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Review

Intralesional cidofovir for the management of refractory cutaneous verrucae: a review of applications and opportunities

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***Abstract*:** Viral warts – manifestations of cutaneous infection by human papilloma virus – can be a significant physical and emotional burden for patients when common treatments fail, particularly for individuals who are immunocompromised or with multiple lesions. Cidofovir, an antiviral agent typically used for the treatment of cytomegalovirus infection, has emerged as an alternative treatment option for viral warts when administered topically or intralesionally. In this review, we highlight the scientific rationale, published evidence, and practical clinical uses of intralesional cidofovir for the management of cutaneous warts as well as ongoing questions requiring further research and exploration of this emerging therapy for refractory verrucae.

Keywords: cidofovir, intralesional therapy, verruca, warts

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Introduction

Cutaneous warts, or verruca vulgaris, are benign cutaneous growths that arise secondary to infection with certain serotypes of the human papilloma virus (HPV) family. Although warts are generally benign in nature, they can cause pain, impair function, and have significant impacts on an individual's quality of life.[1] Warts also represent a significant economic burden, with total costs in the United States exceeding $220 million in 2004 for genital warts alone.[1] Person-to-person transmission and auto-inoculation occur through direct skin-to-skin contact leading to multiplicative burdens for individuals impacted by cutaneous warts. Warts can be disfiguring, particularly when they affect the hands or face and may lead to feelings of embarrassment, shame, and concern about negative perceptions by others.[1] Despite this, physicians may underestimate the psychological distress that patients with warts endure, even when the affected areas of the body are easily visible.[2]

In immunocompetent individuals, the majority of warts resolve spontaneously or relatively quickly with first-line treatment methods such as topical salicylic acid or liquid nitrogen cryotherapy.[2,3] In contrast, immunocompromised patients or those with persistent warts lasting 2 or more years may be refractory to treatment.[4] The lack of patient adherence to long treatment regimens and financial burdens associated with purchasing medication may also present significant barriers to appropriate care for individuals with cutaneous warts.[4]

Various treatments for resistant warts have been explored, including cryotherapy, curettage/cautery, intralesional (IL) immunotherapy, laser therapy, intralesional bleomycin, cimetidine, and vitamin D.[4–6] In recent years, cidofovir has emerged as an option for treatment of refractory warts. Cidofovir is an antiviral medication most commonly used to treat cytomegalovirus retinitis in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).[6] Other off-label indications for its use include infections such as acyclovir-resistant herpes simplex virus infection, BK virus infection, adenovirus infection, and recurrent respiratory

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papillomatosis. Cidofovir can be administered intravenously, intralesionally, or topically depending on the clinical indication. This review aims to describe the use and effectiveness of IL cidofovir in treating recalcitrant warts.

Methods

The search terms 'cidofovir', 'warts', and 'verruca' were used to extract articles from the PubMed database. Article titles and abstract contents were reviewed for clinical relevance in order to compile a review of the literature for inclusion in the article.

Mechanism of action

Cidofovir is a nucleoside analog of deoxycytidine monophosphate.[7] It is taken up by cells through fluid phase endocytosis and is subsequently phosphorylated to yield the active metabolite cidofovir diphosphate.[8] Since cidofovir diphosphate is structurally analogous to other nucleotides, it functions as a competitive inhibitor by incorporating into a growing strand of DNA, thereby inhibiting DNA polymerase and blocking viral DNA synthesis.[8–10] In HPV-infected keratinocytes, cidofovir treatment traps infected cells in the S phase to prevent further DNA synthesis, inducing DNA fragmentation and activating caspase-3 protease activity to promote apoptosis in infected cells.[10,11] In uninfected keratinocytes, cidofovir treatment demonstrates marginal to no decrease in growth.[10] Because cidofovir does not rely on viral thymidine kinase for activation, the medication has also shown effectiveness against herpesviruses that are resistant to acyclovir, ganciclovir, and foscarnet treatment.[12] A main limitation of cidofovir when administered systemically is nephrotoxicity; individuals may be pre-hydrated prior to treatment to avoid this complication. Similar renal impairment is not generally observed when cidofovir is administered locally *via* topical or intralesional methods.[13,14]

Clinical effects of intralesional cidofovir injections

Despite limited literature, case reports and cohort studies suggest that IL cidofovir is an effective treatment for recalcitrant warts when treatments such as cryotherapy, Candida antigen injection, topical salicylic acid, laser therapy, and curettage/cautery are unsuccessful.[2]

Studies of cidofovir for the management of recalcitrant warts are limited, but they have demonstrated the overall effectiveness of IL cidofovir on recalcitrant warts. Immunosuppressed patients may particularly benefit from IL cidofovir; case reports have shown that patients with recalcitrant warts that had underwent organ transplant or had lymphoma have been successfully treated with IL cidofovir (Table 1).[15–18]

An immunosuppressed patient that had undergone renal transplant and subsequently developed recalcitrant warts covering both hands showed resolution of 95% of warts after seven IL cidofovir injections.[15] No recurrence was observed over a 24-month follow-up period. In another case, a lymphoma patient with a large plantar wart measuring 4×5 cm was cured after four injections of IL cidofovir.[16] In a case series of four organ transplant recipients with warts or anal/penile condylomata refractory to treatment, IL cidofovir resulted in dramatic improvement of the lesions.[18] However, one patient experienced recurrence after a 12-month follow-up. Another case report described a wart in the nail fold that was resistant to cryotherapy and curettage.[19] After cidofovir 1% cream was applied for 5 days with no response, IL cidofovir was administered twice, resulting in complete resolution of the lesion without recurrence after 2 years of follow-up.

A recent retrospective study highlighted the benefit of IL cidofovir in the treatment of recalcitrant warts and condylomata in immunocompetent and immunocompromised patients.[20] In the per-protocol population of 43 patients, 100% and 97.6% of warts improved or resolved, respectively, after an average of 3.4 IL cidofovir treatments. In the intent-to-treat population of 58 patients, 98.3% and 75.9% of warts were improved or resolved, respectively, after an average of 3.4 IL cidofovir treatments. Another study comparing IL sodium tetradecyl sulfate treatment to IL cidofovir treatment demonstrated that IL cidofovir was significantly ($p < 0.001$) more effective at completely removing warts.[9] About 26.09% of the sodium tetradecyl sulfate treatment cohort and 90.91% of the IL cidofovir treatment cohort was wart-free after each respective treatment. Complete resolution of warts was noted in all 22 patients receiving cidofovir. However, recurrence of warts following cidofovir treatment was observed in two immunocompromised patients, to whom additional IL cidofovir was administered. In a larger study of

Table 1. Characteristics of immunocompromised patients receiving IL cidofovir treatment.

Study	No. of patients	Age	Gender	Medical history	Location and number of lesions treated	Dosing	Clinical outcome
Bonatti *et al.*[18]	4[a]	33	Female	Renal transplant; one rejection episode treated with bolused steroids; refractory to laser treatment	Multiple lesions in the vaginal, anal, and vulvar regions	7.5 mg/ml IL cidofovir with 0.9% saline solution. 4 injections of 2–10 ml every 2 weeks	Complete resolution of lesions and free of recurrence at a 4-month follow-up
		17	Male	Renal transplant; post-transplant course complicated by acute rejection, peritonitis, and CMV disease; refractory to cryotherapy, surgery and imiquimod treatment	Multiple lesions on nose and bilateral hands and feet	7.5 mg/ ml IL cidofovir with 0.9% saline solution. Multiple injections of 2–10 ml over many 2-week cycles accompanied by topical cidofovir ointment	Significant reduction of lesions after 6 months
		32	Male	Cardiac transplant, refractory to surgery and imiquimod treatment	Anal condylomata	7.5 mg/ ml IL cidofovir with 0.9% saline solution. 1 injection of 2–10 ml	Complete resolution after 2 weeks, with recurrence after 12 months
		30	Male	Renal transplant; suffered from several rejections necessitating multiple courses of steroids; refractory to laser and imiquimod treatment	Urethral condylomata	7.5 mg/ ml IL cidofovir with 0.9% saline solution. 4 injections of 2–10 ml every 2 weeks	Disappearance of most lesions and free of recurrence over a 24-month follow-up
Blouin *et al.*[15]	1	23	Male	Renal transplant, refractory to cryotherapy, cantharidin, imiquimod, salicylic acid/petrolatum, salicylic acid/podophyllin, dinitrochlorobenzene, IL bleomycin, cimetidine, CO2 laser, acitretin, and topical cidofovir treatment	>100 lesions on bilateral hands	7.5 mg/ ml IL cidofovir with 0.9% saline solution. 7 injections of 0.25–1.5 ml over 4-week intervals	Significant resolution of 95% of lesions without recurrence over 24-month follow-up
Moore and Kovarik[16]	1	Unknown	Unknown	Lymphoma	Singular lesion on plantar aspect of right foot	Cidofovir and saline were diluted at a 1:3 ratio for a 3 ml initial injection. 3 more injections, diluted at a 1:4 ratio, were administered over 2 months	Complete resolution of hyperkeratosis at a 4-month follow-up
Oh[9]	2	46	Male	Immunosuppressive medications due to myasthenia gravis	20 lesions across the sole, finger, and toe	Cidofovir and saline were mixed at a 1:4 ratio for a final concentration of 15 mg/ml. A total of three treatments were administered over the course of 92 days	Complete resolution for 2 months, then recurrence of lesions. Additional IL cidofovir injections were administered
		16	Female	Immunosuppressive medications due to liver transplantation	7 lesions across the sole, finger, and toe	Cidofovir and saline were mixed at a 1:4 ratio for a final concentration of 15 mg/ml. A total of two treatments were administered over the course of 60 days	Complete resolution for 2 months, then recurrence of lesions. Additional IL cidofovir injections were administered

CMV, cytomegalovirus; IL, intralesional.
[a]This study involved six patients treated with cidofovir; however, only four were treated with intralesional administration.

280 patients with recalcitrant warts, 276 individuals achieved complete resolution without recurrence after an average of two to three injections.[8] The four patients for whom the treatment was unsuccessful had warts that were smaller and more difficult to access and required additional cryotherapy post-treatment to achieve complete resolution.

Another study evaluating the use of IL and topical gel (TG) cidofovir in 12 HIV-positive patients with genital warts demonstrated mixed findings. Three patients who received IL cidofovir experienced superficial flattening of condylomata, but there was no overall significant improvement in the size, number, and features of the lesions.[21] The large number and size of the lesions were cited as reasons for why IL cidofovir failed to induce a more robust response against the warts. All patients in the study also received TG cidofovir, but only 10 of them were evaluable: 4 were cured, 3 remained stable, and 3 had improved lesions. Complete response was achieved in one of the three patients who received IL and TG cidofovir combination therapy.

IL cidofovir may also have clinical applications in the treatment of verrucous herpes simplex virus (HSV). A case report described a patient receiving 6 IL cidofovir treatments to completely resolve extensive acyclovir-resistant HSV on the scrotum and perianal region.[22]

Taken together, these studies illustrate the effectiveness of IL cidofovir treatment for recalcitrant warts.

Administration and dosage of medication

Technical approaches to the use of IL cidofovir have varied based on various reports as described above. Given local pain associated with the IL injection, administration of local anesthesia around the wart prior to IL injection may be considered in order to increase tolerability. IL cidofovir should then be injected directly into the lesion using a superficial crosshatching or serial puncture technique.[20] Regarding dosage, studies investigating the use of IL cidofovir in the treatment of recalcitrant warts have reported diluting cidofovir 75 mg/ml with normal saline to produce a 15 mg/ml solution.[8,20] Other studies report using IL cidofovir 7.5 mg/ml with a 0.9% saline solution.[15,18] Varying volumes of the diluted solution have been used depending on the number and size of the wart, ranging from 0.2 ml for periungual warts up to a maximum of 5 ml for larger warts per treatment session.[9,20] If clinically indicated, patients should return to clinic on a monthly basis for additional IL cidofovir injections.

Adverse events and special considerations

IL cidofovir treatment is associated with several local adverse events (AE) including blistering, pain, swelling, and erosion.[20] Patients with plantar warts have also reported bulla formation on their feet after IL cidofovir injections.[9] In another study, all 276 patients experienced pain and burning during the IL cidofovir injection.[8] Post-injection AE included hyperpigmentation in the hands, erythema, and pruritus in a minority of patients. Notably, no systemic effects nor deviation from baseline laboratory values were observed post-treatment.

The literature regarding the AE of IL cidofovir is limited. The AEs of intravenous cidofovir are well described and include nephrotoxicity, neutropenia, and metabolic acidosis.[23] IL cidofovir has not been associated with these systemic complications; prior studies have found no statistical differences in neutropenia or renal dysfunction before or after IL cidofovir administration in patients with recurrent respiratory papillomatosis (RRP).[13] In addition, there was no evidence of long-term nephrotoxicity or neutropenia. Similarly, studies varying the volume of 7.5 mg/ml IL cidofovir treatment administered in the airway for RRP did not lead to toxic concentrations in the plasma.[14] However, greater plasma diffusion levels with higher standard deviations were observed in adults compared with children. The authors concluded that for adults, medication should be administered intralesionally at a concentration lower than the intravenous infusion dose leading to toxicity in order to prevent systemic toxicity. Cancer risk from long-term repeated use of cidofovir is a theoretical concern given studies of intravenous cidofovir in animals have shown evidence of tumor formation.[24] Studies in patients with RRP have resulted in mixed findings. A case report found that invasive squamous cell cancer arose from a squamous papilloma after multiple injections of cidofovir.[25] However, a more recent study demonstrated that IL cidofovir use in patients with RRP did not

increase rates of dysplasia or carcinoma development compared with control RRP patients.[26]

Large-scale studies addressing the need for laboratory monitoring of patients undergoing treatment with IL cidofovir are lacking. Regardless of administration route, one should consider close monitoring for possible nephrotoxicity through serum creatinine levels in patients who have pre-existing renal dysfunction, require a large dose of cidofovir, or are on other medications that modify rates of renal excretion. Precautions regularly taken during systemic administration of cidofovir include ensuring an adequate fluid preload before administration of medication, and considering the use of probenecid, although the utility of such precautions prior to use of IL cidofovir is unknown. Increasing the dilution of cidofovir solution may be considered in selected patients receiving IL cidofovir who are at risk for nephrotoxicity.[9,15,18]

Conclusion

While warts often resolve spontaneously or with first-line treatment, resistant cases may require other therapeutic modalities. This review summarizes the current literature on the usage of IL cidofovir for the treatment of recalcitrant warts. Studies suggest that this is a promising treatment in both immunocompetent and immunocompromised patients who are unresponsive to prior therapies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

William C. Lau: Data curation; Formal analysis; Writing – original draft.

Charles B. Lau: Conceptualization; Formal analysis; Investigation; Writing – original draft.

Jason E. Frangos: Conceptualization; Formal analysis; Writing – review & editing.

Vinod E. Nambudiri: Conceptualization; Formal analysis; Investigation; Project administration; Supervision; Writing – review & editing.

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References

1. Ciconte A, Campbell J, Tabrizi S, *et al*. Warts are not merely blemishes on the skin: a study on the morbidity associated with having viral cutaneous warts. *Australas J Dermatol* 2003; 44: 169–173.
2. Buckley D and Pasquali P. *Textbook of primary care dermatology*. Cham: Springer, 2021.
3. Dall'Oglio F, D'Amico V, Nasca MR, *et al*. Treatment of cutaneous warts: an evidence-based review. *Am J Clin Dermatol* 2012; 13: 73–96.
4. Friedman PC. Management of difficult-to-treat warts: traditional and new approaches. *Am J Clin Dermatol* 2021; 22: 379–394.
5. Kaul S, Kaur I, Jakhar D, *et al*. The diverse methods of bleomycin delivery in cutaneous warts: a literature review. *Dermatol Ther* 2021; 34: e14401.
6. Muse ME, Stiff KM, Glines KR, *et al*. A review of intralesional wart therapy. *Dermatol Online J* 2020; 26: 13030/qt3md9z8gj.
7. Fathi R and Tsoukas MM. Genital warts and other HPV infections: established and novel therapies. *Clin Dermatol* 2014; 32: 299–306.
8. Broganelli P, Chiaretta A, Fragnelli B, *et al*. Intralesional cidofovir for the treatment of multiple and recalcitrant cutaneous viral warts. *Dermatol Ther* 2012; 25: 468–471.
9. Oh BH. Cidofovir intralesional injection for recalcitrant common warts: a comparison with

sodium tetradecyl sulfate intralesional injection. *Ann Dermatol* 2020; 32: 273–279.

10. Zabawski E. Cidofovir. *Dermatol Online J* 2000; 6: 3–9.
11. Johnson JA and Gangemi JD. Selective inhibition of human papillomavirus-induced cell proliferation by (S)-1-[3-hydroxy-2(phosphonylmethoxy)propyl]cytosine. *Antimicrob Agents Chemother* 1999; 43: 1198–1205.
12. Morfin F, Snoeck R, Andrei G, *et al*. Phenotypic resistance of herpes simplex virus type 1 strains selected in vitro with antiviral compounds and combinations thereof. *Antivir Chem Chemother* 1996; 7: 270–275.
13. Tjon Pian Gi RE, Ilmarinen T, van den Heuvel ER, *et al*. Safety of intralesional cidofovir in patients with recurrent respiratory papillomatosis: an international retrospective study on 635 RRP patients. *Eur Arch Otorhinolaryngol* 2013; 270: 1679–1687.
14. Naiman AN, Roger G, Gagnieu MC, *et al*. Cidofovir plasma assays after local injection in respiratory papillomatosis. *Laryngoscope* 2004; 114: 1151–1156.
15. Blouin MM, Cloutier R and Noël R. Intralesional cidofovir in the treatment of cutaneous warts in a renal transplant patient. *J Cutan Med Surg* 2012; 16: 462–464.
16. Moore E and Kovarik C. Intralesional cidofovir for the treatment of a plantar wart. *J Am Acad Dermatol* 2015; 73: e23–e24.
17. Leung AK, Barankin B, Leong KF, *et al*. Penile warts: an update on their evaluation and management. *Drugs Context* 2018; 7: 212563.
18. Bonatti H, Aigner F, De Clercq E, *et al*. Local administration of cidofovir for human papilloma virus associated skin lesions in transplant recipients. *Transpl Int* 2007; 20: 238–246.
19. Stragier I, Snoeck R, De Clercq E, *et al*. Local treatment of HPV-induced skin lesions by cidofovir. *J Med Virol* 2002; 67: 241–245.
20. Anshelevich EE, Barbieri JS and Kovarik CL. Intralesional cidofovir for treatment of recalcitrant warts in both immunocompetent and immunocompromised patients: a retrospective analysis of 58 patients. *J Am Acad Dermatol* 2021; 84: 206–207.
21. Orlando G, Fasolo MM, Beretta R, *et al*. Intralesional or topical cidofovir (HPMPC, VISTIDE) for the treatment of recurrent genital warts in HIV-1-infected patients. *Aids* 1999; 13: 1978–1980.
22. Wanat KA, Gormley RH, Rosenbach M, *et al*. Intralesional cidofovir for treating extensive genital verrucous herpes simplex virus infection. *JAMA Dermatol* 2013; 149: 881–883.
23. Zabawski EJ Jr and Cockerell CJ. Topical and intralesional cidofovir: a review of pharmacology and therapeutic effects. *J Am Acad Dermatol* 1998; 39: 741–745.
24. Broekema FI and Dikkers FG. Side-effects of cidofovir in the treatment of recurrent respiratory papillomatosis. *Eur Arch Otorhinolaryngol* 2008; 265: 871–879.
25. Lott DG and Krakovitz PR. Squamous cell carcinoma associated with intralesional injection of cidofovir for recurrent respiratory papillomatosis. *Laryngoscope* 2009; 119: 567–570.
26. Hoesli RC, Thatcher AL, Hogikyan ND, *et al*. Evaluation of safety of intralesional cidofovir for adjuvant treatment of recurrent respiratory papillomatosis. *JAMA Otolaryngol – Head Neck Surg* 2020; 146: 231–236.