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The Efficacy of Intralesional 5- Fluorouracil in Common Wart Treatment

Doaa Mohamed Lotfy Ali

Dermatology, Venereology & Andrology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Doaa Mohamed Lotfy Ali

Email: doaa.moh52@gmail.com,

Abstract:

Fluorouracil, commonly known as 5-fluorouracil or 5-FU, is an antimetabolite drug that has been widely used in systemic oncology and topical dermatological therapy. In dermatology, 5-FU has an important role in the management of several disorders characterized by abnormal or excessive epidermal proliferation, including actinic keratosis, superficial basal cell carcinoma, keratoacanthoma, keloids, and cutaneous warts. Its mechanism of action depends mainly on inhibition of thymidylate synthase, interference with DNA and RNA synthesis, and induction of cytotoxic effects in rapidly proliferating cells. Common warts are benign epidermal proliferations caused by human papillomavirus infection and may be resistant to conventional treatment modalities. Intralesional administration of 5-FU allows direct delivery of a high concentration of the drug into the wart tissue, thereby enhancing its local therapeutic effect while minimizing systemic exposure. Therefore, intralesional 5-FU represents a promising, cost-effective, and relatively safe therapeutic option for the treatment of common cutaneous warts.

Keywords: 5-Fluorouracil; Intralesional therapy; Common warts; Cutaneous warts; Human papillomavirus; Mini review.

Introduction:

Common warts are benign skin lesions caused by human papilloma virus (HPV) with a prevalence rate of 7–12% **(1).** In general, they are asymptomatic but, in some cases cause pain and discomfort, also they may cause psychological impact in patients because of their unsightly appearance especially if presented in face, hands or feet **(2).**

Fluorouracil, commonly known as 5-FU, is a chemotherapy drug utilized in the treatment of various neoplasms. The US Food and Drug Administration (FDA) has approved systemic fluorouracil for the treatment of gastric adenocarcinoma, pancreatic adenocarcinoma, breast adenocarcinoma, and colorectal adenocarcinoma **(3).** Furthermore, topical fluorouracil (5%) has received FDA approval for managing dermatologic conditions, specifically multiple actinic or solar keratoses and superficial basal cell carcinomas, in situations where other treatment modalities are not practical **(4).**

- **Structure and physical properties:**

Fluorouracil is a heterocyclic aromatic organic compound structurally similar to pyrimidine bases in DNA and RNA, distinguished by a fluorine atom replacing hydrogen at its C-5 position. Its unique structure allows it to disrupt nucleoside metabolism and integrate into RNA and DNA, leading to cytotoxicity and cell death **(5).**

➢ **Pharmacokinetic/Pharmacodynamics considerations:**

- **Intravenous formulation:**

Fluorouracil, a highly cytotoxic drug to rapidly growing cells, is broadly absorbed by all tissues after intravenous injection. However, due to this systemic toxicity, topical administration is the preferred method for treating dermatological conditions, allowing for localized action and minimizing widespread side effects **(6).**

- **Topical formulations:**

Topical 5-FU is available in creams and solutions with concentrations typically ranging from 0.5% to 5%. Standard treatment usually involves two daily applications. However, a controlled-release 0.5% microsphere formulation is designed for once-daily use, offering a more convenient application schedule **(6).**

Topical 5-FU is widely used for dermatological conditions characterized by excessive epidermal cell growth, while generally sparing normal skin. In the United States, it is a standard topical treatment for actinic keratosis (AK), which are precancerous lesions, and superficial basal cell carcinomas, especially when conventional therapies are not suitable **(6).**

- **Systemic absorption:**

While initial findings from 1965 suggested only 6% systemic absorption of topical 5-FU, later research indicates that absorption can be significantly higher (up to 75 times more) when applied to diseased skin compared to healthy skin. Despite this, the systemic absorption of topically administered 5-FU in humans remains underexplored **(7).**

- **Intralesional therapy:**

Only about 6% of topically applied 5-FU is absorbed systemically, an amount generally insufficient to cause harmful systemic effects. The absorbed drug is primarily metabolized into inactive waste products such as carbon dioxide, urea, and α-fluoro-β-alanine, with only a small fraction excreted unchanged in the urine**.** Intralesional 5-FU has proven to be a highly effective, safe, and cost-efficient option for treating warts **(8).**

➢ **Mechanism of Action:**

Upon entry into cells via facilitated transport, whether through ingestion or topical application, 5-FU is converted to fluorodeoxyuridine monophosphate (FdUMP). FdUMP then binds to and inhibits thymidylate synthase, an enzyme essential for producing deoxythymidine monophosphate (dTMP). The resulting dTMP depletion disrupts DNA replication and repair, leading to an imbalance in cellular nucleotides and, consequently, endonuclease-mediated double-stranded DNA breaks **(5).**

Beyond inhibiting thymidylate synthase, 5-FU also acts as a pyrimidine analog, getting mistakenly incorporated into RNA and DNA in place of uracil or thymine. This widespread disruption of nucleic acid synthesis and DNA repair pathways ultimately leads to the death of rapidly proliferating cells. Topical 5-FU selectively targets pathologic skin while leaving normal skin largely unaffected. This selectivity is thought to be due to a more profound inhibition of thymidylate synthase in the rapidly dividing cells, with only partial inhibition occurring in healthy skin **(6).**

In addition to its primary action of inhibiting thymidylate synthase and misincorporating into DNA, 5-FU also interferes with various aspects of RNA processing and can increase the expression of p53, a crucial tumor suppressor protein involved in cell cycle arrest and apoptosis. These additional mechanisms contribute to its overall cytotoxic effects on rapidly proliferating cells **(3).**

Fluorouracil's ability to increase p53 expression likely contributes to its effectiveness in treating dermatological conditions like actinic keratosis and squamous cell carcinoma, as these conditions often involve altered p53 pathways. This action may enhance the drug's selective cytotoxicity in diseased skin **(6).**

A primary resistance mechanism against 5-FU is the upregulation of dihydropyrimidine dehydrogenase (DPD) gene expression. DPD is the key enzyme responsible for degrading 5-FU, so increased DPD levels lead to rapid inactivation of the drug, reducing its effectiveness **(9).**

- **Uses of 5-FU:**

- **Non dermatological indication:**

Systemic 5-FU is approved for treating gastric, pancreatic, breast, and colorectal adenocarcinomas. It is also utilized off-label for treating various cancers beyond its approved indications, including anal carcinoma, advanced biliary tract carcinoma, cervical cancer, and esophageal cancer **(7).**

According to the American Society of Clinical Oncology (ASCO) guidelines, 5-FU is suggested for treating nasopharyngeal carcinoma, often as part of combination chemotherapy regimens, particularly in induction or adjuvant settings **(10).**

- **Dermatological indication:**

1- Keloid:

Fluorouracil inhibits the proliferation of fibroblasts and also suppresses the expression of the type I collagen gene in human fibroblasts when stimulated by transforming growth factor-β (TGF-β). This suggests a potential role for 5-FU in modifying fibrotic processes **(11).**

Intravenous 5-FU effectively treats keloids and hypertrophic scars, but intralesional combination therapy with triamcinolone acetonide (TAC) offers superior results. This synergy stems from 5-FU's direct inhibition of fibroblast proliferation and collagen production, complemented by TAC's anti-inflammatory and broader fibroblast-modulating effects, leading to enhanced scar reduction and improved patient outcomes with potentially fewer side effects **(12).**

2- Vitiligo:

In a case series involving 22 patients with 40 treatment-resistant vitiligo patches, a combination of dermabrasion (one to four sessions) and twice-daily topical 5% 5-FU for two weeks yielded positive results. Notably, 10 out of the 40 patches (25%) achieved greater than 75% repigmentation, suggesting that this combined approach can be an effective strategy for challenging vitiligo cases that have not responded to conventional treatments. This efficacy is likely due to dermabrasion creating micro-injuries that enhance 5-FU penetration, while 5-FU itself may stimulate melanocyte activity and migration **(13).**

3- Keratoacanthoma:

A retrospective case series demonstrated that twice-daily topical 5% 5-FU effectively achieved 100% complete clinical resolution of biopsy-proven keratoacanthomas within 4-6 weeks, supporting its anecdotal promise as a non-surgical treatment option by targeting the rapidly proliferating cells characteristic of these lesions **(14).**

While topical 5% 5-FU shows significant promise for keratoacanthomas, local side effects like erythema and irritation are common, leading two patients in the series to temporarily discontinue treatment. Importantly, even a rare variant, keratoacanthoma centrifugum marginatum, demonstrated complete and sustained clinical resolution for at least two years after four months of twice-daily 5% 5-FU, highlighting its potential for long-term efficacy even in challenging cases **(15).**

4- Psoriasis:

When 1% 5-FU is combined with a nail permeability enhancer cream containing urea and propylene glycol, patients with nail psoriasis have shown some improvement in their nail region severity scores. This suggests that the addition of these permeation enhancers is crucial for topical 5-FU to effectively penetrate the nail plate and reach the affected areas (nail bed and matrix), where it can exert its therapeutic effects on the psoriatic pathology, such as reducing subungual hyperkeratosis and oil spots **(6).**

5- Actinic keratosis (AK):

Topical 5-FU is a well-established and effective treatment for AK, with a 5% concentration applied twice daily for up to four weeks demonstrating significant long-term clinical clearance and reduced need for subsequent spot treatments compared to vehicle control. While higher concentrations achieve faster clearance, lower concentrations like 0.5% 5-FU cream, applied once daily, show comparable efficacy with significantly better tolerability and less irritation, leading to higher patient preference and reduced systemic absorption. Combining 5-FU with other therapies, such as tretinoin, salicylic acid, or cryotherapy, further enhances AK clearance rates, with pre- or post-cryosurgery application proving particularly beneficial **(3).**

6-Malignant melanoma:

A case series including 5 patients, evaluating topical 5% 5-FU and 5% imiquimod for 45 melanoma cutaneous metastases, suggests this dual therapy is a promising non-surgical approach for local disease control. This is attributed to 5-FU's direct targeting of rapidly dividing cancer cells by disrupting DNA/RNA synthesis, combined with imiquimod's activation of the local immune system, offering a synergistic, multi-pronged attack against melanoma **(16).**

7-Basal cell carcinoma:

Topical 5% 5-FU, applied twice daily for up to four weeks, demonstrates comparable clinical efficacy to both photodynamic therapy (PDT) and topical imiquimod in treating superficial BCC, with an approximately 80% clinical response rate.

While common side effects include local redness, itching, and erosion, serious adverse events are rare. Higher histopathologic clearance rates (around 90%) have been observed with longer treatment durations (up to 12 weeks). Case reports further illustrate 5-FU's effectiveness for larger or multifocal BCCs, even in challenging locations, with sustained clinical resolution **(3).**

8-Squamous cell carcinoma:

Combining topical 5% 5-FU and 5% imiquimod once daily offers an effective alternative for patients whose superficial skin cancers or precancers have not responded to monotherapy with either agent alone. This dual approach leverages 5-FU's direct cytotoxic action on rapidly proliferating cells and imiquimod's immune-modulating effects, creating a synergistic therapeutic strategy **(17).**

9-Darier's disease:

A retrospective case series suggests topical 1% 5-FU may be effective for therapy-resistant Darier's disease, showing promise in reducing hyperkeratosis and improving lesions, though initial efficacy might diminish and local irritation can occur **(3).**

10- Cutaneous warts:

Fluorouracil has been used to treat warts due to its anti-proliferative properties **(18).** 5-FU is effective against warts because it inhibits DNA and RNA synthesis in rapidly dividing cells, makes intralesional injections of the drug a useful treatment for viral warts caused by HPV. Injecting 5-FU directly into the wart allows for a higher concentration of the medication to reach all parts of the lesion **(19).**

11- Genital warts:

Treatment with 5-FU cream for lesions involves applying a thin layer one to three times weekly, leaving it on for 3 to 10 hours, and then washing it off with soap and water. This regimen can continue for several weeks. Studies indicate patient clearance rates between 41% and 68%, with recurrence rates up to 10%. Reported side effects include vaginal ulceration, moderate to severe itching, and a rare case of vaginal adenosis with clear cell cancer (**20).**

➢ **Side effects of 5-FU:**

- **Side effects of systemic 5-FU (as a chemotherapy):**

Commonly, over 30% of patients experience diarrhea, nausea, vomiting, photosensitivity, mouth sores, poor appetite, metallic taste, neutropenia, and thrombocytopenia. Less frequently, in about 10-20% of patients, side effects include skin discoloration, other dermatologic issues, alopecia, nail changes, and hand-foot syndrome. While rare, occurring in approximately 1% of patients, serious side effects like cardiac effects, hyperammonemia or encephalopathy, and other neurologic effects can occur **(21).**

- **Side Effects of topical 5-FU:**

Localized skin reactions to topical 5-FU can manifest in various ways, including itching, erythema, and scaling at the application site. Patients may also experience localized edema, general discomfort, pruritus, and changes in skin pigmentation, presenting as both hyper- and hypopigmentation. Additionally, allergic contact dermatitis and photosensitivity are among the possible localized dermatological responses **(22)**. Unusual reactions like Onychodystrophy, telangiectasias, and onycholysis may develop **(23).**

- **Side Effects of intralesional 5-FU:**

When 5-FU is administered intralesionally, patients commonly experience intense pain upon injection. Other localized side effects at the injection site can include skin sensitivity, ulceration, erythema, oedema, localized hyperpigmentation, and potentially scarring **(19).**

➢ **Contraindications of 5-FU:**

A crucial contraindication for 5-FU treatment is a documented deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD). DPD is responsible for metabolizing over 80% of 5-FU into inactive forms; therefore, a deficiency in this enzyme can lead to a significant buildup of the active drug in the body, resulting in severe, potentially life-threatening toxicity. This toxicity can manifest as severe myelosuppression, mucositis, diarrhea, and neurotoxicity, highlighting the critical role of DPD in 5-FU pharmacokinetics and the necessity of DPD status assessment before administration **(6).**

Fluorouracil is classified as a FDA pregnancy category D drug. Its use should generally be avoided during pregnancy due to the significant risk of teratogenicity. Both systemic and topical forms of 5-FU have been associated with adverse pregnancy outcomes, including an increased risk of miscarriage and birth defects such as ventricular septal defect **(24).**

Breastfeeding is also a contraindication for systemic 5-FU due to potential harm to the infant, though some studies suggest intermittent therapy might be safely performed with appropriate breaks. Also, it is not advised in hepatic and renal impairment **(7).**

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