and ciliated columnar epithelia meet. The incidence of lower respiratory tract or pulmonary infection is low. High risk factors for spread of RRP towards the lower respiratory tract include HPV-11 infection, age below 3 years and tracheotomy preformed to avoid airway obstruction [9].

RRP arising in the trachea without laryngeal involvement has been reported in only a few cases [10].

Under some conditions such as smoking, irradiation, cytotoxic drugs, p53 mutation, HPV-11 infection, high severity score or high activity of 2'-5'-oligoadenylate synthetase, RRP lesions may undergo malignant transformation [11 12].

Clinical presentation and pathophysiology

Common clinical RRP symptoms include hoarseness, cough, wheezing, voice change, chronic dyspnoea, choking, syncope, etc. Stridor or respiratory harshness is possibly audible on chest auscultation. Chest x-rays are usually unremarkable. Due to its non specific clinical manifestations, RRP is easily mistaken for asthma, acute laryngitis, upper respiratory infection, or bronchitis. However, asthma therapies and anti-infective treatments are inefficacious.

Endoscopy, which is the most reliable method used to reach definite diagnosis, should be performed as soon as possible in patients with persistence of symptoms in order to favour early and correct diagnosis. Multiple cauliflower-like neoplasms with smooth and neat surface and without necrosis can be observed on endoscopy.

Detection of HPV DNA by PCR with consensus primers and subsequent restriction mapping or hybridisation methods using probes for each HPV type are available for specific HPV genotyping [7].

What is the aim of treatment?

Treatment involves surgical removal of the epithelial lesion in order to maintain airway patency and phonation. In many cases, the patient must undergo several surgeries, and sometimes surgical therapy is not sufficient; specific antiviral medical therapy may also be ineffective. The papillomatous lesion never exceeds the basal membrane, involvement of underlying tissues is considered iatrogenic damage, often inevitable, and therefore surgical techniques have evolved to reduce damage to healthy tissue.

Surgical techniques

According to many authors, CO_2 laser is convenient and precise, and represents one of the best options in the management of RRP. Lasers offer surgeons the advantage of unobstructed vision of the surgical field with minimal tissue manipulation and a longer working distance. Decreased risk of postoperative bleeding, increased sterility, minimal surrounding tissue damage, better intraoperative haemostasis, fewer surgeries and complications such as tracheostomy are among the potential benefits of laser surgery (Table I) [13-16]. However, microdebriders with cold instruments are still in use.

Lasers are useful in surgical procedures due to their production of high energy. Laser-tissue interaction is characterised by the conversion of laser energy absorbed by the cells into heat energy. This heat energy can cut, vaporise or coagulate the affected tissue.

Laser energy is delivered to tissue and can be reflected, transmitted, scattered or absorbed. If the light is reflected by or transmitted through the tissue, no heating occurs, while if the light is scattered, it will increase the amount of tissue over which the laser energy is distributed, thus increasing thermal damage to surrounding tissues. The efficiency by which the energy is transferred to the tissue depends on the wavelength of the laser. Lasers that have less depth penetration and cause less damage to surrounding tissues are, in order, erbium:Yag, CO_2 and holmium:Yag, and in these lasers the energy is absorbed largely by water. For flat lesions such leukoplakia, papillomas, or verrucous carcinoma, these lasers are preferred due to their precision. In fact, damage to the submucosa and fibromuscular regions in the larynx is life-threatening for the patient since scarring causes dysphonia and decreases airway patency.

Continuous laser is preferred due to its coagulative and haemostatic properties. Despite the notable benefits, laser surgery does have some disadvantages. Laser heat can increase scarring and cause damage to adjacent tissue. Laser treatment may also cause endotracheal explosion, mucosal burns, vocal fold webs, stenosis, and glottic incompetence [17].

Recent improvements of the CO_2 laser have increased its applicability and efficacy. Remacle et al. tested the reliability and efficacy of the new AcuPulse 40WG CO_2 laser with the FiberLase Xexible waveguide (CO_2 LWG) on patients treated with transoral laser surgery (TLS) [18]. Two patients with laryngeal papillomatosis were tested with this new device.

Burns et al. presented good results with regression of papillomatosis using a 532 nm pulsed potassium-titanyl-phosphate laser (KTP) with short-term follow-up [19]. Although anterior-commissure disease was present in 93% cases, no new webbing/synechia occurred. All patients reported that their vocal function improved after treatment.

According to Carney et al. radiofrequency coblation appears to be an attractive alternative to CO_2 laser in surgical treatment of laryngotracheal papillomatosis [20]. In that study, 6 patients were treated by CO_2 laser vaporisation with or without intralesional cidofovir for at least 2 years. All 6 patients subsequently underwent treatment with radiofrequency coblation with or without intralesional cidofovir. Coblation resulted in longer periods between surgical interventions compared to CO_2 laser.

Treatment with adjuvant drugs

The most used adjuvant drugs are interferon, various virostatics (acyclovir, valacyclovir and cidofovir), indole-3-carbinol [21], and unsedated office-based photoangiolytic laser surgery (UOLS) [22].

cidofovir is an antiviral agent indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Since 1998, cidofovir has been used to treat patients with

Table I. Surgical complications.

Authors	Patients	Complications
Preuss SF et al. [16]	194	9% of patients after laser surgery and 5% after conventional surgery required tracheotomy. 6% of patients after laser surgery and 20% after conventional surgery had postoperative glottic webs and scar formations
Dikkers FG et al. [14]	9	None of the patients had local complications.
Wierzbicka M et al. [13]	32	None of the patients had local complications.
Pudszuhn A et al. [15]	10	1 patient required tracheotomy + temporary PEG.

RRP [3]. Its mechanism of action involves decreasing the efficiency of DNA transcription following incorporation into the growing DNA chain [23].
This review evaluates the therapeutic efficacy of cidofovir in the adjuvant treatment of laryngeal papillomatosis.

Materials and methods

We have selected articles written in English from 1998 up to now on the use of cidofovir as adjuvant therapy in laryngeal papillomatosis treated with CO_2 laser or cold instruments. All articles were found on PubMed by searching with the keywords "recurrent respiratory papillomatosis" and "cidofovir laryngeal papillomatosis". Some data were derived from studies published by members of the panel of the Committee of European Laryngological Society (ELS) dedicated to "Recurrent Respiratory Papillomatosis". We reviewed 6 manuscripts that enrolled a total of 82 patients with "adult onset recurrent respiratory papillomatosis" (AORRP) and 36 patients under 12 years of age with "juvenile onset recurrent respiratory papillomatosis" (JORRP). We excluded manuscript by Chhetri et al. due to the small number of cases enrolled. Our review evaluated the following evaluation parameters: concentration of infiltrated cidofovir (mg/ml); therapeutic response (CR: complete response, PR: partial response, NR: no response); relapse-free time (months); side effects, most common genotype (HPV-6/11/18) and progression to dysplasia. (Table II).

Results

Infiltrated cidofovir concentrations ranged from 2.5 mg/ml to 7.5 mg/ml. As an exception, Friedrich et al. used 15 mg/ml [24]. The best results were reported by Snoeck et al. (82.3%), and worst by Wierzbicka et al. (56.25%). JORRP had worse prognosis (RC mean = 53.8%) than AORRP (RC mean = 72.6%). The best relapse-free times were obtained by Friedrich et al. (mean = 49 months), while the worst by Wierzbicka et al. (mean = 10.05 months). Among the 6 manuscripts examined, Snoeck et al. were the only authors who did not present data on the possible evolution of laryngeal lesions to dysplasia. Only 2/101 patients developed dysplasia during therapy: 1 developed severe dysplasia/carcinoma in situ after 5 treatments (Neumann et al.) and 1 after 6 treatments (Dikkers G). Observation continued for 3-96 months (mean 26.1). Only 4 authors reported, often in an incomplete manner, HPV genotype for a total of 25 patients (21.1%): 10 were infected by HPV-6 (Froehlich P, Neumann K, Dikkers G, Snoeck R); 4 were infected by HPV-11 (Froehlich P, Neumann K); and 10 by genotypes HPV-6 and 11 (Dikkers G, Snoeck R). No authors reported any side effects. Correlation between cidofovir concentrations and relapse-free times are shown in Fig. 1, and there was no correlation between cidofovir concentrations and CR (Fig. 2; Table II).

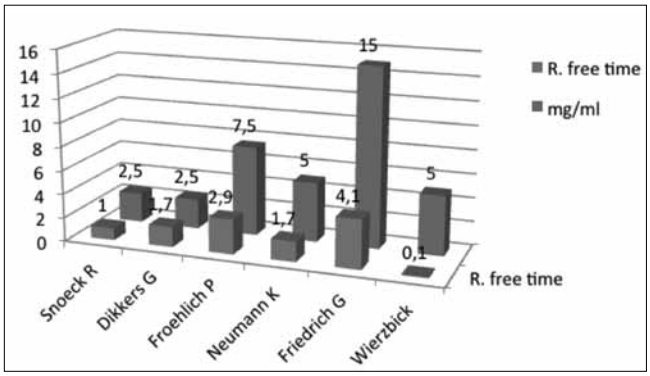

Fig. 1. Correlation between relapse-free time and dose of cidofovir.

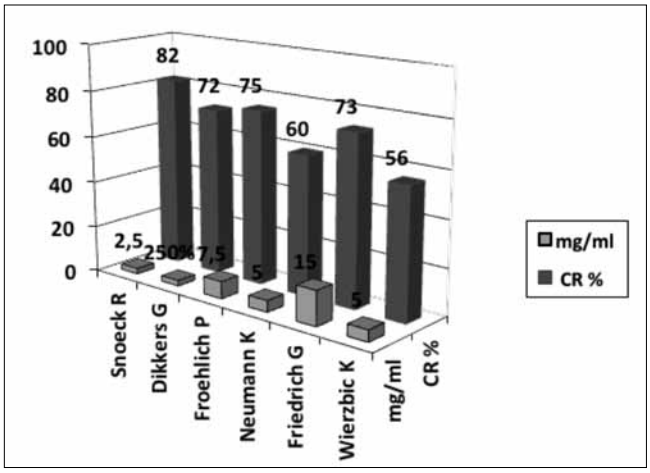

Fig. 2. Correlation between dose of cidofovir and complete response.

Technical and clinical success of treatment options

The study highlighted the good correlation between infiltrated dose and relapse-free times, so although the optimal drug concentration remains unclear, it seems that higher doses are in fact better [13-15 24 26 27]. There is no correlation between infiltrated doses and CR, cidofovir does not significantly change the final disease response. This supports the mechanism of action of the drug which reduces, without stopping, the efficiency of DNA transcription following incorporation into the growing DNA chain [23]. In addition, it seems that JORRP is more aggressive than AORRP, confirming literature data [13 15 24 28].
The use of cidofovir in the treatment of CMV retinitis limits of safety the intralesional injection to 3 mg/kg [29], and higher doses during RRP are off label. In 2011, concerning news was announced by Gilead, the manufacturer of cidofovir, regarding off label use. The warning included reports on cases of nephrotoxicity, neutropenia, oncogenesis and even deaths. However, a recent retrospective international study of 635 RRP patients, including 275 treated with cidofovir from 16 hospitals in 11 countries worldwide showed no statistically significant differences in the incidence of neutropenia or renal dys-

Table II. Use of cidofovir in published reports.

Author	AORRP/ JORRP	Cidofovir concentration	Response	Relapse-free time (months)	Side effects	Genotype HPV	Dysplasia
Wierzbicka M et al. [13]	26 AORRP 6 JORRP Total = 32	5 mg/ml	CR = 56.25% (18 = 2 JORRP + 16 AORRP); PR = 40.6% (13 = 3 JORRP + 10 AORRP); NR = 3,12% (1 JORRP)	10.05 (3-21)	3 patients. 1/3 had weakness and diarrhoea for about 4 days. 2/3 had ALT and AST levels increased.	Not specified	None
Friedrich G. et al. [24] (2013)	26 AORRP 8 JORRP Total = 34	From 7.5 mg/ml to 15 mg/ml during the study (single dose)	CR = 73.5% (25 = 5 JORRP + 18 AORRP); CR after laser = 5.8% (2 JORRP); PR = 17.6% (6 AORRP + 1 JORRP) (2.9%)	49 (12-96)	None	Not specified	None
Froehlich P. et al. [26] (2006)	16 JORRP	From 5 mg/ml to 7.5 mg/ml	CR = 75% (12 JORRP); PR = 25% (4 JORRP)	33.6 (12-76)	None	8 HPV 6; 3 HPV 11; 5 not specified	None
Neumann K. et al. [15] (2007)	7 AORRP 3 JORRP Total = 10	5 mg/ml	CR = 60% (6 = 5 AORRP + 1 JORRP); PR = 20% (2 JORRP); 2 AORRP stopped therapy (one developed dysplasia and another had accidental trauma)	19 (8-30)	None	1 HPV 11; 1 HPV 51; 1 HPV 6; 7 not specified	1 Severe dysplasia / carcinoma in situ. follow-up = 19 months
Dikkers G. [14]	9 AORRP	2.5 mg/ml	CR = 77.7% (7 AORRP); PR = 22.3% (2 AORRP)	19 (6-36)	None	1 HPV 6, 8 HPV 6 and 11	1 dysplasia
Snoeck R. et al. [25] (1998)	14 AORRP 3 JORRP Total = 17	2.5 mg/ml	CR = 82,3% (14 = 2 JORRP + 12 AORRP); PR = 11,7% (2 = 1 JORRP + 1 AORRP); 1 AORRP lost in follow-up	12 (2-27)	None	2 HPV 6 and 11; 15 not specified	Not specified

AORRP: adult onset recurrent respiratory papillomatosis; JORRP: juvenile onset recurrent respiratory papillomatosis; CR: complete response; PR: partial response; NR: No response.

function after administration of cidofovir, and no significant difference in the incidence of upper airway and tracheal malignancies between cidofovir and non-cidofovir groups [30]. Four of the 6 studies evaluated exceeded the recommended limit and in 118 cases there were no side effects except for a few patients who had mild changes in laboratory parameters (neutropenia, Gilbert's syndrome, an increase in AST and ALT). The therapeutic results and side effects excessive doses of cidofovir in patients with RRP and HPV is one of the most discussed topics in the European Laryngological Society (ELS) and has prompted a multicentre retrospective study to provide reliable data on the safety and efficacy of cidofovir in RRP [3]. Preliminary results, presented at the 9th Congress of the ELS, confirm our observation of the low incidence of side effects. Only 25/118 patients enrolled underwent genotypic analysis, so that this information is just an indication. Twenty-four of the 25 patients who underwent genotypic analyses had been infected by HPV-6, HPV-11, or both; HPV-6 and HPV-11 are classified as low risk for neoplastic transformation, which coincides with the only 2 cases of dysplasia reported. Several studies have reported that HPV-11 and HPV-6 can promote bronchogenic and laryngeal squamous cell carcinoma [31-35]. The aim of our review is to confirm the low probability (2.02%) that RRP lesions treated with cidofovir infiltration evolve towards dysplastic lesions. We thus confirm that use of cidofovir does not seem to induce dysplastic changes in HPV-infected laryngeal epithelium. Broekema et al. reported only 5/188 cases (2.7%) that evolved into dysplastic lesions [36]. Hoffman performed biopsies before and after cidofovir injections and dysplastic changes in HPV-infected laryngeal epithelium did not appear to develop. Sajan et al. affirmed that JORRP is rarely associated with laryngeal epithelial dysplasia [37]. Hall et al. affirmed the natural progression of dysplasia into RRP if patients are not treated with adjuvant therapy. In that study, 27/54 adult patients (50%) had dysplasia, and 9 cases (16.7%) developed a higher dysplastic grade during treatment. One of 54 patients (2%) developed squamous cell carcinoma [38]. This review shows that cidofovir does not seem to induce dysplastic changes in HPV-infected laryngeal epithelium, and its use has shown promising results in treatment of RRP. Nevertheless, there is still insufficient information regarding the natural progression of dysplasia in RRP [39].

Conclusions

Treatment involving surgical removal, especially with digital scanning CO_2 and cidofovir, has a good adjuvant action in RRP. The drug shows a high efficiency by increasing the relapse-free time and decreasing the number of surgeries required. Cidofovir has no side effects even after high cumulative doses. However, further research is necessary to define the most adequate doses, frequency of administration and duration of therapy.

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