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Genital warts and other HPV infections: Established and novel therapies

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Abstract Wart therapies involve methods of targeted lesion destruction, as well as selective immunologic modification. While there are several therapeutic options, no treatment has been proven to be superior in terms of clinical clearance or recurrence. Controlled trials comparing treatments are currently lacking. Many factors are used in the selection of treatment. Variables that should be taken into account include but are not limited to the morphology of the lesions such as thickness and size, quantity, anatomic location, human papilloma virus (HPV) classification, immunocompromized or immune competent status, as well as the preferences of the patient and the provider, cost and availability. No current treatment completely eradicates the human papillomavirus virus. The availability of vaccinations against HPV infection is contributing to the decreasing incidence of this disease. This contribution highlights conventional therapies, off-label treatment strategies including combination therapies, and prophylaxis for condylomata acuminata.

Introduction

Condylomata acuminata (CA) or anogenital warts: Significance

Condylomata acuminata (CA), or anogenital warts, is the most common viral sexually transmitted disease in the United States. The incidence in the United States is approximately 1% in sexually active adults and has been reported to be as high as 3% in sexually active adolescents. Recurrent anogenital warts, a frequent cause of medical visits (approximately 360,000 in 2008 in the United States), may be disfiguring and thus impose a considerable psychological burden. The economic burden is also substantial as genital HPV infections cost the United States $6 billion annually.[1]

While CA affects both genders, women account for 67% of the patient population.[2] Between 50% and 80% of sexually active women will be infected with the causative virus, the human papillomavirus (HPV), at some point during their lifetime.[3] One study showed 26% of 608 sexually active college women were diagnosed with genital HPV at study entry. Over the next 3 years, 43% acquired cervical HPV infections.[4] Another study showed sexually active college men to have a 60% incidence of new genital HPV infections over 2 years.[5] HIV-infected patients and organ transplant patients are at a higher risk for HPV infection and progression to intraepithelial neoplasias due to immune suppression. Anal swabs for HPV DNA were positive in 93% of HIV-seropositive men who have sex with men compared to 60% of HIV-negative men who have sex with men.[6]

The high prevalence of genital HPV infection in sexually active young adults is a major concern due to the fact that there are no radical antiviral treatments. CA most commonly occurs by intimate contact as the basal keratinocytes, the primary targets of HPV, are exposed through minor abrasions. Through maceration, infection is promoted, and autoinoculation from lesion to adjacent skin is frequently observed. As a result, treatment does not prevent further

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transmission of the virus. Autoinoculation also helps to explain the high recurrence rates of CA (approximately 20%-50%).[7] In general, the majority of warts may spontaneously regress within 1 to 2 years. Genotype-specific immunity may also develop, thus protecting against reinfection.[8]

HPV genotype: Role in infections and its significance in treatment

HPV is a family of non-enveloped, circular, double-stranded DNA viruses. Depending on the subtype of HPV, these viruses are capable of causing a wide spectrum of disease in humans of varying morbidity and mortality. While most of the infections of HPV are subclinical, part of the spectrum of clinically relevant disease is CA with the possibility of progression from intraepithelial neoplasia to life-threatening invasive carcinoma.[9] CA is highly contagious through sexual contact with an estimated transmission rate near 65%. The incubation period tends to run between 3 weeks and 8 months with clinical appearance within 2 to 3 months.[10]

HPV is differentiated by approximately 120 genotypes that infect the epithelia of skin or mucosa, and these are subdivided into low-risk and high-risk variants based on potential for oncogenesis. Genital warts are caused by the low-risk types of HPV (6, 11, 42, 43, and 44) with 90% caused by 2 genotypes, HPV-6 or -11.[11] While the high-risk HPV variants cause most of the cervical carcinomas, one study has shown that 31% of adults suffering from CA are co-infected with a high-risk HPV variant.[12]

The HPV genome contains six early genes and two late genes. The late genes (L1 and L2) encode for the spherical capsid, which protects the viral DNA from degradation and allows it to efficiently bind to the target cell .[13] L1, which encodes for the major capsid protein of the virion when expressed in cell culture self-assembles into virus-like particles (VLPs) that are structurally similar to the native virions.[14] These VLPs serve as the basis for prophylactic vaccinations.[15] The early genes (E1, E2, E4, E5, E6, and E7) are responsible for the viral life cycle and oncogenesis. They play important roles in regulatory function and encode proteins involved in viral replication and cell transformation.[16] The integration of viral and host cell DNA may result in the dysregulation and uncontrolled activation of the E6 and E7 genes, which promotes the transcription of oncoproteins. These two early genes bind and inactivate the tumor suppressor genes p53 and Rb, resulting in cell proliferation and the potential for malignancy.[3] The E1 and E2 genes are responsible for controlling transcription of other viral genes and replication of the viral genome.[9]

The persistency of CA and other papillomaviruses are due in part to their mechanisms of evading immune surveillance. First, because there is no viremic phase, there is no systemic immune response that is elicited. Secondly, the basal cell layer, where Langerhans cell and lymphocyte recognition is highest, expresses low levels of viral proteins. The highest production of virion proteins tends to be in the terminally differentiated layers of the epithelium, which are subsequently shed.[17]

Clinically, CA typically are found on the external genitalia and the perineum, perianally, or in adjacent areas such as the inguinal fold and mons pubis.[18] Lesions can also extend into the vagina, urethra, or anal canal; however, they rarely cross the dentate line. The lesions are described as sessile, smooth-surfaced exophytic papillomas. They are usually discrete and skin-colored, brown or whitish in appearance. Typically, they do not have extensive horny scale, but they may be pedunculated or broad-based and vary in size from 1 mm to several cm in diameter.[19]

Histologically, anogenital warts features include epidermal hyperplasia, parakeratosis, koilocytosis, and papillomatosis. Detection of cytoplasmic vacuolization within the deeper portions of the stratum malpighii may be specific for CA. Typically, mitotic figures may be evident. Prior wart treatment with podophyllotoxin may induce aberrant mitoses histopathologically resembling squamous cell carcinoma.[20]

No specific antiviral therapy is available to cure anogenital warts, although numerous potential antiviral targets have been postulated. At the current time, existing modalities employ destruction, antiproliferative therapy, or immunomodulation. Additionally, therapies can be either patient-applied or provider-administered. Recurrence rates are typically high (eg, 25%-65%); however, due to the widespread infection and subclinical lesions. Limiting sexual partners and condom use should be promoted regardless of the therapy employed.[21] Regardless of the therapy chosen, treatment is typically time-consuming and uncomfortable. While there are many available treatment options, there is a lack of comparative trials.[22] As a result, there is no definitive first-line treatment. No single treatment is ideal for all patients. Several factors should be considered when deciding on therapy including the number, size, morphology, degree of keratinization, anatomic location, patient preference, provider experience, and side effects.[23] Currently available treatments yield clearance rates ranging from 60% to 90% and can be expected to be less effective in immunosuppressed individuals.[22-24]

Topical treatments

Podophyllotoxin and podophyllin

Podophyllotoxin, a purified extract of the podophyllum plant, binds to cellular microtubules to induce wart necrosis by inhibiting mitosis.[41] It is inexpensive and easily self-administered, making it the preferred first-line therapy of many physicians. Clearance rates range from 45% to 77%.[41-44] Recurrence rates have been reported to be as low as 38%. Currently, it is available as a gel, cream, or solution. The solution is found to be convenient for penile lesions, whereas the gel and cream seem to be preferred by patients

for anal, introital, and vulvar lesions. Regardless of the vehicle, it should be applied twice daily for three consecutive days of the week for a maximum of four weeks. Patients should be counseled as to not exceed a total surface area of 10 cm^2. Patients should also minimize application to normal tissue and fingertips. Typical side effects include local burning, redness, pain, itching, and swelling. Erosions, which are associated with successful necrosis of the warts, are generally self-limited.[42]

Podophyllin, an unpurified extract from the same plant and formerly used as a provider-applied treatment, is not currently recommended for therapy due to the low efficacy and high toxicity. It is also contraindicated in pregnancy due to the potential for mutagenicity. It may be excessively absorbed systemically, leading to enteritis, bone-marrow suppression, and neurological deficits.[40-44]

Imiquimod

Imiquimod is a patient-applied therapy that acts as an immunomodulator. It is believed to bind to membranous toll-like receptor 7, activating dendritic cells, macrophages, and keratinocytes to release type I interferons (IFNs) and other pro-inflammatory cytokines to enhance cell-mediated cytolytic activity against HPV.[25-28] It is available in 5.0% and 3.75% topical cream. The clearance rate for the 5.0% cream has been reported to be 40% to 70%. For the 3.75% cream, the clearance rate is 28%. The recurrence rates for both are similar: 9% to 19% for the 5.0% cream and 15% for the 3.75% cream. Imiquimod 5.0% cream should be applied at bedtime three times per week for up to 16 weeks. The 3.75% cream, which is found to have higher patient compliance, is applied daily for a maximum of 8 weeks.

Local side effects for the 5.0% cream include itching, redness, burning, irritation, tenderness, ulceration, and pain. Systemic side effects such as headaches, muscle aches, fatigue, and general malaise have also been reported. Patient education for expected reaction can improve compliance during therapy. The side effect profile for the 3.75% cream is similar to, yet less severe than, the 5.0% cream with no reported systemic symptoms.

Sinecatechins

Polyphenon E (sinecatechins 15% ointment) is a patient-applied therapy approved by the FDA in 2006 for external genital and perianal warts. The active ingredient is a green tea extract, which is thought to contain antioxidant, antiviral, and antitumor sinecatechins.[29] The mechanism of action remains unclear, although it is thought to produce immunostimulatory effects through multiple pathways not limited to transcription factors NF-(kappa)B and AP-1, IL-1, IFN-c, and TNF-(alpha). Three different double-blind, randomized, placebo-controlled trials have demonstrated clearance rates ranging from 54% to 65% and recurrence rates of 5.9% to 12%.[29-31] Complete clearance is higher in women than in men. While the gender difference is small, it may be attributed to decreased drug penetration in men due to greater relative keratinization of the penile shaft. The ointment is applied three times a day for up to four months. If no improvement is seen within a few weeks, the treatment should be stopped.[29]

Adverse reactions are generally mild and include local redness, burning, itching, and pain. Rare but more severe reactions include lymphadenitis, vulvovaginitis, balanitis, and ulceration. Patients should be advised that erosions, ulcerations, and erythema are correlated with higher clearance rates.[29-31]

Intralesional immunotherapy with skin test antigens

Intralesional immunotherapy using an injection of *Candida*, mumps, or trichophyton skin test antigens has been used to treat benign HPV infections for years. The treatment involves three sessions approximately 4 to 6 weeks apart. Untreated warts that resolve after antigen injection has prompted speculation that intralesional immunotherapy induces HPV-directed immunity. Intralesional injections of purified protein derivative (PPD), an extract of *Mycobacterium tuberculosis* used for testing exposure to tuberculosis, has recently been evaluated as an approach in the treatment of anogenital warts in pregnant women. Lessening of the clinical lesion occurred in 85% of the subjects and was related to the extent of tuberculin reactivity. 47.5% of the patients demonstrated complete clearance, and 37.5% had a partial response. Side effects were minimal, and tuberculin skin testing is considered valid and safe throughout pregnancy.[38,39,49]

Cidofovir

Cidofovir, a nucleoside analog of deoxycytidine monophosphate, acts by selectively inhibiting DNA polymerase and blocking viral DNA synthesis and replication. The goal of this therapy is to induce apoptosis in virally infected cells. It is not presently FDA approved for CA. Topical cidofovir has also been effective in management of herpes simplex, molluscum contagiosum, and HPV lesions. For CA, cidofovir may be administered topically (pharmacy-compounded in 3% and 1% cream and patient-administered) or intralesionally (physician-administered).[37]

A double-blind, placebo-controlled study of immunocompetent patients using topical cidofovir demonstrated a 50% reduction in the wart area in 16 of 19 patients, with 9 patients demonstrating 100% clearance. Another cidofovir study in patients with AIDS demonstrated a 65% partial or complete response rate. Multiple case reports have also shown examples of children and transplant patients with warts recalcitrant to other therapies who have responded favorably to topical or intralesional cidofovir.[37]

The most common adverse reactions are pain, pruritus, and dermatitis. Less commonly, patients may develop erosions or ulcerations at the application site. Finally, patients with a history of renal insufficiency should be treated with caution. There has been one report of topical cidofovir therapy resulting in acute renal failure due to systemic absorption in a bone marrow transplant patient with underlying chronic renal failure.[37]

5-Fluorouracil (5-FU)

5-FU has gained favor as a therapy for genital warts, especially urethral warts, despite not being FDA approved. Compared to imiquimod, 5-FU has similar clearance rates and a slightly higher recurrence rate with the added disadvantage of more severe side effects. For this reason, it is generally not recommended as first line therapy for genital warts.[36]

Destructive and surgical treatments

TCA

Trichloroacetic acid (TCA) is an inexpensive, physician-applied therapy that chemically burns, cauterizes, and erodes skin and mucosa.[50] It typically is prepared in 80% to 90% solutions. Clearance is estimated to be 70% to 80% with recurrence of 36%.[51] Multiple treatments are generally required; however, occasionally clearance occurs with just one treatment. It is safe to use in pregnancy due to the low risk of systemic absorption. Side effects include pain or burning during administration and destruction of surrounding healthy tissue. On occasion, ulceration and crust formation can occur. In general, TCA is an attractive treatment option due to the relatively low morbidity, high clearance rates, and safety in pregnancy.[50-55]

Cryotherapy

Cryotherapy involves freezing abnormal tissue through the use of cooling agents such as liquid nitrogen. The temperatures involved with cryotherapy are cold to the point that there is permanent dermal and vascular damage. Eventually, an immune response is initiated, resulting in necrosis and clearance of the abnormal cells. Clearance rates are excellent at 79% to 88% within three treatment sessions. The variability of cryotherapy may depend on the temperature, the administrator, and the time of contact. Side effects include local tissue destruction with blistering, ulceration, infection, and loss of pigmentation. There is also a small risk for permanent scarring.[48]

Cryotherapy is considered a first-line provider-administered therapy due to its relative ease of administration, efficacy, and cost. It is very effective for multiple and small warts. One disadvantage is that it does not treat subclinical lesions in the surrounding skin, although the immune response during the healing process may facilitate healing of adjacent lesions to those primarily treated. In addition, treatment of a widely involved area may not be tolerated well by patients due to pain. Recurrence rates are estimated between 25% and 40%. Additionally, multiple visits are needed, and the pain associated can result in patients not following up for therapy. The effects, though, are entirely local, efficacious, and safe to use in pregnancy.[48] In practice, cryotherapy is used as monotherapy or in conjunction with other treatments listed in this publication.

Potassium hydroxide

Potassium hydroxide (KOH) is a strong alkali that has been used as a low-cost patient-applied therapy for genital warts. Due to its ability to dissolve keratin and deeply penetrate the skin in patients with molluscum contagiosum, an open-label study looked at the efficacy of treating genital warts in men. In one trial, 35 patients were taught how to apply a KOH 5% aqueous solution on warts located on the glans, foreskin, scrotal area, and penile shaft once daily until mild inflammation was observed. At the end of the trial there was a clearance rate of 87.5% with a 9% recurrence rate. Clearance occurred anywhere from 1 to 8 weeks from the date of the first application. All patients experience mild inflammation (erythema and edema). About half experienced superficial erosions, and less patients experienced stinging and hypopigmentation. More studies are needed to evaluate this treatment.[66]

Surgical excision

Warts may be removed surgically via shave excision, scissor excision, curettage, and/or electrocautery.[45-47] Clearance rates for surgical excision have been reported from 35% to 72% with recurrence in 19% to 29% of cases. The high recurrence rates may be attributed to the clinically inapparent surrounding tissue that continues to harbor the HPV virus. In randomized, controlled trials, electrocautery has demonstrated clearance rates as high as 94% by six weeks, but these were similar to cryotherapy over a 3-month period. Electocautery is usually performed in conjunction with curettage of the lesion in three different directions on the same plane (horizontally, vertically, and diagonally) in order to assure effective destruction of the growth. The advantage of surgical intervention is immediate results, especially in patients with large, obstructive or extensive condylomata. This approach also provides the benefit of histopathological assessment for lesions suspicious of malignancy. Disadvantages include bleeding, longer healing course, and pain. Electrocautery is effective for smaller warts located on the shaft of the penis, the rectum, or the vulva but is associated with permanent scar formation. Both surgical intervention and electrocautery are painful procedures requiring local

anesthesia or nerve blocks and rarely general anesthesia. Additionally, electrocautery adds the added risk of aerosolized virion particles putting the clinician at infectious risk for HPV-caused diseases such as recurrent respiratory papillomatosis. Clinicians, nursing staff, and the patient, should use protective equipment, including masks and smoke suction systems, to prevent particle transmission. Electrocautery also may be contraindicated in patients with cardiac pacemakers or other implanted devices due to the potential disruption of the electrical current, and specific cautery settings should be considered in those cases.

Mohs surgery has also been used more recently for anogenital warts, especially for biopsied areas that have demonstrated cytologic atypia. In Mohs surgery, skin is removed in very thin layers and subject to immediate microscopic analysis for pathology. Additional slices are taken until margins of healthy tissue free of viral features remain. The advantages of Mohs are maximal healthy skin preservation with minimal scar formation; however, it is expensive compared to other treatment modalities.

Laser therapy

Carbon dioxide (CO_2) laser has been a valuable tool as a destructive therapy for genital warts and other HPV infections that uses infrared light energy to vaporize targeted areas.[35,52,56,60] Because warts are vascular, this therapy provides instant coagulation to provide bloodless removal. The energy from the lasers is absorbed by the intracellular water but not by any proteins or nucleic acids. Efficacy of the laser has reported clearance rates ranging between 23% and 52% with recurrence rates as high as 77%. One study found a 67% overall cure rate after one intervention for male patients with extensive 'cauliflower-like' CA. HIV-negative patients responded better to treatment with a 71% cure rate versus 58% for HIV-positive patients. Finally, the study determined that endoanal location was a risk factor for recurrence with laser therapy.

Similar to electrocautery, CO_2 laser therapy may cause dispersal of HPV DNA during vaporization; however, studies have shown that contamination of the operator is unlikely provided that there is an appropriate vacuum ventilation system for evacuating HPV DNA-positive smoke. Surgical masks were found to be capable of removing virtually all laser- or electrocoagulation-derived virus.

One of the limitations of laser therapy is that it is rather expensive and not widely available. Side effects are generally mild and are limited to burning of tissue surrounding the lesion. Despite these limitations, this treatment should be strongly considered in immunosuppressed individuals as well as pregnant women with extensive lesions who are unresponsive to cryotherapy or TCA. Other lasers that have been evaluated to have success in eradicated CA and other HPV infections include holmium:YAG, erbium:YAG, and ND:YAG. One study has shown that the vapor plume from the erbium:YAG laser contained undetectable levels of HPV DNA, a significant safety feature of the laser.

The CO_2 laser in continuous or pulsed mode can be used as monotherapy or in combination with other modalities when indicated. The treatment with carbon dioxide laser and, in particular, fractional resurfacing lasers can achieve significant decrease of volume of CA and prepare the lesional skin for additional topical therapies like the application of imiquimod, 5-FU creams, or in more persistent lesions, cidofovir cream.

Photodynamic therapy

Topical aminolevulinic acid (ALA)-mediated photodynamic therapy (PDT) has demonstrated good clinical outcomes in the treatment of genital warts. PDT is a noninvasive therapy based on photosensitization and light-induced phototoxicity.[57-59,61-65] The mechanism of action involves applying the pro-drug ALA or its ester derivative to the area of concern where it is internalized by superficial cells and converted to the photosensitizing protoporphyrin IX. Activation of PDT occurs when PPIX is exposed to certain wavelengths of light, according to the photosensitizer's absorption spectrum. PDT results in "targeted phototoxicity," due to production of singlet oxygen and free radicals that can cause selective lesion destruction. Both topical and systemic PDT may trigger various immune reactions. A recent study demonstrates that ALA PDT can induce a favorable infiltration of immune cells (eg, $CD4^+$ T cells and dendritic cells) in condylomata lesions in various locations, which could be responsible for healing and long-term efficacy.

PDT specifically has been shown to be attractive for the lower female genital tract as the ALA can be topically applied directly to the cervix with minimal risk of causing incompetency as compared to direct surgical intervention. Additionally, no anesthesia is needed. One study containing 56 patients with cervical and external condylomata showed an overall complete remission rate of 98.2% after one to four sessions with a HPV clearance rate of 83.9%. Recurrence rate was 3.6%. The cervical lesions were treated with PDT by applying 10% ALA gel to the surface of the cervix for a 4-hour incubation. They were then irradiated with a 635 nm laser at 100 J cm^{-2} with follow-up every 2 weeks if the lesion and HPV infection remained. ALA PDT is associated with low recurrence rate possibly owing to the eradication of HPV infections. In addition, ALA-mediated photodiagnosis and PDT were also useful for subclinical and latent HPV infections. Adverse effects for this therapy include mild bloating in the lower abdomen during light irradiation, stinging pain, and vaginal discharge following cervical irradiation. Even presently not officially approved, PDT appears to be safe in pregnancy.

Systemic

Interferon

Interferons are small protein and glycoprotein cytokines produced by T cells, fibroblasts, and other cells

that bind to specific receptors on cell membranes in order to induce enzymes, suppress cell proliferation, inhibit viral proliferation, enhance the phagocytic activity of macrophages, and augment the cytotoxic activity of T lymphocytes.[32-34] Interferon has been widely used in the treatment of genital warts for its immunomodulatory, antiproliferative, and antiviral properties. It can be administered locally (intralesionally or topically) or systemically (oral medication or intramuscular injection). A meta-analysis comparing locally-used interferon to placebo showed a complete response rate of 44.4% as compared to 16.1%. The same meta-analysis compared systemically-used interferon to placebo and showed no difference (27.4% complete response rate compared to 26.4%). The recurrence rate of locally-used interferon as compared to placebo was not statistically significant (21.2% recurrence rate for interferon compared to 34.3% placebo recurrence rate).

Adverse effects include mild to moderate flu-like symptoms and depression. Application-site reactions, such as itching, burning, and pain, may occur with intralesional interferon. Additionally, some trials reported transient leukopenia and thrombocytopenia that normalized after the end of interferon treatment. Overall, interferon tends to be

Table 1 Current treatments used for genital warts and other HPV infections

Treatment type	Mechanism of action	Administration	Pregnancy safety	Clearance %	Recurrence %	Comments
Podophyllotoxin	Binds cellular microtubules	Patient	Podophyllotoxin unknown; Podophyllin contraindicated	45%-77%	38%	Cost-effective
Imiquimod	Binds TLRs to induce cell-mediated immune response	Patient	Unknown	5%: 40%-70%; 3.75%: 28%	5%: 9%-19%; 3.75%: 28%	Available in 5% and 3.75% cream.
Sinecathecins	Immunostimulatory through multiple pathways	Patient	Unknown	54%-65%	5.9%-12%	Higher complete clearance in women
Intralesional PPD	Intralesional antigen triggers immune response against HPV	Physician	Yes	47.5%	Unknown	Larger studies needed
Cidofovir	Nucleoside analog inhibits DNA polymerase	Patient		65%	Unknown	Larger studies needed
5-FU	Irreversible inhibition of thymidylate synthetase	Physician	No	10%-50%	50%	Not generally recommended
TCA	Chemically burns, cauterizes, and erodes mucosa	Physician	Yes			
Cryotherapy	Freeze-induced dermal and vascular damage	Physician	Yes	79%-88%	25%-40%	Entirely local therapy
Electrosurgery	Surgical excision and cautery	Physician	Yes			
Scissor Excision	Surgical removal	Physician	Yes			
Photodynamic therapy	ALA converted intracellularly to photosensitizing protoporphyrins	Physician	Yes			
Laser therapy	Infrared light energy vaporizes target areas	Physician	Yes			Carbon dioxide most often used; ideal for immunosuppressed
Mohs Surgery	Surgical removal	Physician	Yes			
Interferon	Immunomodulatory, antiproliferative, and antiviral therapy	Physician	No			
Isotretinoin	Gene-regulator via vitamin A derivative	Patient	No			

well-tolerated but should only be considered as a local treatment due to efficacy.

Isotretinoin

Oral isotretinoin has been used to treat CA due to its effects as a retinoid, immunomodulator, and affecter of epithelial differentiation and proliferation. Retinoids have also been shown to regulate HPV transcription down in affected cells and tissues. The effects are mainly mediated by 6 nuclear transcription factors that are known to regulate transcription of target genes. One study evaluated the efficacy of oral isotretinoin in males with refractory CA and reported a 39.6% clearance rate and a 9.5% recurrence rate. A separate double blind placebo controlled trial of refractory CA of the cervix found a similar clearance rate of 32.1% with 11.1% recurrence during a 12-month follow-up. Side effects are generally mild or moderate, reversible, and include cheilitis, mucosal dryness, retinoid dermatitis, epistaxis, conjunctivitis, desquamation, pruritus, elevation of triglycerides, and elevation of cholesterol. In conclusion, isotretinoin may be most effective as an adjunct when used for CA refractory to more commonly used modalities. Isotretinoin is contraindicated in pregnancy.

Conclusions

A spectrum of therapies for anogenital warts and HPV-related disease can be available in clinical practice. While there are potential molecular targets for HPV, no current antiviral therapy exists. Although monotherapies in repeated sessions can be effective, combination modalities can be more effective at treating CA and warts, especially in cases of refractory disease and in immunocompromised patients. These combination therapies provide advantage of several mechanisms of action to treat the virus and achieve debulking of the tumor simultaneously. Excision/destruction, and combination therapy with immunomodulators may provide better results than monotherapy alone. Treatment with imiquimod followed by excision of residual lesions has been reported with long-term clearance of anogenital warts in those patients for whom monotherapy was insufficient.[28] Data on combination therapies are limited regarding the efficacy or risk of complications. For example, combination therapy with podophyllin or imiquimod plus cryotherapy is practiced in some centers, although there is no evidence for increased effectiveness with this approach. Additionally, PDT when used in combination with CO_2, cryotherapy, or immunomodulatory therapy has been shown to be more effective than PDT alone; however, the optimal sequential order of combination modality can be tailored per individual patient needs and still needs to be determined in the future Table 1. Table 1 provides a summary of the treatments discussed.

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