Before OR After: Is There a Connection Between the Use of Adjunctive Nonmelanoma Skin Cancer Treatments and Subsequent Invasive Tumors?

Emily Stamell Ruiz MD,[a] Joel L. Cohen MD,[b,c] and Adam Friedman MD[d]

[a]Department of Dermatology, Brigham & Women's Hospital, Boston, MA
[b]AboutSkin Dermatology and DermSurgery, Englewood, CO
[c]Department of Dermatology, University of Colorado, Denver, CO
[d]Division of Dermatology, Department of Medicine, and Department of Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY

Although the therapeutic gold standard for basal cell carcinomas (BCCs) is surgical excision, imiquimod, fluorouracil cream, and photodynamic therapy are frequently used. All 3 modalities have been shown to be efficacious for the treatment of superficial BCCs as well as other nonmelanoma skin cancers; however, recent reports have emerged implicating these agents in causing more aggressive recurrent subtypes of BCCs. Here we review this literature as well as offer an alternative explanation for these tumors.

Basal cell carcinomas (BCCs) account for 80% of nonmelanoma skin cancers (NMSC) in the United States.[1] Although surgical excision remains the treatment gold standard, less invasive modalities are increasingly being employed.[2] Imiquimod, fluorouracil cream, and photodynamic therapy (PDT) are 3 such treatments that are widely used. Recently, reports emerged implicating each of these modalities in causing more aggressive recurrent subtypes of BCCs.[2-4] Yet an alternative plausible explanation relates to the concept that the BCCs were "lying beneath."[5] Here we review the mechanism and indications for PDT, imiquimod, and topical fluorouracil, discuss the recent literature implicating these agents in causing aggressive BCCs, and elaborate on the concept that the BCCs were "lying beneath."

Photodynamic Therapy

PDT consists of application of a photosensitizing agent followed by its photoactivation by light. This process generates singlet oxygen within biologic tissues, which induces cellular destruction.[6] There are 2 different photosensitizers: 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). ALA is approved by the U.S. Federal Drug Administration (FDA), Canada, Korea, and several Latin American countries for minimally to moderately thick actinic keratoses (AKs) of the face or scalp. MAL is approved for the treatment of AKs and BCCs in over 30 countries and is a recognized treatment option for Bowen's disease in 22 European countries.

The application of either photosensitizer leads to conversion by the neoplastic tissue to photoactive porphyrins, which upon exposure to a light source causes direct cytotoxicity. A 417 nm blue light is used for ALA and a 635 nm red light is used for MAL.[7] PDT does have the ability to cause selective tumor destruction—in addition to confining drug application to the area of the tumor, there is inherent difference in the permeability barrier and accumulation of porphyrins in the neoplastic cells and normal skin.[6] PDT has been shown to be efficacious in the treatment of AKs, Bowen's disease, superficial BCC, and nodular BCC.[7] Sustained clearance at 12 months ranges from 50.7%[8] to 72.8%.[9] However, Fiechter et al[2] retrospectively identified 12 patients with 16 post-PDT recurrent BCCs and compared the histologic features pre-PDT and post-PDT. The authors found that 62.5% of recurrent BCCs transitioned from a non-aggressive to aggressive subtype. From this data, they concluded that PDT may favor selection of more aggressive tumor cells.

Imiquimod

Imiquimod 5%, an imidazoquinolone, is an immunostimulating agent that binds to toll-like receptor (TLR)-7 andTLR-8, activating nuclear factor-κB and inducing proinflammatory cytokines resulting in a T helper type 1 (TH1) immune response.[10] Imiquimod is FDA-approved for the treatment of AKs, external genital warts, and non-head or neck superficial BCCs.[9] Sustained clearance at 12 months ranges from 83.4%[9] to 92%.[11] Skaria reviewed his patients treated with Mohs surgery since 2012 and identified 8 who had previously been treated with imiquimod therapy.[4] Although only 5 had been biopsied before imiquimod, he noted that 7 out of 8 of the patients had increase in the "aggressivity in their tumor". Similar to Fiechter et al,[2] this author raised concerns that imiquimod may select more aggressive tumor cells.

> "More aggressive tumor subtypes may be deeper than clinically apparent, making treatment beyond reach."

Fluorouracil

Fluorouracil is a structural analog of thymine and irreversibly inhibits the enzyme thymidylate synthase, arresting protein synthesis and ultimately leading to cell death. Although fluorouracil does not specifically target tumor cells, the effects are more pronounced in rapidly proliferating cells.[10] There are 4 strengths of topical fluorouracil: Efudex® (5% and 2%

fluorouracil cream), Fluoroplex® (1% fluorouracil cream), and Carac® (0.5% fluorouracil cream). Topical fluorouracil is FDA-approved for the treatment of AKs (Efudex, Carac, and Fluoroplex) and superficial BCCs (Efudex). Sustained clearance at 12 months ranges from 33%[12] to 81.1%.[9] Although not FDA-approved for the treatment of squamous cell carcinoma *in situ*, 5% fluoruracil cream has been shown to be efficacious.[13,14] However, despite approval since the 1970's, the Veterans Affairs Topical Tretinoin Chemoprevention trial noted that prior treatment with topical fluorouracil was associated with a higher risk of development of morpheaform BCCs. These authors concede that fluorouracil may have destroyed superficial cancer cells while leaving deeper pockets untouched. However, they open the door to a causal relationship between therapy and these tumors by stating that "fluorouracil treatment may predispose to development of morpheaform BCC."[3]

As presented above, these 3 recent reports suggest that the topical therapies may be associated with future development of histologically more aggressive BCCs. However, it is important to recognize that each modality is only indicated for the treatment of superficial neoplastic tumors. More aggressive tumor subtypes may be deeper than clinically apparent, making treatment beyond reach. This concept was clearly illustrated in a case series by Sambandan and Goldman[5] in which they presented 8 patients initially treated for AKs who failed to improve with destructive modalities. Upon biopsy the lesions were noted to have underlying BCCs. Although there is a possibility that the BCC developed in response to the destructive modality, it is more likely that the tumor was always present but not clinically apparent.

In this context, it is important to recognize that the findings of histologically aggressive tumors in these 3 studies may be due to their lack of response to the PDT, imiquimod, or fluoruracil, and not to the therapy itself. Furthermore, the 3 studies provide weak evidence supporting their causal relationship in causing aggressive skin cancers. These therapeutics play an important role in the treatment of NMSC, but they do have their limitations. In addition to thorough clinical examinations, other imaging modalities such as high-frequency ultrasound may be useful in identifying deeper tumors.[15] Close clinical follow up after topical field therapy is prudent in order to not miss deeper, aggressive tumors.

Disclosures

Dr. Cohen has served as a consultant for Valeant and DUSA.

References

1. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146(3):283-287.
2. Fiechter S, Skaria A, Nievergelt H, Anex R, Borradori L, Parmentier L. Facial basal cell carcinomas recurring after photodynamic therapy: a retrospective analysis of histological subtypes. *Dermatology.* 2012;224(4):346-351.
3. Xiong MY, Korgavkar K, Digiovanna JJ, Weinstock MA; Veterans Affairs Topical Tretinoin Chemoprevention Trial Group. Fluorouracil and other predictors of morpheaform basal cell carcinoma among high-risk patients: the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *JAMA Dermatol.* 2014;150(3):332-334.
4. Skaria AM. Facial basal cell carcinomas recurring after imiquimod therapy. *Dermatology.* 2013;226(1):13-14.
5. Sambandan PG, Goldman GD. Infiltrative basal cell carcinomas presenting as actinic keratosis: implications for clinical practice. *Dermatol Surg.* 2008;34(1):9-13.
6. De Rosa FS, Bentley MV. Photodynamic therapy of skin cancers: sensitizers, clinical studies and future directives. *Pharm Res.* 2000;17(12):1447-1455.
7. Braathen LR, Szeimies RM, Basset-Seguin N, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. *J Am Acad Dermatol.* 2007;56(1):125-143.
8. Ko DY, Kim KH, Song KH. Comparative study of photodynamic therapy with topical methyl aminolevulinate versus 5-aminolevulinic acid for facial actinic keratosis with long-term follow-up. *Ann Dermatol.* 2014;26(3):321-331.
9. Lecluse LL, Spuls PI. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial: a critical appraisal. *Br J Dermatol.* 2015;172(1):8-10.
10. Desai T, Chen CL, Desai A, Kirby W. Basic pharmacology of topical imiquimod, 5-fluorouracil, and diclofenac for the dermatologic surgeon. *Dermatol Surg.* 2012;38(1):97-103.
11. Stockfleth E, Christophers E, Benninghoff B, Sterry W. Low incidence of new actinic keratoses after topical 5% imiquimod cream treatment: a long-term follow-up study. *Arch Dermatol.* 2004;140(12):1542.
12. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol.* 2007;157(suppl 2):s34-s40.
13. Welch ML, Grabski WJ, McCollough ML, et al. 5-fluorouracil iontophoretic therapy for Bowen's disease. *J Am Acad Dermatol.* 1997;36(6 pt 1):956-958.
14. McGillis ST, Fein H. Topical treatment strategies for non-melanoma skin cancer and precursor lesions. *Semin Cutan Med Surg.* 2004;23(3):174-183.
15. Desai TD, Desai AD, Horowitz DC, Kartono F, Wahl T. The use of high-frequency ultrasound in the evaluation of superficial and nodular basal cell carcinomas. *Dermatol Surg.* 2007;33(10):1220-1227.

AUTHOR CORRESPONDENCE

Adam Friedman MD FAAD

E-mail:..... adfriedm@montefiore.org