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Synergistic Mechanisms of 5-Fluorouracil and Imiquimod in the Treatment of Actinic Keratoses

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INTRODUCTION

Actinic keratoses (AK) are common precancerous lesions characterized by rough, scaly patches resulting from chronic sun exposure. With the potential to progress to squamous cell carcinoma, effective treatment of AKs is crucial. Topical chemotherapies have been a mainstay of AK treatment, particularly in patients with field cancerization. While most of these topical treatments are used as monotherapies, various combination therapies have been established to enhance treatment efficacy and minimize recurrence.[1,2] The combination of 5-fluorouracil (5-FU) with calcipotriol or salicylic acid has shown promise in enhancing therapeutic outcomes. 5-FU's cytotoxic effects are complemented by the immunomodulatory properties of calcipotriol, while salicylic acid aids in deeper penetration of 5-FU, further boosting its efficacy.[2]

To date, the combination of 5-FU and imiquimod, 2 of the most used monotherapies, remains underexplored. In addition to a study published by these authors, a comprehensive literature search on the topic reveals only 2 additional studies employing the use of these creams in combination, all of which suggest dual therapy with 5-FU and imiquimod may be more effective in treatment of AKs than with either therapy alone.[2,3] This implies their distinct mechanisms of action may have synergistic effects.

5-FU acts by inhibiting thymidylate synthase, which is essential for DNA replication and repair. This inhibition causes DNA damage, cell cycle arrest, and apoptosis of cancer cells. Additionally, 5-FU incorporation into RNA and DNA interferes with nucleic acid biosynthesis and function.[4] Imiquimod has pleiotropic effects on the immune system. Stimulation of toll-like receptors 7 and 8 activates nuclear factor kappa B (NF-κB) and results in production of pro-inflammatory cytokines (interferon-alpha (IFN-α), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12)), while adenosine receptor signaling results in impaired suppression. Imiquimod also promotes the maturation and activation of antigen-presenting (dendritic) cells, induces apoptosis in tumor cells, and enhances the cytotoxic activity of natural killer (NK) and cytotoxic T cells.[5]

The synergistic effects of these drugs likely stem from their complementary actions on precancerous cells and the immune system. The DNA damage induced by 5-FU results in apoptosis and necrosis, enhancing the immunogenicity of damaged cells. By amplification of the immune response, imiquimod promotes clearance of damaged cells. Moreover, imiquimod-induced cell death and enhancement of NK cell cytotoxicity may complement the cytotoxic effects of 5-FU, promoting cell death. Finally, the disruption of the skin barrier caused by 5-FU may increase the penetrance and bioavailability of imiquimod, potentiating a more robust immune response against cancer cells.

Overall, the combination of 5-FU and imiquimod holds significant promise as a synergistic therapy for AK/field cancerization therapy by simultaneously maximizing the number of pathways for cell death and harnessing the power of the immune system for cellular clearance.

DISCLOSURES

The authors have no conflicts to disclose.

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