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ORIGINAL ARTICLE

Local administration of cidofovir for human papilloma virus associated skin lesions in transplant recipients

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Summary

Human papilloma virus (HPV)-associated diseases are increasingly diagnosed in solid organ recipients. Cidofovir (CDV) is a broad-spectrum antiviral agent with activity against all human herpes viruses and HPV. From 2000–2004, a total of 1303 solid organ transplants (SOT) were performed at our center. Six transplant recipients were treated with topical CDV for HPV-associated lesions. One cardiac recipient responded to a single injection of CDV into his recurrent anal condylomata. In a renal recipient with recurrent penile condylomata CDV was injected into the lesions four times (2 week interval) until lesions regressed. One renal recipient developed multiple vaginal and anal intradermal neoplasias, which relapsed after laser ablation. The lesions were repeatedly injected with CDV and completely disappeared. Two renal recipients with widespread verrucae vulgares were treated with CDV gel, which resulted in regression of the lesions. One patient developed donor derived verrucae vulgares on both transplanted hands, which responded to CDV gel. Four of the six patients were switched from calcineurin inhibitors (CNIs) to Sirolimus (SIR). CDV was found effective in the treatment of HPV-associated skin lesions in SOT recipients. It needs to be determined whether switch from CNIs to SIR might have contributed to the beneficial effect of CDV.

Introduction

As a result of epidemiological factors and intensified immunosuppression, the spectrum of opportunistic infections in solid organ transplant recipients has become more diverse now, including some rare viruses. The currently available armamentarium against viruses is limited and most agents have a narrow spectrum [1]. There has been a growing number of reports on viral diseases for which only recently adequate virustatic treatment options have been suggested [2,3]. These include adenoviruses, polyoma viruses (e.g. BK virus) and human papilloma virus (HPV) among others [4]. HPV is increasingly seen in organ transplant recipients presenting with warts and condylomata acuminata, as well as neoplastic manifestations which may potentially lead to anal, vulvar, cervical or penile carcinoma [5–7].

Cidofovir (CDV) is a broad-spectrum antiviral agent with activity against a variety of different pathogens including cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zooster virus (VZV), Epstein-barr virus (EBV), human herpes virus-6 (HHV), -7 and -8, and also pox-, polyoma-, papilloma- and adenoviruses [8–10]. CDV is a potent inhibitor of herpetic viral DNA polymerase; however, activity against HPV, which does not encode its own DNA polymerase is based on a different

mode of action [11]. CDV shows an extremely long half-life and is administered intravenously at bi-weekly intervals [12]. As yet, the primary indication has been the treatment of CMV retinitis in patients with AIDS [13]. Ample experience with CDV has been reported for local application in larynx papillomatosis [14–16]. The major limitation for the broad-scale use of CDV is the risk of nephrotoxicity. Although this risk may be largely reduced or prevented by adequate predose hydration and concomitant administration of probenecid, it presents at least a theoretical threat for most organ recipients frequently showing concurrent and pre-existing renal damage and nephrotoxic co-medication such as calcineurin inhibitors (CNIs) [17]. Consequently, the use of CDV for transplant recipients has been limited to the so-called 'rescue settings' and rare indications [18,19].

The aim of the present study was to describe our experience with topical application of CDV in the treatment of HPV-associated skin and mucosa lesions in severely immunosuppressed, solid transplant recipients.

Table 1. Manufacturing of cidofovir gel 1% and 5% (g).

CDV: 1%	
Alcohol 96%	10.0 g
Propylene glycol	30.0 g
Hydroxyethylcellulose	1.0 g
Paraben* 10%	1.0 g
Aqua purificata ad	100.0 g
CDV: 5%	
Alcohol 96%	10.0 g
Propylene glycol	30.0 g
Hydroxyethylcellulose	5.0 g
Paraben* 10%	1.0 g
Aqua purificata ad	100.0 g
*Paraben 10%	
Methyl-*p*-hdroxybenzoeacid	7.0 g
Propyl-*p*-hdroxybenzoeacid	3.0 g
Propyleneglycol ad	100.0 g

*Preparation of the gel takes approximately 4 h. Thereafter, cidofovir is added to the gel at the appropriate concentration. CDV, cidofovir.

Patients and methods

Patients and transplants

Between January 1st 2000 and December 31st 2004, a total of 1303 solid organs were transplanted at our Department. There were 639 renal, 299 liver, 157 pancreas, 101 cardiac, 69 lung, 16 intestinal, 20 islet and two composite tissue allograft transplants (one bilateral hand and one bilateral forearm transplant, respectively). During the above period, five patients from this cohort (0.4%of all patients) and one patient who received a renal transplant at another center and was followed at our outpatient clinic received topical CDV for HPV-associated skin lesions. Three patients received intralesional CDV injection and three were treated with CDV ointment. No other patients received local administration. During the same time period systemic CDV was used in six patients for complicated CMV disease ($n = 5$) and polyoma virus associated nephritis ($n = 1$). None of the latter patients developed HPV-associated lesions.

Application of topical CDV

For topical treatment different concentrations were used. The gel was manufactured at the hospital pharmacy department: 375 mg (5 ml) starting from a commercially available CDV solution in sterile sodium solution. Table 1 shows the composition of CDV gel. The gel was applied using sterile Q-tips directly into the warts. The decision whether either gel or injection would be more appropriate was based on the clinical presentation. For localized lesions such as anal or penile condylomata injection was used, whereas for widespread HPV-associated warts and for the hand recipient it seemed reasonable to use CDV gel. In terms of intervals of application and CDV concentration of the gel, for the two patients with widespread verrucae vulgares we initially used the 5% gel. After the first application the lesions were investigated daily and a second application was performed only if no signs of local irritation or necrosis were observed. During the second week, two applications were performed and from the third week the gel was applied every other day until lesions had completely regressed. In the bilateral forehand recipient, the lower concentration was used and during the first two weeks only the nondominant limb was treated for safety reasons and only thereafter both grafts were treated.

For intralesional injection 75 mg (1 ml) was collected from the sterile solutions and diluted to 7.5 mg/ml using 0.9% saline solution. A total of 2–10 ml of this solution (i.e. 15–75 mg) was injected into the lesions. Following first injection, patients were closely observed in order to manage severe side effects. The second application was performed after two weeks. This interval was maintained until lesions had completely disappeared. Adequate fluid preload was ensured in all patients who received CDV injection. Probenecid was not given to any of the patients.

Patients were informed that the drug was not approved for this indication and potential side effects – in particular nephrotoxicity may develop. All patients gave verbal consent for the study. The use of the formulation was according to the rules of the local ethics committee.

Clinical charts were studied in detail and a database was created using Microsoft EXCEL 2004. Data are given as mean, median with minimum-maximum range.

Results

The six patients with topical treatment included four kidney, one composite tissue allograft and one cardiac recipient. Three patients with verrucae vulgares, and three patients with recurrent anogenital HPV-associated lesions including one patient with anal condylomata acuminata, one with penile condylomata acuminata and one with vaginal and anal intradermal neoplasia were treated. The forearm recipient presented with complicated CMV disease and viral warts and received systemic and topical CDV [20]. Table 2 shows demographic and clinical data of the cohort. In four of the five patients immunosuppression was switched to rapamycin (trough levels 4–8 of ng/dl) because of its known anti-tumor effects and lower nephrotoxicity of the mamalian target of rapamycin (mTOR) inhibitor. Renal function was monitored closely in all patients.

Patient 1

This patient was a cardiac recipient, who developed perianal warts. These lesions were removed twice by a surgical means, but relapsed within several weeks after both interventions. Therefore, local treatment with imiquimod (Aldara®, St. Paul, MN, USA) was introduced without any response. Multiple small HPV lesions still could be found perianally and within the anal canal. Intralesional CDV was applied (Fig. 1) and following the first application the lesions disappeared within 2 weeks. Maintenance therapy consisted of local CDV gel for 3 months. The patient remained free of recurrence for a 12-month follow-up before developing again new lesions, which were surgically removed and imiquimod was reapplied with improvement during further follow-up.

Patient 2

This renal recipient had developed several acute rejection episodes and therefore received multiple courses of bolused steroids and intensified prophylactic immunosuppression. He developed urethral condylomata acuminata and was treated twice using radical laser surgery and also imiquimod was applied. The condylomata recurred each time within few weeks. This patient received a total of four treatment courses with intralesional CDV injections and immunosuppression was changed to rapamycin. Most of the lesions disappeared and the remnant warts were removed by laser coagulation. The patient remained free of recurrence after a follow-up of 24 months.

Table 2. Demographic and clinical data.

Patient no.	Initials	Transplanted organ	Date of transplant	Age	Gender	Rejection	Onset of cidofovir therapy post Tx	Indications	Pretreatment	Mode of cidofovir application	Duration of therapy	switch to sirolimus	Response	Recurrence	Secondary treatment
1	HA	Heart	February 2002	32	M	No	2 years	Anal condylomata	Surgery, imiquimod	Injection	1 setting	No	Yes	Yes	Surgery, imiquimod
2	MM	Kidney	January 2001	30	M	Yes	2. 8 years	Penile condylomata	Laser, imiquimod	Injection	4 settings	Yes	Yes	No	Ablation of remnant lesions
3	AA	Kidney	November 2000	33	F	Yes	3.8 years	VIN, CIN, AIN	Laser	Injection	4 settings	Yes	Yes	Yes	CDV
4	BS	Kidney	October 2003	32	M	No	8 days	Systemic verrucae	No	Ointment	Multiple cycles	No	Yes	Yes	CDV
5	KA	Kidney	March 2001	17	M	Yes	4.2 years	Systemic verrucae	Laser, cryotherapy, imiquimod	Injection, ointment	Multiple cycles	Yes	Yes	No	No
6	J	Bilateral forearms	February 2003	34	M	Yes	6 months	Verrucae graft	Systemic CDV	Ointment	Multiple cycles	Temporarily	Yes	Yes	CDV

M, male; F, female; CDV, cidofovir; VIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia.

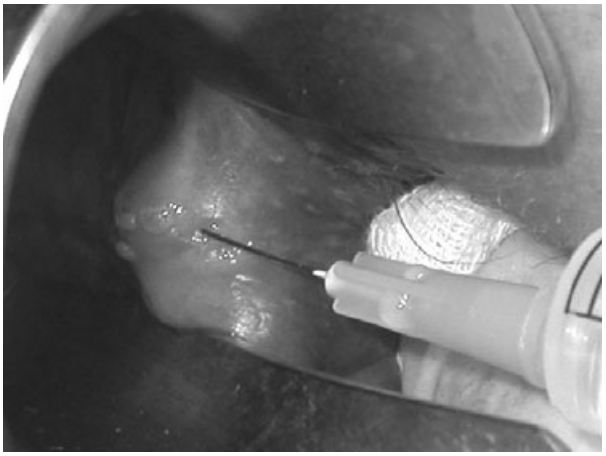


Figure 1 Recurrent anal condylomata accuminata: sub- and intralesional injection of cidofovir.

Patient 3

This patient underwent kidney transplantation in 2001 for nephrotic syndrome. After an unremarkable post-transplant course, she developed one rejection episode, which was successfully treated with bolused steroids. In 2002, the patient showed a positive papanicolaou (PAP) smear on routine examination and was further tested. A noninvasive carcinoma of the cervix uteri was found and treated by conisation. The resection margins were tumor free, however, within few weeks new lesions at the cervix occurred. Therefore, the patient underwent resection of the uterus. After a 10-month tumor-free interval she developed similar lesions within the vagina and ultimately also at the vulva and anal canal. These lesions were biopsied and revealed vaginal (VAIN), vulvar (VIN) and anal intraepithelial neoplasia (AIN) stage II (Fig. 2a). The initial approach was laser ablation, however, the lesions rapidly relapsed and therefore it was decided to administer intralesional CDV injections (Fig. 2b). Also this patient was switched to rapamycin. She received a total of four consecutive injection treatments and the lesions completely disappeared. After a 4-month follow-up she remained free of recurrence. Thereafter, biopsy revealed PAP IV and repeat injection therapy was initiated, which resulted again in a complete remission. The patient has remained recurrence-free 6 months after the last injection with now a cytology reading PAP II.

Patient 4

This patient underwent kidney transplantation in October 2003 because of end-stage renal insufficiency associated with autoimmune uveitis. He had been pretreated with long-term prednisone. As a result of pulmonary hypertension the patient could not be hyperhydrated post-transplant and as a consequence of a prolonged cold ischemia he developed acute tubular necrosis. At the time of transplantation this patient presented with a generalized mutilating spread of HPV-associated warts. Predominant sites of the lesions were face and both forearms and hands. Post-transplant course was complicated by two episodes of cardiac arrest requiring resuscitation. Immunosuppression consisted of tacrolimus (TAC), mycophenol-mofelil (MMF) and rapidly tapered prednisone and induction with basiliximab. As a result of persistent oliguria he was switched to rapamycin. He developed recurrent infectious

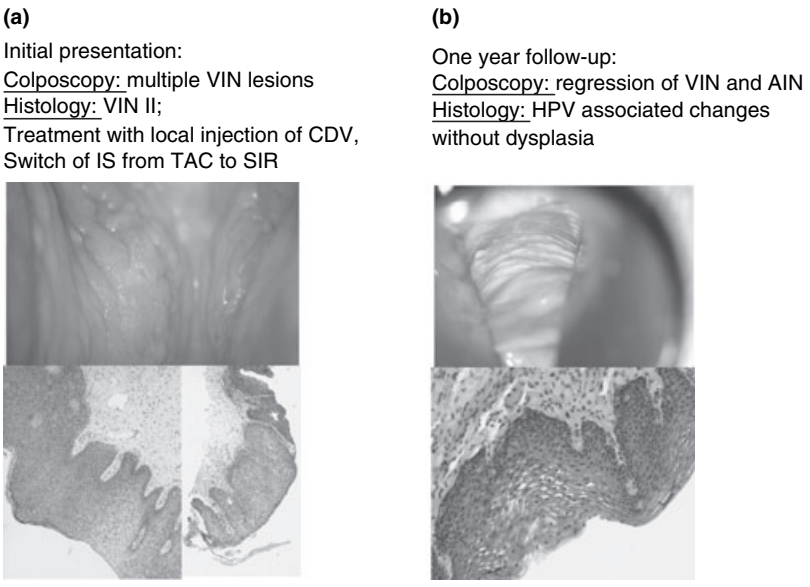


Figure 2 Vaginal intraepithelial neoplasia (VIN) in a renal recipient. (a) Initial presentation. Colposcopy: multiple VIN lesions; histology: VIN II; treatment with local injection of cidofovir, switch of immunosuppression from tacrolimus to sirolimus.
(b) One-year follow-up. Colposcopy: regression of VIN and anal intraepithelial neoplasia; histology: human papilloma virus associated changes without dysplasia.

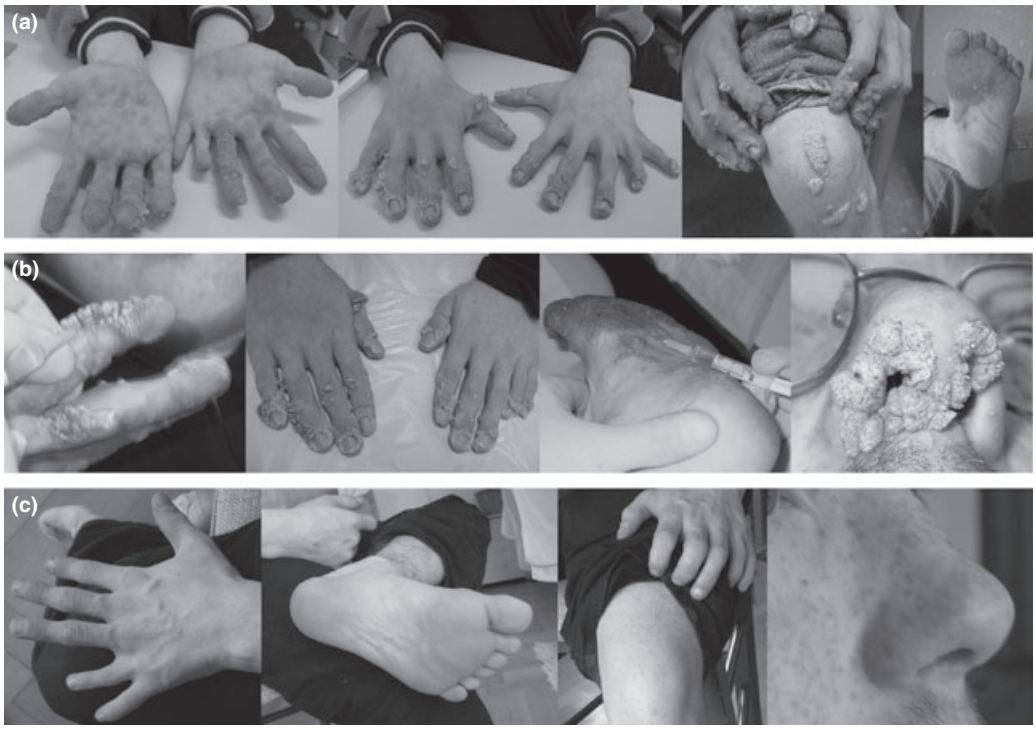
complications including bacterial pneumonia and candidaemia. Furthermore, CMV infection was treated with valganciclovir. During the second post-transplant week treatment with topical CDV (2.5% ointment) was started. Initial interval of treatment was 1 week and during the third week the patient received the ointment every other day. Total treatment duration was 16 weeks and significant regression of the warts was achieved. After a 1-year interval he developed lesions again and received a second treatment course and a complete response was achieved. The patient was listed for a retransplantation but died after 1 year cardiac failure.

Patient 5

This patient underwent renal transplantation at another center. The post-transplant course was complicated by acute rejection, peritonitis and CMV disease. During the 2-year post-transplant course he developed mutilating systemic verrucae vulgares (Fig. 3a) predominantly at both hands, feet and at the nose. He underwent cryotherapy and surgical resection without sustained success. Moreover, imiquimod was applied without any effect. Thereafter he was referred to our center. Immunosuppression was tapered and CDV ointment and local injections were applied. This resulted in a significant reduction of the lesions after 6 months (Fig. 3b) and almost complete resolution of the warts after the patient was also switched to rapamycin and TAC was withdrawn (Fig. 3c).

Patient 6

This patient received a bilateral forearm transplant after loss of both forearms in an accident with high voltage electric current. As donor and recipient were CMV-positive, prophylaxis with ganciclovir (GCV) was started immediately after transplantation. During the early post-transplant course, three rejection episodes occurred on day 10, 46 and 95, the third of which was severe and further progressed rapidly under steroid as well as anti-thymocyte globulin (ATG) treatment. Alemtuzumab (Campath-1H) was given at 20 mg intravenously on two consecutive days. The patient responded promptly to this treatment, clincal and histological features of rejection disappeared completely within 2 weeks [21]. Systemic CDV was given because of persistent CMV replication during GCV and the development of neutropenia. This



Initial presentation: Massive mutilating HPV associated skin lesions: start with CDV ointment and taper IS

Three months visit: Partial regression, intralesional CDV application: switch from TAC to SIR, maintanance therapy with CDV ointment

One year follow up: Complete regression of lesions at hands (note hexadactyly), feet, legs and nose; renal graft function improved after switch SIR; CDV withdrawn

Abbreviations: IS: Immunosuppression, CDV: Cidofovir, TAC: Tacrolimus, SIR: Sirolimus

Figure 3 Renal recipient with human papilloma virus associated lesions 2 years post-transplant (a) Initial Presentation (b) Three month visit: partial regression (c) One-year follow-up: complete regression of lesions.

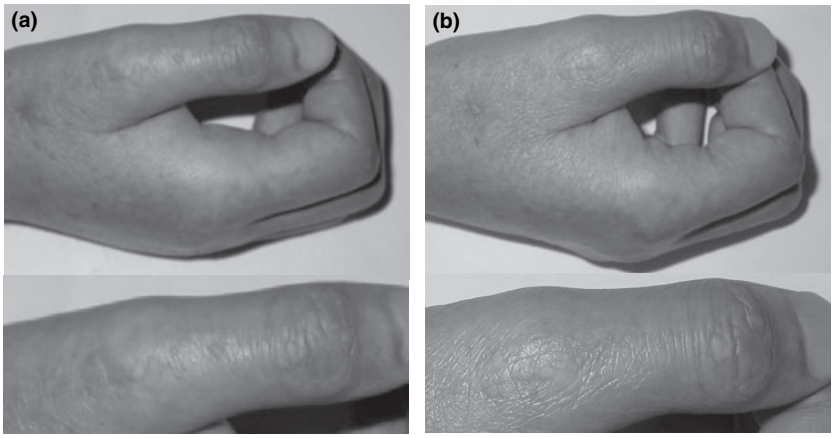


Figure 4 Papilloma virus associated warts following bilateral forearm transplantation.

Severe extent of disease on transplanted hands

Significant regression following 6 weeks topical treatment using Cidofovir 2.5% ointment

treatment resulted in a sustained response. Five months later, multiple plane warts-like lesions on the dorsal site of fingers and distal hand were observed (Fig. 4a). Biopsy revealed HPV-associated lesions. CDV gel (1%) was started on one hand for evaluation of treatment efficacy. After regression of lesions on this side topical treatment was applied on both hands (Fig. 4b). Further improvement was achieved when intervals between applications were shortened to 2 days. Warts did not disappear completely; however, only few lesions persisted without progression in size or number. The patient developed recurrent further rejection episodes. Temporarily, he was switched to rapamycin. Nevertheless, the patient presented with ongoing rejection and immunosuppression had to be intensified. He was again given Campath-1H, which again resulted in complete resolution of rejection. Of notice, whenever TAC was increased, HPV-associated lesions flared, whereas after application of alemtuzumab and TAC dose reduction the warts partially regressed. This patient also required a second course of systemic CDV therapy for persistent CMV infection. CDV gel was intermittently applied and no further progression of the warts was observed.

All patients showed response to topical CDV therapy. Four patients had a relapse and required retreatment or additional treatment including surgical ablation of remnant/recurrent lesions. Renal failure in one kidney recipient was because of poor primary function together with post-transplant cardiac arrest. The bilateral hand recipient received many other nephrotoxic drugs, including liposomal amphotericin B and TAC and systemic CDV for complicated CMV infection. During systemic CDV treatment no change in the appearance of the lesions was observed.

Discussion

Viral diseases are common complications in transplant recipients. Early onset of viral replication or *de novo* infection with several potentially oncogenic viruses such as EBV, HPV, HHV-8 and human T-cell lymphoma virus (HTLV)-1 is explained by immune modulation following organ transplantation [22]. HPV is known to play a crucial role in the development of Non-melanoma skin cancers, which show a markedly incidental increase in the long-term follow-up after organ transplantation [23]. In contrast, hematopoietic malignancies such as Non-Hodgkin lymphomas show a drastically increased relative risk during the first year with descending tendency in the following years after transplantation [24].

Cidofovir has shown promising therapeutic options for a variety of viral diseases in transplant recipients including those caused by CMV, adenovirus and polyomavirus. For HPV, little data are available, however, HPV-associated diseases have been successfully treated with CDV [25–28]. HPV-induced skin lesions and precursors for intraepithelial neoplasias and invasive cancers in immunodeficient patients other than allograft recipients, such as HIV-positive individuals, have been reported to be successfully treated by topical CDV administration [29]. This is the first study presenting the use of topic CDV for treatment of HPV-associated lesions in a series of transplant recipients. All six treated patients showed a sustained response, and HPV-associated skin and mucosal lesions regressed dramatically. Imiquimod has been recently reported to be of benefit. However, immunostimulatory agents in the transplant setting should be used with caution and in particular when considering application on a transplanted hand [30]. Benson reported on an

imiquimod-triggered significant flare of human leucocyte antigen (HLA) B27-associated spondyloarthropathy after local application [31]. An antiviral agent seems to be the more logical approach in the treatment of a virus-associated disease. Surgical approaches such as total or partial excision as well as laser vaporization or electrocauterization are more likely to be useful in immunocompetent patients. Extensive surgery for HPV-induced skin lesions (condylomata acuminata, anal/cervical intraepithelial neoplasias) may be associated with significantly more complications in immunodeficient patients as a result of impaired wound healing and the potential risk for infection [32].

A major concern with CDV is toxicity [33]. When using the agent topically the total dose that can be achieved systemically most likely can be neglected [34]. A major concern was the possible development of necrosis following injection; however, none of the patients developed local irritations. In contrast, the patient's acceptance of the drug when compared with surgical treatment was much better because of the easy application. Laser ablation at the urethra and the vagina and electrocauterization of anal condylomata are known to be very painful. More importantly, in all three patients the lesions recurred within few weeks after ablation.

The successful use of CDV in the patient with VIN/AIN stage II is in particular promising [35]. This patient was offered already amputation of the vagina to treat the multiple recurrent lesions. She is currently under close observation. For diagnosis of anogenital intraepithelial neoplasias a defined algorithm for screening methods in high-risk patients has to be established. As AIN does not show any specific clinical signs, especially at lower grades, histological assessment of all anal lesions, including condylomata, is mandatory. Allograft recipients under immunosuppression should be screened like HIV positive patients and reviewed every 4–6 months with the aid of anal cytology or colposcopy to diagnose subclinical AIN. This was the case in Patient 3 of our series. This recommendation is supported by another study, showing that 20% of the renal transplant patients had biopsy proven AIN I-III [35,36]. The switch to mTOR-inhibitors such as rapamycin in the immunosuppressant regimen might be of additional benefit because of the anti-tumor effect of these agents [37]. The development of HPV-associated skin lesions on a transplanted hand has never been described thus far and most likely this is a donor-derived disease. Therefore, HPV must be added to the expanding spectrum of pathogens and potentially tumors that may be transmitted through human allografts [38]. In this patient, the high level of immunosuppression including the application of anti-thymocyte globulin and alemtuzumab might have additionally contributed to the outbreak of HPV-associated warts [39].

From this series, we conclude that topical application of CDV may be a suitable treatment of HPV-associated lesions in transplant recipients similar to other immunosuppressed patients and the setting of laryngeal papillomatosis [40–43]. Even if there was no complete cure achieved in some patients and also recurrence must be expected, one must consider that five of the six patients had been extensively pretreated with other therapy modalities. The best effect was achieved when patients received topical application of CDV and were switched to an mTOR inhibitor. This seems not only logical from an antiviral/antineoplastic point of view, but also when considering nephrotoxicity. Renal failure has been described after topical use of an excessively high dose of CDV for a prolonged duration in a nontransplanted patient with prior renal insufficiency [33]. Therefore, particular assessment of renal function is mandatory before using CDV in transplant recipients and any additional nephrotoxic drugs should be avoided.

New orally available prodrugs of CDV are in the stage of development [44]. The unique mode of action of CDV in HPV-infected cells may also stimulate research in new targets of antiviral therapy, in particular for oncogenic viruses such as HPV [45]. This is not a randomized study and such studies are needed before making final conclusions. Moreover, it needs to be determined if CDV application together with switch from calcineurin inhibitor to mTOR inhibitor based immunosuppression has superior outcome [46]. Nevertheless, from this series, we conclude that treatment of HPV-associated skin lesions with local application of CDV seems to be a promising strategy. If the development of non-melanoma skin cancer, which shows a significantly high standardized incidence ratio (SIR 56.2) after organ transplantation, might also be prevented by CDV treatment cannot be answered [24].

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