## ABOUT THE AUTHOR

**Toni Burbidge, MD**

Dr. Toni Burbidge is a is a dermatologist based in Calgary, Alberta where she practices medical and surgical dermatology. She is board-certified in both Canada and the United States. She completed her medical degree at the University of Toronto, and dermatology residency at the University of Calgary. She has a special interest in cutaneous oncology and is involved in melanoma research with the multi-disciplinary Cutaneous Oncology team at the Tom Baker Cancer Centre in Calgary. She also teaches medical residents and other learners in her affiliation with the University of Calgary as a clinical lecturer.

**Affiliations:** Skin Health and Wellness Centre, Calgary, AB
Cumming School of Medicine, University of Calgary, Calgary, AB

# TREATMENT OF FIELD CANCERIZATION: BEYOND TOPICAL AGENTS

## Introduction

Field cancerization (FC) is defined at the cellular level as the growth of a mutant clone that creates a field of cells predisposed to subsequent tumour growth.[1] Cutaneous FC is a phenomenon that occurs in areas of the skin exposed to chronic ultraviolet radiation (UVR), including the face, balding scalp, forearms, and dorsal hands.[2] This then leads to fields of clonal proliferations of p53-mutated keratinocytes and is characterized by multifocal actinic keratoses (AK), squamous cell carcinomas in situ (SCCis), and cutaneous squamous cell carcinomas (CSCC).[3] Risk factors for FC are similar to those for AKs and CSCCs, including exposure to UVR, lighter skin types, increasing age, male sex, and immunosuppression.[3] Topical therapies for FC were previously discussed in a previous article in this journal.[4] This review will therefore focus on field ablation treatment options and oral medications.

## Field Ablation

Field ablation with chemical peels or laser resurfacing has been studied for the treatment of AK and FC. Unlike topical treatments discussed previously,[4] field ablative options are non-selective and treat the entire area to which they are applied, not just atypical cells.

### *Chemical Peels*

**Chemical peels** are indicated in the management of AK and work by nonspecific chemical ablation of defined skin layers followed by regeneration of the epidermis and superficial dermis. Chemical peels that have been studied for AK include 70% glycolic acid peels, 30–35% trichloroacetic acid (TCA) peels, and peels combining Jessner's solution with 35% TCA.[5] Studies have demonstrated that glycolic acid alone did not provide a significant improvement in AK, and that combination treatment with 5-fluorouracil (5-FU) was required to achieve a 91% clearance of AK lesions. For instance, Jessner's solution combined with 35% TCA achieved AK clearance rates of 75–78%, and 30–35% TCA alone achieved 48–89% clearance rates of AK.[5] Studies that included comparator arms have shown that chemical peels were not as effective in clearing AK lesions or decreasing the recurrence of AK as that of photodynamic therapy (PDT) or 5-FU.[5,6] Side effects of chemical peels can include discomfort, bacterial superinfection, and scarring.[6] However, chemical peels require only one application in a clinician's office, which can be helpful for patients where compliance may be an issue. However, the relative lack of specificity of treatment with chemical peels may lead to a larger area of the skin requiring

aftercare and has a higher risk of scarring compared with more targeted medical field therapies.

### *Laser Resurfacing*

**Laser resurfacing** works by removing the superficial layers of skin (epidermis and dermis) that contain actinic damage, which promotes re-epithelialization of healthy skin. Laser resurfacing can be conducted as monotherapy with fully ablative lasers (CO2 and erbium-doped yttrium aluminum garnet [Er:YAG]) or with non-ablative fractional lasers (e.g. CO2, Er:YAG, Thulium).[7] A review article that summarized the findings of several small studies has demonstrated that laser resurfacing monotherapy had comparable efficacy to 5-FU and 30% TCA peel for reducing AK lesions, although it was inferior to PDT.[7] A major limitation of these studies is the small number of patients analyzed and the use of different protocols and lasers in each study.[7] Several studies have shown that PDT coupled with laser resurfacing increases clearance rates of AK compared with PDT monotherapy or ablative laser resurfacing monotherapy alone, especially with hyperkeratotic AK lesions or on sites such as the limbs.[8] This finding is thought to be achieved by facilitating the delivery of photosensitizers into the skin. Side effects include pain, edema, temporary hyperpigmentation, erythema, itching, and peeling. In rare instances, patients can develop scarring or hypopigmentation. It is important to keep in mind that laser resurfacing is not typically covered by insurance plans; consequently, the cost to patients may be prohibitive. Similar to chemical peels, a benefit of laser resurfacing is that it is often a "one-time" treatment in comparison to many topical therapies. However, further study is required to determine if this treatment is more effective than topical therapies to justify its higher cost.

## Oral Medications

### *Nicotinamide*

**Nicotinamide** (also known as niacinamide), is a vitamin B3 derivative that augments the repair of UV-induced DNA damage and reduces UV-associated immunosuppression.[9] Nicotinamide taken at a dose of 500 mg orally twice daily is generally considered safe, with no concerning side effects being reported with this dosing. Three small phase 3 studies have demonstrated that oral nicotinamide reduced the rates of AK and keratinocyte carcinoma (KC) (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC] combined) in immunocompetent patients. Notably, in the landmark clinical trial by Chen et al., the number of AK lesions was reduced by 13% ($P<0.001$) at 12 months, and the number of KC lesions was decreased by 23% ($P=0.02$).[9] However, no evidence of benefit was found after nicotinamide was discontinued, suggesting that nicotinamide treatment must be continued long term.

The evidence for benefit of nicotinamide treatment in immunosuppressed patients is mixed. Some small case-control studies have shown improvement in AK, but not SCC. Furthermore, a 2023 phase 3 trial on nicotinamide did not demonstrate a decrease in the number of KCs or AKs in solid-organ transplant recipients, though this study was closed early owing to low recruitment and was underpowered.[10] While the benefits of nicotinamide therapy are promising, current evidence is not definitive, especially in the immunosuppressed population. In addition, longer-term prospective studies are lacking. Nicotinamide treatment is however a low-risk option that may be helpful in treating high-risk individuals and should be considered as an option for these patients.

### *Acitretin*

**Acitretin** is an oral retinoid used for chemoprevention that works by normalizing keratinocyte differentiation in the epidermis, as well as hindering the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), migration inhibitory factor-related protein 8 (MRP-8) and interferon-γ (IFN-γ).[11] Acitretin has been studied for chemoprevention in solid organ transplant recipients (SOTRs), and guidelines suggest consideration of acitretin in patients with >5 KCs over the course of 2 to 3 years, significant field disease with diffuse AKs/SCCis despite treatment, high-risk KCs, or metastatic KCs.[12]

A 2021 systematic review showed a 56% reduction in KC formation,[13] and several small retrospective studies have demonstrated sustained efficacy and safety for up to 5 years of treatment with acitretin.[14] Similar to nicotinamide, continuous treatment is required to maintain chemoprevention, with some studies noting a "rebound effect" of a rapid increase in KC lesions after discontinuation of acitretin.[14] Dosing is 10–30 mg daily, depending on side effects. Common side effects include hypertriglyceridemia, liver function test abnormalities, headache, mucocutaneous xerosis, myalgias, and alopecia.[11] Most studies have been conducted in SOTRs[15] and patients with genodermatoses such as xeroderma pigmentosa. As such, while acitretin is a common medication to use in the SOTR population, its benefit in immunocompetent individuals requires further study.

### *Capecitabine*

**Oral capecitabine** can be considered as an option for patients with FC who continue to develop large numbers of KC lesions despite the use of field-directed therapies and other chemopreventative agents. Capecitabine is a prodrug of 5′-deoxy-5-fluorouridine, which is converted to its active metabolite 5-FU, and has been used off-label for prevention of KC.[12] Case reports and small case series have shown that capecitabine treatment reduces both SCC and BCC, as well as AK in SOTRs.[16] Capecitabine is typically administered at a dose ranging from 0.5–1.5 g/m$^2$ daily for days 1 to 14 of a 21-day treatment cycle.[17] The treatment cycles are repeated until disease progression or the development of intolerable side effects, which occur in up to 30% of patients.[16] Side effects include fatigue, diarrhea, hand-foot syndrome, febrile neutropenia, and stomatitis.[16] Although capecitabine shows promise as a chemopreventative agent for KC, studies have only been conducted in a small population of SOTR and further larger studies are needed to truly determine efficacy.

## Conclusion

Patients with FC are at higher risk of developing multiple CSCCs and often experience significant morbidity and mortality from their disease. Early intervention to treat FC with field ablative methods, as well as chemoprevention with oral medications, can potentially prevent progression to CSCC and decrease the cost to the individual and the health care system. Further studies will need to be conducted in both immunosuppressed and immunocompetent individuals to discover the most effective treatments, both in terms of cost and improved patient outcomes.

## Correspondence

**Dr. Toni Burbidge**
**Email:** toni.burbidge@gmail.com

## Financial Disclosures

**Advisory Boards:** Abbvie, Bausch Health, Leo, Lilly, Janssen, Sun Pharma, UCB, Novartis
**Honoraria:** Abbvie, Amgen, Galderma, Janssen, La Roche Posay, Leo, Lilly, Novartis, Sun Pharma, Sanofi, Pfizer, UCB

## References

1. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63(8):1727-1730.
2. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. J Am Acad Dermatol. 2008;58(5):S129-S132. doi: 10.1016/j.jaad.2007.04.034
3. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020 83(3):709-717. doi: 10.1016/j.jaad.2020.03.126
4. Burbidge T. Topical treatment options for field cancerization. Can Dermatol Today. [Internet]. 2022 December 1 [cited Date of Access 2023 October 6];3[4]:35-42. Available from: https://canadiandermatologytoday.com/article/view/3-4-burbidge
5. Jiang AJ, Soon SL, Rullan P, Brody HJ, Monheit GD, Lee KC. Chemical peels as field therapy for actinic keratoses: a systematic review. Dermatol Surg. 2021;47(10):1343-1346. doi: 10.1097/DSS.0000000000003144
6. Holzer G, Pinkowicz A, Radakovic S, Schmidt JB, Tanew A. Randomized controlled trial comparing 35% trichloroacetic acid peel and 5-aminolaevulinic acid photodynamic therapy for treating multiple actinic keratosis. Br J Dermatol. 2017;176(5):1155–1161. doi: 10.1111/bjd.15272
7. Tai F, Shah M, Pon K, Alavi A. Laser resurfacing monotherapy for the treatment of actinic keratosis. J Cutan Med Surg. 2021;25(6):634-642. doi: 10.1177/12034754211027515
8. Steeb T, Schlager JG, Kohl C, Ruzicka T, Heppt MV, Berking C. Laser-assisted photodynamic therapy for actinic keratosis: a systematic review and meta-analysis. J Am Acad Dermatol. 2019;80(4):947-956. doi: 10.1016/j.jaad.2018.09.021
9. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med. 2015;373(17):1618-1626. doi: 10.1056/NEJMoa1506197
10. Allen NC, Martin AJ, Snaidr VA, Eggins R, Chong AH, Fernandéz-Peñas P, et al. Nicotinamide for skin-cancer chemoprevention in transplant recipients. N Engl J Med. 2023;388(9):804-812. doi: 10.1056/NEJMoa2203086
11. Allergan Inc. Product Monograph Soriatane (acitretin capsules) [Internet]. Health Canada website [Revised 2018, August 10;Cited 2023, September 28] Available from: PRODUCT MONOGRAPH (hres.ca)
12. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol. 2011;65(2):263-279. doi: 10.1016/j.jaad.2010.11.063
13. Badri O, Schmults CD, Karia PS, Ruiz ES. Efficacy and cost analysis for acitretin for basal and squamous cell carcinoma prophylaxis in renal transplant recipients. Dermatol Surg. 2021;47(1):125-126. doi: 10.1097/DSS.0000000000002423
14. Allnutt KJ, Vogrin S, Li J, Goh MS, Brennand S, Davenport R, et al. A long-term cohort study of acitretin for prevention of keratinocyte carcinoma in solid organ transplant recipients. Australas J Dermatol. 2022;63(2):e121-e126. doi: 10.1111/ajd.13821
15. Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, Schmults CD, Arron ST, Ruiz ES. Field cancerization: treatment. J Am Acad Dermatol. 2020;83(3):719-730. doi: 10.1016/j.jaad.2020.03.127
16. Anderson JM, Moy L, Moy RL. Preventative options and the future of chemoprevention for cutaneous tumors. Dermatol Clin. 2023;41(1):231-238. doi: 10.1016/j.det.2022.07.020
17. Breithaupt AD, Beynet D, Soriano T. Capecitabine for squamous cell carcinoma reduction in solid organ transplant recipients. JAAD Case Rep. 2015 24;1(6):S16-S18. doi: 10.1016/j.jdcr.2015.09.009