Recurrent respiratory papillomatosis
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Safety of intralesional cidofovir in patients with recurrent respiratory papillomatosis: an international retrospective study on 635 RRP patients

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Abstract

Objectives: Intralesional use of cidofovir (Vistide®) has been one of the mainstays of adjuvant therapy in patients with recurrent respiratory papillomatosis (RRP) since 1998. In 2011, a communication provided by the producer of cidofovir addressed very serious side effects concerning its off-label use. As this was a general warning, it was inconclusive whether this would account for its use in RRP. The aim of this study is to determine whether nephrotoxic, neutropenic, or oncogenic side effects have occurred after intralesional use of cidofovir in patients with RRP.

Methods: Update of recent developments in RRP, a multicentre questionnaire and a multicentre retrospective chart review.

Results: Sixteen hospitals from eleven countries worldwide submitted records of 635 RRP patients, of whom 275 were treated with cidofovir. RRP patients received a median of 3 intralesional injections [interquartile range 2-6]. There were no statistical differences in occurrence of neutropenia or renal dysfunction before and after cidofovir. There was no statistical difference in occurrence of upper airway and tracheal malignancies between the cidofovir and the non cidofovir group.

Conclusions: In this retrospective patient chart review, no clinical evidence was found for more long-term nephrotoxicity, neutropenia or laryngeal malignancies after the administration of intralesional cidofovir in RRP patients.
Introduction

Recurrent respiratory papillomatosis (RRP) is a rare, sometimes debilitating disease compromising voice and airway. It is characterized by a variable course of disease, potentially leading to frequent surgical procedures, the number of which may exceed a hundred during a lifetime.

Epidemiology
The disease has been reported in people aged 1 day through 84 years (1). The first peak incidence occurs at an age before 5 and the second between 20-40 years of age (2,3). The incidence of juvenile onset recurrent papillomatosis (JoRRP) is approximately 0.17-4.3 per 100.000 and approximately 0.54-3.94 per 100.000 in adult onset recurrent respiratory papillomatosis (AoRRP). The disease is predominantly seen in male (1,3-5). Most JoRRP patients are firstborns, and have young prima gravida mothers (6,7). A child has 200 fold increased risk of acquiring RRP if the mother has condylomata acuminata (6).

Etiology
RRP is caused by the low risk human papilloma virus (HPV) types 6 and 11, where HPV 11 is associated with a more aggressive course (8). However, other types of HPV are associated with RRP as well (9). The clinical recurrence is due to the activation of latent HPV DNA infection in normal appearing mucosa (10,11). There is no consensus in the literature on HPV typing and the malignant transformation of RRP. In general, the most frequently reported risk factors for head and neck squamous cell carcinomas are alcohol and smoking. A substantial portion of oropharyngeal cancers are associated with oncogenic HPV types 16 and 18 (12).

Histology
The characteristic clinical appearance of papillomata is that of multinodular growth, each with a core of vascular connective tissue covered by stratified squamous cell epithelium (13). A papilloma is histopathologically typified by basal cell hyperplasia, increased mitoses in the basal layers of the epithelium, koilocytotic changes, nucleomegaly, and dyskeratotic cells (14). The reported incidence of malignant transformation ranges from 1.6% to 4% (15,16).
Clinic
Dysphonia is the most common presenting symptom of RRP for patients of all ages. Stridor and obstruction are less common, and are almost exclusively seen in childhood. Therapy focuses on repeated surgical removal of the mucosal lesions in order to keep the airway open and the voice satisfactory (17). Up till now, no curative therapy exists for the virus infection itself. As repeat surgery alone is insufficient in many cases, adjuvant therapy is increasingly used e.g. interferon, bevacizumab (Avastin®), human papillomavirus quadrivalent (Types 6, 11, 16, and 18) vaccine (Gardasil®). One of the most commonly used adjuvant therapies is the administration of intralesional cidofovir (Vistide®).

Cidofovir
Cidofovir is an antiviral agent, registered for intravenous treatment of cytomegalovirus (CMV) retinitis in patients with human immunodeficiency virus (HIV), and is approved by the US Food and Drug Administration. Since 1998 the drug has also been one of the mainstays in the treatment of RRP (18).

Cidofovir \(\{(S)-1-[3\text{-}\text{hydroxy}\text{-}2\text{-}(\text{phosphonomethoxy})\text{ propyl}\text{]}\text{ cytosine dehydrate, HPMPC}\}\) is a deoxynucleoside triphosphate analogue of cytosine and can be regarded as a prodrug, since it has inactive compounds that require metabolic activation by cellular enzymes (19). The active diphosphorylated form exerts the antiviral effect by decreasing the efficiency of DNA transcription following incorporation into the growing DNA chain (19). Cidofovir is a broad spectrum antiviral medicine against papilloma-, herpes-, and poxviruses (19) and is contraindicated in patients with renal impairment. Maximum plasma concentrations after intralesional cidofovir were 62 % of the levels after intravenous administration (20).

Some reviews conclude that intralesional use of cidofovir is a safe treatment in patients with RRP lesions (21,22). Animal studies have shown contradictory results on cidofovir and suggest that it causes nephrotoxic or carcinogenic side effects (22). An in vitro study by Donne et al. shows that cidofovir can increase cell survival and induce alterations in gene expression that are associated with malignant transformation in cells (23). The use of cidofovir has been advocated in cases of papilloma refractory to repeated surgery, either due to its spread, or to its recurrence rate. Some case series showed good effect of cidofovir treatment, with few or no side effects (24-29).
On January 31st, 2011, alarming news by the producer of cidofovir addressed very serious side effects associated with its off-label use (30). The indications for use of cidofovir in these cases were not revealed. The warning included reports on nephrotoxicity, neutropenia, oncogenicity and even some fatalities. Compared to its use in laryngology, in other medical specialties (e.g. internal medicine or ophthalmology) the dosage of cidofovir is much higher (5 mg/kg once a week), or has another route of administration (intravenously or intraocular). The manufacturer did not specify the severity of the reported complications, the off-label indication of the drug, or its way of administration or concentration dosage. This warning has made many otorhinolaryngologists reduce or stop the administration of cidofovir and has caused much concern among RRP patients.

Until now, previous human studies have not shown significantly more side effects in RRP patients who received intralesional cidofovir compared to RRP patients treated without cidofovir. The purpose of this study is to determine whether these side effects are present in RRP patients who were treated with intralesional cidofovir.

Methods

A newsletter and editorial were written to call on otorhinolaryngologists who treated RRP patients with intralesional cidofovir (31). The newsletter was sent to all members of the European Laryngological Society (ELS), the main laryngological organization in Europe, representing laryngologists from more than 50 countries in all six continents.

Centres were eligible for inclusion if they treated patients for RRP between 1998 and 2012. All patients with histopathologically confirmed RRP were included, no patients were excluded.

All participating centres received a research design which consisted of two parts:
   A) Questionnaire
   B) Retrospective case file report
To make the observations of the otorhinolaryngologists as objective as possible, a manual was attached. This document with definitions was a guideline for filling out the entry forms of the questionnaire and the retrospective case file report.

A) Information on the use of cidofovir was obtained by a two page questionnaire. Questions involved surgical technique, concentration of administered intralesional cidofovir, dose, intervals between the administrations and which considerations were made to subject the patient to surgical treatment. One question referred to side effects other than neutropenic, nephrotoxic or oncogenic after the use of cidofovir.

B) In a retrospective case file review laboratory parameters for kidney function and neutrocyte levels were compared before and after administration of cidofovir. Furthermore, the incidence of upper airway and tracheal malignancies were compared between RRP patients who had undergone cidofovir treatment and RRP patients who did not receive cidofovir. The retrospective case file review was divided into two parts: a clinical segment and a laboratory segment.

In the clinical segment, all patient charts were reviewed by the otorhinolaryngologist of the participating centre. The patient characteristics existed of: sex, age, onset of RRP (before or after 18th birthday), HPV typing, use of cidofovir and number of cidofovir gifts. Charts were reviewed for follow-up after diagnosis (date of diagnosis of RRP until the last clinical outpatient visit), and follow-up after cidofovir (first gift of cidofovir until the last clinical outpatient visit) and malignancy of the upper airway and trachea. Clinical signs of renal toxicity were defined as: anuria, dialysis, admission on intensive care because of renal failure, mortality from renal failure. Carcinoma in situ was defined as malignancy. Malignancies were counted if the malignancy occurred after the diagnosis RRP.

In the laboratory segment test values collected before and after the first cidofovir injection were retrospectively reviewed and listed by the participating centres. These included blood neutrocytes (normal range 1.8-7.7 x 10⁹ g/l), serum creatinine (normal range 0-110 mmol/l) and eGFR (normal range 52-max ml/min/1.73 m²). Serum creatinine levels documented in mg/dl were converted by factor 88.4 to mmol/l (32). Proteinuria was defined as > 20 mg/l.
Statistical methods
To compare the demographic characteristics, the chi square test was used. The laboratory values before and after cidofovir were compared by paired sample T tests. Box plots were used to visualize the abnormalities in laboratory values. For the comparison of development of a malignancy in RRP patients between the cidofovir group and non cidofovir group, a survival analysis was performed using the method of Kaplan and Meier. Occurrence of malignancies in the upper airway or the trachea between the cidofovir and non cidofovir group was compared by the log rank test. To show the differences between the malignancies in the upper airway / trachea and non malignancies chi square test and the Fisher Exact test were used. Non-parametric variables are given as medians [interquartile range]. An increase of 1% occurrence of malignancies after intralesional cidofovir was considered as clinically relevant. P-values of <0.05 were considered significant.

All data was collected and entered into a database (Microsoft Excel 2003). Statistical analyses were executed using SPSS 20.0. Medical ethics committee approval is not required in The Netherlands for a retrospective case file study.

Results
Sixteen hospitals from 11 countries worldwide submitted 635 RRP patients, of whom 275 were treated with cidofovir (table 1). In total, RRP patients received intralesional cidofovir in 1323 procedures. The mean follow-up after the diagnosis of the whole RRP group was 7.7 years with a median of 4.3 years [1.6 – 9.1 years]. During follow-up 25 (3.94%) patients developed an upper airway or tracheal malignancy. 71.2% of all RRP patients were male. When RRP patients are divided into JoRRP and AoRRP, the ratio m:f is approximately 1:1 (53.4% : 46.6%) for JoRRP, and 3:1 (75.2% : 24.8%) for AoRRP. This is a statistically significant difference in ratio m:f between JoRRP and AoRRP (p<0.001). Further baseline characteristics of the cidofovir and non cidofovir group are listed in table 1. There were statistically more women and more patients with JoRRP in the cidofovir study group. HPV typing was performed in 198 patients (31%).
Table 1. Demographic characteristics of 635 RRP patients treated with (cidofovir) and without (non cidofovir) cidofovir.

*A) There was a lot of variation in how cidofovir was used. The concentration during administration of intralesional cidofovir varied between 5 mg/ml and 75 mg/ml. The maximum dose ranged from 20 mg to 375 mg per intervention. One centre gave 25 mg per lesion, so the maximum dose was dependent on the amount of lesions. One patient received 7500 mg cidofovir in 137 intralesional administrations. There were centres with a maximum of cidofovir injections (6 - 15 administrations). Four centres had a protocol with a minimum of intralesional administrations (3 - 6 administrations), whilst the other centres gave cidofovir depending on symptoms and viewable recurrence. In one centre Gardasil® vaccination was applied to every new RRP patient.
Five centres routinely checked renal function pre and post cidofovir admission. Two centres hydrated the patients before giving cidofovir. Two patients received cidofovir intravenously beside intralesional administrations; they both developed no side effects.

Side effects other than neutropenia, nephrotoxicity or oncogenesis after the use of intralesional cidofovir were: diarrhoea in two patients, nausea in one patient and chronic uveitis in one patient. Elevation of liver enzymes ALT and AST occurred in two patients (in the first patient ALT and AST increased from respectively 14 and 12 U/L before, to 189 and 102 U/L after intralesional cidofovir; in the second patient from 18 and 13 U/L before, to 92 and 47 U/L after intralesional cidofovir).

B) When laboratory values tested before and after administration of cidofovir were compared, no statistically significant differences emerged in blood neutrocyte count, eGFR or proteinuria (table 2). Creatinine concentrations controlled after cidofovir treatment were significantly higher compared to those tested before cidofovir injections. However, there was no significant difference in number of patients with results exceeding the normal values. Figures 1, 2 and 3 show the unpaired boxplots with concentrations of neutrophilic granulocytes, creatinine and eGFR before and after use of cidofovir. None of the patients developed clinical nephrotoxicity after receiving intralesional cidofovir. One patient had proteinuria both before and after cidofovir application (30 and 100 mg/l respectively).

<table>
<thead>
<tr>
<th></th>
<th>Pre cidofovir</th>
<th>Post cidofovir</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrocytes</td>
<td>35</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>93</td>
<td>68.5</td>
<td>71.6</td>
</tr>
<tr>
<td>eGFR</td>
<td>22</td>
<td>101.0</td>
<td>103.4</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>20</td>
<td>1.55</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 2. Individual dependent laboratory values before and after intralesional cidofovir.
Figure 1. Neutrophilic granulocytes before and after use of cidofovir in patients with RRP. Dotted lines indicate borders of normal value.

Figure 2. Creatinine before and after use of cidofovir in patients with RRP. Dotted line indicates maximum normal level.
Two hundred seventy-five RRP patients received intralesional cidofovir with a median follow-up after the first cidofovir injection of 2.8 years [1.3 - 4.6 years] and a mean of 3.3 years. Four of them developed an upper airway or tracheal squamous cell carcinoma after receiving cidofovir. Three patients had been diagnosed with an upper airway or tracheal malignancy before their first administration of cidofovir (not shown in table 3). Three hundred sixty RRP patients did not receive cidofovir. They had a median follow-up of 4.7 years [1.4 – 11.0 years] with a mean of 8.9. Of those patients 18 developed an upper airway or tracheal malignancy. One patient in the non cidofovir group developed a malignancy 83 days after being diagnosed with RRP, and one patient in the cidofovir group developed a malignancy 60 days after receiving the first gift of intralesional cidofovir. Malignancies occurred less frequently in the cidofovir group, although there was no statistically significant difference (p=0.155) between the cidofovir and the non cidofovir group (Figure 4).

Figure 4 shows the duration of follow-up and occurrence of malignancies in the cidofovir group, starting with 273 patients. Two patients out of 275 who received cidofovir were under surveillance in another hospital, with no follow-up data available for the study. In the non cidofovir group 1 of the 360 patients had only one visit to the participating centre, and thus no follow-up documentation.
Table 3 shows an overview of locations where the upper airway and tracheal malignancies occurred. In two centres with 312 RRP patients, charts were reviewed for all malignancies (table 3). Two patients in the cidofovir subgroup developed malignancies outside upper airway or trachea: one patient had an oligoastrocytoma of the brain, and another patient a squamous cell lung carcinoma.

Table 4 shows the differences in demographic characteristics between patients who developed an upper airway or tracheal malignancy, and those who stayed free of cancer after the RRP diagnosis.
### Localisation of malignancy N (%)

<table>
<thead>
<tr>
<th>Location</th>
<th>Cidofovir 275</th>
<th>Non cidofovir 360</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glottis</td>
<td>1 (0.4)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Subglottis</td>
<td>1 (0.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Trachea</td>
<td>1 (0.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Larynx not specified</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4 (1.6)</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td><strong>B. Subgroup: n=312</strong></td>
<td>64</td>
<td>248</td>
</tr>
<tr>
<td>Lung</td>
<td>1 (1.6)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Prostate</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Lymph</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Brain</td>
<td>1 (1.6)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Blood</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2 (3.1)</td>
<td>14 (5.6)</td>
</tr>
</tbody>
</table>

Table 3. A. Malignancies of the upper airway and trachea diagnosed after intralesional cidofovir treatment in the cidofovir group, and after RRP diagnosis in the Non cidofovir group. B. A subgroup from two of the biggest participating centres with all reported malignancies outside upper airway and trachea. Patients are divided into those treated with (cidofovir) and without (non cidofovir) cidofovir.

<table>
<thead>
<tr>
<th>N</th>
<th>No malignancy</th>
<th>Malignancy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JoRRP</td>
<td>116</td>
<td>2</td>
<td>0.199*</td>
</tr>
<tr>
<td>AoRRP</td>
<td>517</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>434</td>
<td>118</td>
<td>0.927</td>
</tr>
<tr>
<td>Female</td>
<td>176</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup HPV n=198</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV negativity</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low risk virus</td>
<td>165</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>High risk virus</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Both low and high risk virus</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HPV positivity, unspecified</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup cidofovir n=274</strong></td>
<td>270</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Mean number of injections</strong></td>
<td>4.8</td>
<td>7.0</td>
<td>0.691**</td>
</tr>
</tbody>
</table>

Table 4. Demographic characteristics of RRP patients with and without malignancies of the upper airway and trachea. JoRRP: juvenile onset RRP. AoRRP: adult onset RRP.

* Fishers Exact  
**Independent t test
Discussion

To the best of our knowledge, this is the largest retrospective case study describing the side effects of intralesional cidofovir in RRP patients. This study shows that the use of cidofovir varies between different countries. Due to differences in the treatment of RRP patients the ELS will develop treatment guidelines for RRP. There are a lot of case series that show significantly better results after cidofovir. In those studies there is often no control group and no reference to the fact that the natural course of RRP decreases in severity (33). The only randomized double blind placebo controlled study showed a significant better improvement in voice handicap index in the cidofovir group (34). This study did not show any differences in Derkay severity score or surgical interventions. Placebo controlled RCT with other commonly used adjuvant medical treatment as interferon or bevacizumab do not exist.

Gardasil® seems highly effective as prevention against HPV related diseases. Vaccination was associated with reduced risk of subsequent low risk HPV diseases by 60.3% (35). Pawlita et al. showed in two patients only a humoral immune response after vaccination with Gardasil® (36). These results with Gardasil® seems to be very encouraging. More research is needed to find clinical benefits in RRP patients. Predisposition of males in RRP patients is a well-known phenomenon (1,4,5). In this study the predisposition was particularly seen in the AoRRP group, and to a lesser extent in the JoRRP patient. There is no explanation for the fact that there are statistically more women in the cidofovir group. An occurrence of more JoRRP in the cidofovir group can be explained by the fact that JoRRP is associated with a worse clinical course (37), and therefore JoRRP patients are more likely to receive cidofovir.

Some side effects not related to neutropenia, nephrotoxicity or malignancies may have been missed by the questionnaire because it did not specifically ask for every possible side effect. However, we found no evidence of other encountered side effects during the use of intralesional cidofovir in RRP patients.

Limitations of this study include those inherent to a retrospective analysis. Because of the small amount of patients per centers, statistic correction for the multicenter character was impossible. A concern of this study was that a few patients were
only admitted to the participating centres for cidofovir treatment, and thereafter were treated in other hospitals. Although severe side effects should normally be reported to the hospital in which patients received cidofovir, it cannot be assured that all neutropenia, renal toxicity, and malignancies have come to our attention.

Multicenter studies have the advantage that a large patient population can be included. However, in this study there are also some disadvantages. In the 16 participating centres, 16 different otorhinolaryngologists reviewed all their RRP patient charts. Considering the observers bias it would be better for the data consistency to have one person go through all patient charts. The bias was managed by attaching a manual to make the observations of the otorhinolaryngologists as objective as possible. To search for additional adverse events, contacting all RRP patients personally is possible. However the risk of a selection bias would be inevitable, since patients with an extensive disease are more likely to reply. The laboratory tests were done in different laboratories all over the world. Although this can cause bias, the laboratorial tests were simple tests and no differences were to be expected on the basis of these findings between the cidofovir group and non cidofovir group. The serum creatinine levels are time, sex and person dependent. Their levels alone are difficult to interpret. That is why eGFR and proteinuria are included to describe the renal function. Beside the increased serum creatinine levels there were more patients with an increasing than decreasing serum creatinine level. In this study it seems not clinically relevant because there were no significant differences in the number of patients with results exceeding the normal values, and there were no patients with clinical signs of impaired renal function. However these measurements give enough reason to monitor renal function during the use of intralesional cidofovir. There were more patients with a decrease than an increase of neutrocyte count after the use of cidofovir. This has no clinical significance as the neutrocyte count remains the same within the normal limits. In this study, a wide range of normal values was used. However, even with smaller ranges of normal values, there were no differences between laboratory values. A prospective study with controlled measurements of laboratory values during intralesional cidofovir is recommended.

Two patients developed an early malignancy (one in the cidofovir group and one in the non cidofovir group). It might be possible that they were misdiagnosed or that the malignancy already occurred before cidofovir therapy. Retrospectively the cause of the malignancy could not be determined.
Table 4 shows a significant difference in the distribution of HPV types between the malignancy group and the non malignancy group. Malignancy seems to be more common in HPV negative patients and in patients with high risk HPV. These results should be interpreted carefully because different HPV typing systems (ISH, PCR) were used, and the participating centers tested different HPV types. Skepticism about the correct diagnosis of patients with HPV negative RRP should be deliberated. Because table 4 raises questions, and there is no consensus about HPV typing and the malignant transformation, the ELS RRP study group decided to conduct further research.

**Conclusion**

Within laryngology, the use and application of cidofovir differs from other medical specialties. The dosage of cidofovir is much lower and has another route of administration than that used in other specialties (e.g. ophthalmology, internal medicine). Our study, concerning the use of cidofovir therapy in RRP, found no further evidence of side effects comparable to those described in the newsletter from its manufacturer. However, only long surveillance can determine whether or not RRP patients with previous cidofovir therapy have increased risk of malignant transformation compared to RRP patients without cidofovir therapy.

Cidofovir is one of the mainstays in additional treatment against RRP. This study shows that there is a worldwide variation of intralesional use of cidofovir in RRP patients. After use of intralesional cidofovir a statistically significant increase in the creatinine level was found. The change of the values has no clinical significance as the values remain within normal limits. Although this retrospective patient chart review found no clinical evidence for more nephrotoxic, neutropenic or oncogenic side effects after the use of intralesional cidofovir in patients with RRP caution should be exercised and laboratory values should be monitored before and after cidofovir. More prospective controlled research is necessary to determine the safety and clinical impact of intralesional cidofovir.
References


Chapter 5


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