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The Role of 5-Fluorouracil in Basal Cell Carcinoma: From Classic Use to Novel Approaches

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ABSTRACT

***Background*:** Basal cell carcinoma (BCC) is the most prevalent cutaneous malignancy worldwide, accounting for approximately 80% of all non-melanoma skin cancers. Although surgical excision remains the gold standard for most cases, non-invasive treatment modalities are increasingly sought due to their potential for improved cosmetic outcomes, patient convenience, and suitability in anatomically or functionally challenging sites. Among these options, 5-fluorouracil (5-FU), a pyrimidine analog and antimetabolite chemotherapeutic, has played a significant role in the topical management of BCC, particularly for superficial subtypes.

The pharmacological mechanism of 5-FU involves the inhibition of thymidylate synthase, resulting in disrupted DNA synthesis and apoptosis of rapidly proliferating tumor cells. Topical formulations of 5-FU have been employed for decades in dermatology, initially for actinic keratosis and later extended to superficial BCC, demonstrating efficacy and safety in appropriately selected cases. Over time, clinical trials and real-world evidence have solidified its role as a non-invasive treatment alternative in patients unsuitable for surgery or in cosmetically sensitive regions such as the face.

Recent years have witnessed renewed interest in 5-FU due to advancements in drug delivery systems and combination regimens. Novel formulations such as liposomal encapsulation, microneedle-assisted delivery, and nanoparticle-based carriers have been investigated to enhance dermal penetration, reduce systemic absorption, and improve therapeutic indices. Furthermore, combination approaches integrating 5-FU with imiquimod, photodynamic therapy, or laser-assisted drug delivery have shown synergistic effects, yielding higher clearance rates and reduced recurrence.

Despite its clinical benefits, challenges remain regarding local adverse reactions, patient adherence, and variable efficacy across BCC subtypes. Nodular and infiltrative forms respond poorly to monotherapy, highlighting the need for personalized therapeutic strategies. Current clinical guidelines recommend 5-FU primarily for superficial BCC, though its potential in multimodal treatment regimens is increasingly recognized.

This review aims to provide a comprehensive overview of the role of 5-FU in BCC management, tracing its evolution from classic topical use to innovative applications. Emphasis is placed on pharmacological mechanisms, historical and current evidence, novel delivery technologies, combination therapies, safety considerations, and future directions. Ultimately, the review underscores the enduring relevance of 5-FU as a cornerstone of topical oncologic dermatology while exploring its expanding horizons in precision medicine.

Keywords: 5-Fluorouracil , Basal Cell Carcinoma

INTRODUCTION

Basal cell carcinoma (BCC) represents the most common form of skin cancer, with an ever-increasing global incidence due to factors such as aging populations, ultraviolet (UV) radiation exposure, and improved surveillance strategies. While BCC is associated with low metastatic potential, its ability to cause local tissue destruction and recurrence makes it clinically significant. The burden of disease is particularly relevant in regions with high UV indices, where the incidence has risen sharply over the past decades. This trend underscores the need for effective, safe, and cosmetically favorable treatment modalities beyond traditional surgical approaches [1].

Conventional management of BCC includes surgical excision, Mohs micrographic surgery, and destructive techniques such as cryotherapy and electrodessication. Although these methods achieve high cure rates, they are not always ideal for all patients. Anatomical site restrictions, patient comorbidities, cosmetic considerations, and patient preference can limit surgical feasibility. In these contexts, non-invasive therapies, including topical treatments, photodynamic therapy, and systemic hedgehog pathway inhibitors, have gained importance. Among these, 5-fluorouracil (5-FU), an antimetabolite chemotherapeutic agent, occupies a unique position due to its longstanding use in dermatology and expanding evidence base in BCC treatment [2].

The role of 5-FU in dermatologic oncology began with its application in actinic keratosis, later extending to superficial BCC. Early studies demonstrated its potential to selectively target dysplastic keratinocytes while sparing normal tissue. However, despite decades of clinical use, 5-FU remains underutilized in BCC management compared to other topical agents such as imiquimod. This discrepancy stems partly from variability in response rates, particularly across histologic subtypes, and concerns about local irritation. Nonetheless, recent advances in drug delivery systems and combination regimens have revitalized interest in 5-FU as a cornerstone of non-invasive BCC therapy [3].

A significant research gap exists in understanding how best to integrate 5-FU into modern treatment paradigms. While guidelines acknowledge its utility in superficial BCC, the drug's broader role in multimodal therapy, especially in combination with novel technologies, is only beginning to emerge. Furthermore, predictors of response, optimal dosing regimens, and long-term outcomes require more rigorous investigation. Addressing these gaps is essential to refining patient selection, maximizing therapeutic benefit, and minimizing recurrence [4].

The aim of this review is to critically examine the role of 5-FU in BCC, from its classic application to innovative future directions. By exploring pharmacology, historical context, clinical efficacy, comparative data, novel formulations, and combination strategies, this article highlights both the enduring relevance and evolving potential of 5-FU in the management of BCC. Emphasis is placed on its integration into contemporary dermatologic oncology, with particular attention to challenges, limitations, and opportunities for advancing precision-based, patient-centered care [5].

Pharmacology of 5-Fluorouracil

5-fluorouracil (5-FU) is a pyrimidine analog that has been utilized in oncology for over six decades. Its primary mechanism of action is through inhibition of thymidylate synthase, an enzyme critical for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). This disruption in nucleotide synthesis leads to impaired DNA replication and repair, causing apoptosis in rapidly proliferating cells such as those found in tumors. Additionally, 5-FU is metabolized into fraudulent nucleotides that incorporate into RNA, further impairing cellular function and survival [6].

When administered topically, 5-FU exhibits a favorable pharmacokinetic profile for dermatologic use. Penetration occurs through the epidermis into the superficial dermis, where proliferating keratinocytes are targeted. Systemic absorption is generally minimal when applied to intact skin, making it a relatively safe option compared with systemic chemotherapy. However, absorption may increase when applied to ulcerated, inflamed, or large surface areas, warranting caution in vulnerable populations such as the elderly or those with renal impairment [7].

The topical formulations most widely used are 5% and 0.5% creams. The 5% formulation is generally preferred in the treatment of superficial basal cell carcinoma (sBCC), while lower concentrations are often employed in actinic keratoses to improve tolerability. The drug induces a characteristic inflammatory reaction, marked by erythema, scaling, erosion, and crusting, which reflects the destruction of dysplastic and malignant keratinocytes. This visible reaction serves as both a therapeutic marker and a challenge to patient adherence, as discomfort and cosmetic effects may limit treatment compliance [8].

Beyond conventional cream formulations, the pharmacological performance of 5-FU is being optimized through advanced delivery systems. Encapsulation in liposomes or nanoparticles has been shown to enhance penetration and prolong drug release, while microneedle-assisted administration allows for precise intradermal delivery. These innovations aim to overcome limitations of traditional topical therapy by improving efficacy, reducing irritation, and expanding indications to more aggressive BCC subtypes [9].

Furthermore, the interaction of 5-FU with tumor microenvironment dynamics has become an area of growing research interest. Studies suggest that 5-FU not only induces direct cytotoxicity but also modulates local immune responses, potentially enhancing antigen presentation and antitumor immunity. This dual mechanism underpins its potential synergy with immunomodulatory agents such as imiquimod, supporting its inclusion in combination regimens designed for more comprehensive BCC management [10].

Historical Use of 5-Fluorouracil in Basal Cell Carcinoma

The use of 5-fluorouracil (5-FU) in dermatology dates back to the 1960s, when topical formulations were first introduced for actinic keratoses and Bowen's disease. Its extension into basal cell carcinoma (BCC) was a natural progression, given its established efficacy in treating keratinocyte-derived neoplasms. Early observational studies demonstrated that 5-FU cream applied twice daily for several weeks could induce regression of superficial BCC, offering a non-invasive alternative to surgical procedures in selected cases. However, these initial results were heterogeneous, with variable clearance rates depending on lesion subtype and patient adherence [11].

In the 1970s and 1980s, randomized and non-randomized clinical trials explored the role of 5-FU in BCC management more systematically. These studies consistently showed higher efficacy in superficial BCC compared to nodular or infiltrative subtypes, which were less responsive due to deeper tumor extension beyond the reach of topical penetration. Typical clearance rates for superficial lesions ranged between 70–90% after 3–6 weeks of treatment, though recurrence rates were reported to be higher compared to surgical excision. Despite these limitations, 5-FU became recognized as a valuable therapeutic tool for patients with multiple superficial BCCs or those unfit for surgery [12].

The role of 5-FU was further refined in the 1990s as dermatologic oncology increasingly emphasized patient-centered care and cosmetic outcomes. Unlike destructive methods such as curettage or cryotherapy, topical 5-FU offered the advantage of tissue preservation and minimal scarring, making it particularly attractive for cosmetically sensitive areas like the face. In this era, case series and small clinical cohorts highlighted the drug's ability to provide excellent cosmetic results while maintaining reasonable oncologic control in carefully selected patients [13].

Another important historical development was the exploration of 5-FU as an adjunct to other therapies. As early as the late 1980s, clinicians investigated the sequential use of 5-FU with cryotherapy or surgical debulking to improve clearance rates. These early combination approaches laid the groundwork for later synergistic regimens involving 5-FU with photodynamic therapy or imiquimod, which remain active areas of research today. Thus, the historical use of 5-FU reflects not only its role as a stand-alone therapy but also as a forerunner of multimodal treatment strategies [14].

Importantly, the widespread adoption of 5-FU in BCC treatment has been geographically variable. In North America and parts of Europe, its use has been overshadowed by the increasing popularity of imiquimod and photodynamic therapy, both of which received stronger endorsement in clinical guidelines. However, in resource-limited settings, 5-FU remains a widely accessible, cost-effective treatment, demonstrating its enduring relevance across diverse health systems. Historical patterns of use therefore highlight the adaptability of 5-FU to varying clinical, economic, and patient-centered contexts, contributing to its ongoing legacy in dermatology [15].

Efficacy in Different BCC Subtypes

The therapeutic performance of 5-fluorouracil (5-FU) varies significantly across different histologic subtypes of basal cell carcinoma (BCC). Among these, **superficial BCC (sBCC)** has consistently shown the most favorable response. This subtype, characterized by multifocal nests of basaloid cells confined to the epidermis and upper dermis, allows 5-FU to penetrate sufficiently to exert its cytotoxic effects. Clinical trials and long-term follow-up studies have reported clearance rates ranging from 70–90% with topical 5-FU monotherapy, making it an effective option for small, well-defined superficial lesions. Recurrence rates are higher than those observed with surgical excision, but the cosmetic outcomes are excellent, particularly in

areas where scarring could cause functional or psychosocial impact [16].

In contrast, **nodular BCC (nBCC)** poses a greater challenge for 5-FU therapy. Nodular lesions extend deeper into the dermis and often form well-circumscribed tumor islands that are poorly accessible to topical agents. Studies evaluating the efficacy of 5-FU in nBCC have shown clearance rates significantly lower than those achieved in sBCC, often below 50%. For this reason, 5-FU is generally not recommended as monotherapy for nodular BCC. However, selected cases with thin or early nodular lesions may benefit from adjunctive approaches, such as curettage or laser-assisted delivery followed by 5-FU application, which can enhance penetration and cytotoxicity [17].

Infiltrative and morpheaform BCC, known for their aggressive behavior and subclinical extension, represent the least responsive subtypes to 5-FU. Their irregular and deep growth patterns make them unsuitable candidates for topical therapy alone. Available data show poor clearance rates and high recurrence, rendering 5-FU inappropriate as a stand-alone treatment for these variants. Nevertheless, ongoing research into novel delivery systems—such as microneedle patches and nanoparticle formulations—aims to extend the reach of 5-FU into deeper dermal layers. Although promising, these approaches remain largely experimental and require validation through larger clinical trials before being incorporated into routine practice [18].

Another clinical scenario of interest is **multiple BCCs in patients with genetic syndromes** such as basal cell nevus syndrome (Gorlin syndrome). In these patients, surgery is often impractical due to the sheer number of lesions and the cumulative cosmetic burden. Several case reports and small series have described the use of topical 5-FU as a field therapy, targeting both clinically apparent and subclinical superficial BCCs. While efficacy is variable, the drug offers a non-invasive means to manage tumor burden and delay surgical intervention, highlighting its utility in highly selected, difficult-to-treat populations [19].

Finally, the **cosmetic outcome** associated with 5-FU use is a consistent advantage across BCC subtypes. Even in cases where complete clearance is not achieved, residual tumors often present with reduced size and less aggressive histology, potentially simplifying subsequent surgical excision. This debulking effect has been particularly relevant in recurrent or multifocal superficial BCCs, where cosmetic preservation is paramount. These observations emphasize that the role of 5-FU should not be viewed solely in terms of tumor eradication but also in terms of functional and aesthetic contributions to comprehensive patient care [20].

Comparison with Other Topical Therapies

Topical therapies have gained prominence in the management of superficial basal cell carcinoma (sBCC), particularly for patients unsuitable for surgery or those seeking non-invasive alternatives. Among these, **imiquimod** has emerged as the most widely studied and clinically adopted alternative to 5-fluorouracil (5-FU). Imiquimod acts as an immune response modifier, stimulating Toll-like receptor 7 and promoting interferon-alpha release, thereby inducing a local antitumor immune response. Randomized controlled trials have demonstrated superior long-term clearance rates with imiquimod compared to 5-FU, often exceeding 80% at 5 years. However, imiquimod is associated with more intense local inflammatory reactions, prolonged treatment regimens, and higher costs, which can affect patient adherence and accessibility [21].

Photodynamic therapy (PDT) represents another established non-invasive option for sBCC. PDT combines a topical photosensitizer, usually 5-aminolevulinic acid (ALA) or methyl-aminolevulinate (MAL), with illumination by a specific wavelength of light to generate reactive oxygen species that destroy tumor cells. PDT is particularly advantageous in treating multiple or large superficial lesions due to its ability to target broader fields of cancerization. Comparative studies have shown that PDT achieves similar or slightly higher clearance rates than 5-FU but with better cosmetic outcomes. However, its disadvantages include the need for specialized equipment, high procedural costs, and the pain experienced during illumination, which can limit patient acceptance [22].

Another agent occasionally compared with 5-FU is **diclofenac in hyaluronic acid gel**, primarily approved for actinic keratosis. Diclofenac exerts its effect by inhibiting cyclooxygenase and reducing prostaglandin-mediated tumor promotion. Although some case series have suggested modest activity against sBCC, its efficacy is markedly lower than that of 5-FU or imiquimod. As such, diclofenac is not recommended as a primary therapy for BCC but may have a niche role in patients unable to tolerate stronger topical agents. Its favorable tolerability and minimal local irritation, however, remain attractive in frail or elderly populations [23].

Ingenol mebutate, derived from *Euphorbia peplus*, has also been investigated for non-melanoma skin cancers, including BCC.

While initial enthusiasm was high due to its rapid treatment course, subsequent studies failed to demonstrate consistent efficacy in BCC management. Safety concerns, including severe inflammatory reactions and potential carcinogenicity signals, have led to the withdrawal of ingenol mebutate from many markets. Its comparison with 5-FU therefore remains largely historical, underscoring the superior long-term evidence and safety profile of 5-FU as a cornerstone topical therapy [24].

In summary, while imiquimod and PDT generally outperform 5-FU in long-term clearance and recurrence prevention, 5-FU remains a valuable option due to its accessibility, lower cost, and ease of use. Moreover, the choice between topical agents must consider not only oncologic outcomes but also cosmetic results, treatment tolerability, patient comorbidities, and socioeconomic factors. The availability of multiple topical therapies allows for personalized treatment planning, where 5-FU often serves as a pragmatic and effective solution, particularly in resource-constrained settings [25].

Novel Formulations and Delivery Systems

Advances in **nanotechnology and lipid-based carriers** are reshaping how 5-fluorouracil (5-FU) is delivered into tumor-bearing skin. Liposomes, ethosomes, solid-lipid nanoparticles, and nanoemulsions can enhance partitioning into the stratum corneum, prolong residence time in the viable epidermis, and reduce peak surface concentrations that drive irritation. In preclinical and early clinical studies, nanoencapsulation has improved percutaneous flux and tumor uptake while maintaining low systemic exposure—an attractive profile for treating multifocal superficial BCC (sBCC) across large fields of cancerization. These platforms also permit co-loading with penetration enhancers or anti-inflammatory excipients to balance efficacy and tolerability, a key barrier to adherence with conventional 5% cream regimens [26].

Laser-assisted drug delivery (LADD)—typically using ablative fractional lasers (AFLs) such as fractional CO_2 or erbium:YAG—creates controllable microthermal channels that bypass the stratum corneum and deposit 5-FU directly into the upper dermis. Small trials and case series in keratinocyte carcinomas report higher histologic clearance and faster clinical response versus cream alone, with acceptable healing and excellent cosmesis. LADD can be titrated (density, energy, number of passes) to lesion thickness, enabling a "dose-to-depth" strategy that is conceptually well-suited to thin nodular or mixed sBCC/nodular lesions that are otherwise suboptimal for topical monotherapy [27].

Microneedle technologies—**solid, coated, hollow, and dissolving microneedles**—offer another minimally invasive route to intradermal 5-FU delivery. By creating uniform microchannels (typically 200–700 μm), microneedles enhance deposition into the viable epidermis and superficial dermis without significant pain or downtime. Early dermatologic oncology studies demonstrate improved pharmacodynamic effects (erythema/erosion as a surrogate of cytotoxicity) at lower total doses, suggesting a path to shorten treatment courses and mitigate irritant dermatitis. Emerging "smart" patches combine dissolvable microneedles with sustained-release matrices, enabling once-weekly or biweekly administration while maintaining cytotoxic exposure [28].

Adjunctive **physical enhancement methods**—including iontophoresis, sonophoresis (low-frequency ultrasound), and occlusion with hydrocolloid dressings—have been explored to drive 5-FU across the skin barrier. Iontophoresis uses a mild electric current to increase transappendageal transport, while sonophoresis transiently disrupts lipid bilayers, both improving flux without ablating tissue. When paired with lower 5-FU concentrations (e.g., 0.5–1%), these techniques can produce comparable clinical responses to 5% cream but with reduced inflammation, which may be useful on cosmetically sensitive facial sites or in patients with adherence-limiting irritation [29].

Beyond topical paradigms, **intralesional 5-FU** has re-emerged for select keratinocyte cancers, including difficult BCCs in poor surgical candidates. Injecting small aliquots (e.g., weekly or biweekly) directly into tumor nodules can achieve high local drug levels with minimal systemic exposure. Reports describe meaningful tumor shrinkage and, in some cases, complete responses of low-risk nodular lesions, especially when combined with curettage or fractional laser pretreatment. Although evidence remains limited and operator-dependent, intralesional therapy exemplifies a pragmatic, resource-sensitive option where surgery or radiotherapy are contraindicated or declined [30].

Adjuvant and Combination Approaches

Ablative fractional laser–assisted delivery (LADD) of 5-FU leverages microthermal channels to bypass the stratum corneum and place drug into the viable epidermis/superficial dermis, improving penetration and potentially "rescuing" borderline-thick lesions that are suboptimal for cream alone. Prospective series in keratinocyte carcinomas—including superficial BCC (sBCC)—

report encouraging histologic clearance with acceptable downtime, and clinician-administered protocols can help adherence-limited patients. Parameter titration (density/energy/passes) enables a dose-to-depth strategy and is often paired with short, supervised treatment courses, supporting LADD-5-FU as a pragmatic option when surgery is declined or impractical. [27, 22, 8]

Photodynamic therapy (PDT) combined with 5-FU has two principal rationales: (i) pretreating with 5-FU to debulk dysplastic epithelium and increase protoporphyrin IX formation/uptake; and (ii) using PDT to eradicate residual tumor foci after 5-FU. Intra-individual randomized data show that 5-FU pretreatment enhances aminolevulinate/MAL-PDT efficacy (demonstrated robustly in actinic keratoses and extrapolated to sBCC), while systematic reviews of PDT combinations highlight mechanistic synergy and improved field control. In practice, clinicians use short 5-FU "priming" (e.g., 3–7 days) before MAL-PDT to boost response, particularly for broad, multifocal sBCC fields where single-modality therapy underperforms. [21, 7]

Immunochemotherapy with imiquimod plus 5-FU targets BCC via complementary mechanisms—cytotoxic antimetabolite plus TLR7-driven antitumor immunity. Small studies and case series (including teledermatology-guided regimens) suggest higher clinical clearance and regression of nearby untreated nodules when agents are layered or alternated, especially when combined with local destructive steps (e.g., curettage/cryotherapy) to reduce bulk and expose tumor nests. While 5-year randomized data identify imiquimod monotherapy as superior to either PDT or 5-FU alone for sBCC, real-world "blend" protocols may help patients who cannot complete longer imiquimod courses or who need accelerated field control. [11, 25, 21]

Multimodal bundles—such as cryotherapy followed by short-course imiquimod and/or 5-FU, with or without topical retinoids—are increasingly reported for locally advanced or multiply recurrent BCC in nonsurgical candidates. Recent prospective/retrospective reports describe meaningful downsizing and, in select cases, complete responses of large facial or periocular tumors, alongside regression of adjacent nodules ("field effect"), albeit with significant local inflammation that requires counseling and supportive care. Such bundles are heterogeneous and operator-dependent but illustrate a cost-sensitive pathway when radiotherapy, Mohs surgery, or hedgehog inhibitors are not feasible. [31, 32]

AFL-facilitated intralesional or combination cytotoxics broaden the toolkit for challenging lesions. In a cohort study, double sessions of AFL-assisted **cisplatin + 5-FU** achieved acceptable clearance in low-risk sBCC, whereas single sessions and nodular BCC fared worse—useful nuance when considering intensified office-based regimens for multifocal disease or patients unable to self-apply creams reliably. These data reinforce that depth and histologic subtype remain the key determinants of success for any topical/intradermal strategy. [33]

Field-directed immuno-synergy with calcipotriol + 5-FU, which induces tissue-resident memory T cells in actinic fields, has reduced subsequent keratinocyte carcinoma formation and is being explored as a way to lower future BCC burden in high-risk patients (e.g., severe photodamage, Gorlin syndrome). Although most evidence centers on AKs (and SCCis), early translational/clinical signals justify cautious extrapolation for preventive field therapy around superficial BCCs after lesion-directed treatment, pending BCC-specific trials. [34, 35, 36]

Tailoring combinations to patient priorities is essential: for cosmetically sensitive sites, short 5-FU "priming" plus PDT may balance efficacy and cosmesis; for adherence challenges, clinic-based LADD-5-FU or brief bundled protocols (cryotherapy → imiquimod/5-FU) can compress timelines; and for syndromic/multifocal disease, iterative field therapy (including salicylic-acid–facilitated keratolysis) may reduce surgical load over time. Across strategies, transparent counseling about expected inflammation, downtime, analgesia, and the likelihood of staged treatments improves satisfaction and real-world effectiveness. [27, 7, 37]

Safety, Tolerability, and Cosmetic Outcomes

Topical 5-fluorouracil (5-FU) produces a predictable **local inflammatory cascade**—erythema, edema, burning, erosions, crusting, and post-treatment desquamation—that correlates with cytotoxic engagement of dysplastic keratinocytes. Although these reactions reassure clinicians that pharmacodynamic activity is underway, they can be **intense and prolonged** when treating broad fields or cosmetically sensitive sites. Secondary impetiginization and eczematization occur infrequently but necessitate brief pauses, topical antibiotics, or low-potency corticosteroids. Patient counseling that inflammation **peaks during weeks 2–4** and gradually resolves after cessation is central to maintaining adherence and avoiding premature discontinuation. Patch testing is rarely required; true allergic contact dermatitis to 5-FU itself is uncommon compared with irritant reactions to vehicles or concomitant agents. [38–41]

Systemic safety of topical 5-FU is favorable due to low percutaneous absorption through intact skin; nevertheless, caution is warranted when treating **ulcerated lesions, large surface areas, or compromised barriers**, where absorption increases. Rare case reports describe systemic symptoms (e.g., mucositis, cytopenias) in settings of extensive application or **dihydropyrimidine dehydrogenase (DPD) deficiency**, the key enzyme for 5-FU catabolism. Although routine DPD testing is not recommended for topical therapy, clinicians should inquire about prior severe reactions to systemic 5-FU/capecitabine. Use during pregnancy and lactation is generally **contraindicated**, and occlusive dressings that might augment absorption should be avoided unless deliberately employed with close supervision. [42–45]

From a **cosmetic standpoint**, 5-FU is associated with excellent post-inflammatory remodeling and **minimal scarring** compared with destructive modalities and surgery, particularly for **superficial BCC (sBCC)** on the face. Randomized comparisons and long-term follow-up cohorts consistently report superior or non-inferior **global cosmetic ratings** versus photodynamic therapy (PDT) and favorable outcomes relative to imiquimod when inflammation is properly managed. Transient **post-inflammatory dyspigmentation** is common in darker phototypes and can be mitigated by photoprotection and short courses of topical steroids or calcineurin inhibitors during the resolution phase. Importantly, even when definitive clearance is not achieved, partial responses may **debulk** lesions and simplify subsequent tissue-sparing surgery. [16,25,46–48]

Adherence and quality-of-life considerations are pivotal because local reactions can impair sleep, work, and social interactions. Practical tactics include **pulse regimens** (e.g., 1–2× daily, 5 days on/2 off), **short-contact protocols** (rinse after 2–4 hours in sensitive areas), and early co-prescription of bland emollients plus **low-potency topical corticosteroids** once brisk inflammation begins. Clear, illustrated action plans; scheduled check-ins (including teledermatology); and analgesia/antipruritic support improve completion rates. Education should emphasize **sun avoidance**, gentle cleansing, and the expectation that **clinical worsening precedes improvement**, which reduces unplanned cessation and unnecessary emergency visits. [2,7,49–51]

Special populations merit tailored precautions. In **immunosuppressed patients** (e.g., solid-organ transplant recipients), topical 5-FU remains useful for sBCC field control but may show **lower clearance and higher recurrence**, necessitating closer histologic confirmation and maintenance strategies. **Periocular or periorificial BCCs** can be treated selectively with 5-FU under ophthalmologic/dermatologic co-management, but risks of conjunctival irritation and ectropion-like symptoms require meticulous application and frequent review. In **frail older adults** or those with polypharmacy, short supervised courses (e.g., laser-assisted delivery or clinic-applied regimens) can minimize caregiver burden while preserving cosmesis. Documentation of **phototype, barrier status, and comorbidities** helps anticipate tolerability and personalize supportive care. [52–55]

Conclusion

5-fluorouracil (5-FU) has evolved from a classic topical chemotherapeutic agent into a versatile component of modern basal cell carcinoma (BCC) management. Its role is most firmly established in superficial BCC, where it offers a non-invasive, cost-effective, and cosmetically favorable alternative to surgery, particularly in patients with contraindications to excision or in cosmetically sensitive sites. While less effective for nodular and infiltrative variants, advances in drug delivery systems, laser-assisted methods, and intralesional applications are expanding its therapeutic boundaries.

When compared with other topical and non-invasive modalities such as imiquimod and photodynamic therapy, 5-FU remains a valuable option—often less potent but more accessible and pragmatic, especially in resource-limited settings. Its utility is further enhanced in combination approaches, where synergistic effects with immunomodulators, physical delivery systems, and photodynamic methods significantly improve outcomes. These strategies highlight the adaptability of 5-FU across different clinical scenarios, ranging from field-directed therapy in high-risk patients to adjunctive roles in multimodal regimens.

Despite its benefits, limitations persist. Patient adherence is often challenged by intense local inflammatory reactions, and long-term recurrence rates remain higher than with surgical treatments. Nonetheless, favorable cosmetic outcomes, low systemic toxicity, and ongoing innovations in delivery technologies maintain 5-FU's relevance. Its ability to preserve tissue integrity while addressing oncologic goals reflects a broader paradigm shift in dermatologic oncology toward patient-centered and cosmetically conscious care.

Looking forward, integration of 5-FU into personalized treatment pathways—guided by histological subtype, tumor depth, patient comorbidities, and lifestyle preferences—will optimize its value. As new formulations, immuno-synergistic regimens, and predictive biomarkers emerge, 5-FU is poised to remain a cornerstone of non-invasive BCC therapy. Its enduring role exemplifies how established agents can be continuously repurposed and refined to meet evolving clinical needs in the era of

precision dermatology.

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