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TOPICAL TREATMENT OPTIONS FOR FIELD CANCERIZATION

Introduction

Field cancerization (FC) was first described by Slaughter et al[1] in 1953. In that study, pathologic atypia was noted in normal appearing epithelial tissue adjacent to oropharyngeal carcinomas. Multiple new primary tumors were found to subsequently arise within this field.

Later research defined FC at the cellular level as the growth of a mutant clone that creates a field of cells predisposed to subsequent tumor growth.[2] Cutaneous field cancerization occurs in areas exposed to chronic ultraviolet radiation (UVR), which 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 the risk factors for AKs and CSCC, including exposure to UVR, light skin, increasing age, male sex, and immunosuppression.[3] Cutaneous FC is located on areas of the body that receive extensive sun exposure, including the face, balding scalp, forearms, and dorsal hands.[4]

Data regarding the epidemiology of FC is limited, so the prevalence and incidence of AK or CSCC is often used as a proxy. Rates of AK in Canada have not been published, however in 2014, Canadian Cancer Statistics reported that 76,100 Canadians will be diagnosed with non-melanoma skin cancer (NMSC) per year and 440 Canadians will die from it.[5] While the risk of transformation of individual AKs to invasive CSCC is low (0-0.53% per lesion-year; 2.88% at 5 years),[6] patients with FC carry significantly higher risks of invasive CSCC due to the high burden of actinic damage.

Treatment options for AK and FC include local destructive therapies (e.g. surgery, cryotherapy, and curettage), topical medications (e.g., 5-fluorouracil, imiquimod, diclofenac, Photodynamic therapy [PDT], and tirbanibulin), and field ablation treatments (e.g., chemical peels and laser resurfacing). In general, lesion-directed treatments are the primary approach for isolated lesions or lesions requiring pathologic diagnosis. However due to the large number of AK in individuals with FC, topical field-directed therapies are often more appropriate.

The goal of treating cutaneous FC is to prevent the development of CSCC. Field therapy has been proven to reduce the number of actinic keratoses as well as the number of new CSCC cases.[7,8] There is an abundance of data supporting the effectiveness of different field therapies, however indirect treatment comparisons are difficult due to variable study endpoints and the lack of standardized, objective methods for assessing field cancerization.[9] As such, the choice of treatment is mainly dictated by patient and physician related preferences around cost, side effect profile, and duration of treatment. Currently available topical field therapy options include 5-fluorouracil, imiquimod, PDT, diclofenac gel, and terbanibulin (**Table 1**). Ingenol mebutate gel was previously commonly used but was recalled by Health Canada in 2020 due to a potential increased risk of skin cancer.

5-Fluorouracil

5-fluorouracil (5-FU) is approved by Health Canada in a 5% concentration or a 4% concentration for the treatment of actinic keratoses and superficial basal cell carcinoma (BCC). It is an antimetabolite, inhibiting thymidylate synthase and interfering with the synthesis of DNA and RNA, provoking unbalanced cell growth and death.[10] Side effects include application site erythema, crusting, burning, and ulceration. A systematic review of thirteen randomized clinical trials relating to the treatment of AK lesions, measured 3 months after treatment demonstrated clearance of 93.8% of AK lesions at 24 weeks, and an average of 49% of patients were reported as achieving complete clearance of all AK lesions.[11]

5-fluorouracil plus calcipotriol

Off-label combination therapy with calcipotriol plus 5-FU has been shown to have a synergistic effect on the treatment of AKs by inducing a CD4+ T-cell–mediated immune response.[12]

Both creams are applied to the affected area twice daily for 4 days, significantly shortening the treatment time as compared to the traditional 2-4 week application time for 5-FU alone. A randomized controlled trial (RCT) of 131 patients comparing 5% 5-FU plus 0.005% calcipotriol and 5-FU combined with petroleum jelly resulted in a mean reduction in the number of facial AKs of 87.8% vs 26.3%.[13] Additionally, the combination regimen showed a complete response of 27% vs 0% with the control regimen at 8 weeks. Calcipotriol plus 5-FU also lowered the risk of CSCC on the face and scalp area over a 3-year period.[14] While the combination of these two treatments results in rapid clearance of AK it is also associated with increased reports of skin redness and burning.[13] However further research is required comparing this regimen with traditional 5-FU monotherapy before any claims of superiority can be made.

Imiquimod

Imiquimod is a topical immune response modifier that is approved by Health Canada for the treatment of AK and superficial BCC. It is also used off-label for the treatment of SCCis. It is supplied in 5%, 3.75% and 2.5% concentrations, with differing application instructions depending on the concentration used. The 5% imiquimod cream is approved for the treatment of superficial BCC, but lower concentrations do not have the same indication. Typical side effects are skin directed and include local erythema, scabbing, irritation, and pain.[15] Influenza-like symptoms are also a known side effect, though less common, occuring in 3.2-10.3% of patients.[10] A systematic review of 8 RCTs demonstrated complete clearance rates of up to 84% (average 40.8%) using 5% imiquimod.[10] The lower concentrations had lower clearance rates. 3.75% imiquimod cream had a complete clearance rate of 35.6% when used daily for 2 weeks, followed by a 2 week break, and a repeat 2 week application cycle.[10] Using the same treatment regimen, 2.5% imiquimod cream demonstrated a complete clearance rate of 30.6%.[10]

Photodynamic therapy

Conventional photodynamic therapy (c-PDT) utilizes the combination of a photosensitizing protoporphyrin (5- aminolaevulinic acid (5-ALA) or methyl aminolaevulinate [MAL] and specific wavelengths of visible light to generate reactive oxygen species (ROS) and induce cell death of premalignant and malignant cells.[16] PDT is approved in Canada for the treatment of non-hyperkeratotic actinic keratoses (AK)[17,18] and superficial BCC outside the H-zone of the face.[17] This treatment is performed in a physician's office in 1 treatment, with 1 to 2 optional repeat treatments 4 to 8 weeks apart. For AK, clinical trials have demonstrated a lesion clearance rate of 83-92% at 3 months and a one-year sustained clearance of up to 78-80%.[19] Superficial BCC have a primary clearance rate of 92-97% at 12 weeks using MAL-PDT, with a 1-year recurrence rate of 9% and 5-year recurrence rate of 22%.[20] The most common side effect of PDT is pain or discomfort during irradiation of the treatment site. Patients will develop erythema, scaling and peeling post-procedure. Herpes simplex infections, dyspigmentation, milia or hypersensitivity reactions may rarely occur.[21] Daylight PDT (d-PDT) is a variation that uses ambient daylight to activate the photosensitizer. This modality is approved by Health Canada for AK, but not superficial BCC. Advantages of this approach include minimizing associated treatment- related discomfort and allowing for exposure of large fields, both of which are 2 limiting factors of c-PDT. Daylight PDT has similar AK reduction rates compared to c-PDT.[22]

Diclofenac

Topical diclofenac 3% in 2.5% hyaluronan gel is a therapeutic option for AK, but is not approved by Health Canada for this purpose, though the product is available in Canada. Diclofenac is applied twice daily for 60 to 90 days, with the long treatment course being a limiting factor in its use. In RCTs, diclofenac demonstrated a complete clearance rate of 33% (with a 60-day course) to 42% (with a 90-day course).[23] The most common adverse effects of diclofenac gel are dry skin, pruritus, erythema, and rash at the application site.[23]

Diclofenac is a nonsteroidal anti-inflammatory drug that inhibits both cyclooxygenase enzymes and upregulates the arachidonic acid cascade. The production of prostaglandins from arachidonic acid may play a role in keratinocyte carcinomas, and thus inhibition of this cascade by diclofenac may explain its efficacy in the treatment of AK. However, the exact mechanism by which diclofenac induces response in AK is unclear.

Tirbanibulin

Tirbanibulin is a synthetic agent that inhibits Src kinase signalling and tubulin polymerization leading to arrest of cell division and mitosis in rapidly proliferating cells.[24] It was approved by the FDA in 2020 and is under review by Health Canada. In phase 3 trials, treatment with 1% tirbanibulin ointment for five days was found to result in complete clearance of AK in 49% of patients and partial clearance in 72% of patients at day 57. Median reduction in AK count in patients receiving tirbanibulin was 87.5%.[25] Of the patients who received tirbanibulin therapy, 27% remained clear at 1 year follow-up. Side effects included mild-to-moderate local skin erythema, flaking, scaling, itching or pain. Some cases of severe erythema and blistering were reported as well.[25] As it is a new agent, studies comparing the safety and long-term efficacy of tirbanibulin with other available agents are lacking.

Conclusion

Patients with FC are at higher risk of developing multiple CSCCs and often suffer significant morbidity and mortality from their disease. Early intervention with topical therapies to treat AK and FC can hopefully prevent progression to CSCC and decrease the cost to both the individual and the health care system. Further studies will need to be done comparing treatment options and regimens to find the most cost-effective and efficacious treatments.

Therapy	Health Canada status and indications	Recommended application	Mechanism of action
5-fluorouracil	Approved for AK (5% and 4%) Approved for superficial BCC Off label usage for SCCis	**AK** 5% cream: apply twice daily for 2-4 weeks 4% cream: apply twice daily for 4 weeks **Superficial BCC** 5% cream: apply twice daily for 3-6 weeks, may be continued for up to 10-12 weeks **SCCis (off label)** 5% cream: apply twice daily for 3-6 weeks	Inhibition of thymidylate synthase and misincorporation into DNA and RNA leading to cell death of rapidly dividing keratinocytes
5-fluorouracil and calcipotriol	Off-label use	**AK (off label)** Twice daily for 4 days	Induction of a CD4+ T–cell–mediated immune response
Imiquimod	Approved for AK (5%, 3.75%, 2.5%) Approved for superficial BCC (5%) Off label for SCCis	**AK** 5% cream: apply twice weekly for 16 weeks (limit treatment area to ≤25 cm^2) 3.75% cream and 2.5% cream: apply once daily for 2 weeks for 2 treatment cycles separated by a 2-week rest period **Superficial BCC** 5% cream: apply 5 days per week for 6 weeks (maximum 2 cm diameter tumour plus 1 cm of normal skin around tumour) **SCCis (off label)** 5% cream: apply once daily for 16 weeks	Stimulation of the innate and adaptive immune system through activation of toll-like receptors 7 and 8. Resulting in anti-tumour and anti-viral activity.
Photodynamic therapy	Approved for AK and BCC (MAL) Approved for AK only (5-ALA)	**AK** c-PDT with 5-ALA: Application of cream, 3 hour incubation under occlusion followed by exposure to blue light (Blu-U 400nm) for 16 minutes 40 seconds	Photochemical reaction following exposure of topically administered precursors of photoactive porphyrins (5-ALA or MAL) to light of appropriate wavelength and energy

	Off-label for SCCis	c-PDT with MAL: Application of cream, 3 hour incubation under occlusion followed by exposure to red light (630-635nm) to a total dose of 37 J/cm^2 d-PDT with MAL: Application of cream, 30 minute incubation with no occlusion. 2 hour exposure to outdoor ambient daylight. Day must be sunny and >10°C **Superficial BCC** c-PDT with MAL: Application of cream, 3 hour incubation under occlusion followed by exposure to red light (630-635nm) to a total dose of 37 J/cm^2 2 separate treatments are performed 1 week apart. **SCCis (off label)** c-PDT with MAL: Application of cream, 3 hour incubation under occlusion followed by exposure to red light (630-635nm) to a total dose of 37J/cm^2 2 separate treatments are performed 1 week apart.	
Diclofenac	Not approved for actinic keratoses in Canada	**AK** 3% gel: apply twice daily for 60 to 90 days	Unclear in AK. Inhibits both cyclooxygenase enzymes and upregulates the arachidonic acid cascade
Tirbanibulin	Under review by Health Canada	**AK** 1% ointment: apply once daily for 5 consecutive days (treatment area up to 25 cm^2)	Src inhibition and microtubule inhibition leading to cell cycle arrest and apoptosis

Table 1: *Summary of treatment options for field cancerization; courtesy of Toni Burbidge, MD*

References

1. *Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium. Clinical implications of multicentric origin. Cancer. 1953 Sep;6(5):963-8.*
2. *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;63:1727-1730.*
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 Sep;83(3):709-717.*
4. *Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. J Am Acad Dermatol. 2008;58(5):S129-32.*
5. *Non-Melanoma Skin Cancer. Public Health Agency of the Government of Canada. https://www.canada.ca/en/public-health/services/chronic-diseases/cancer/non-melanoma-skin-cancer.html. Published December 9, 2019. Accessed September 25, 2022.*
6. *Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The natural history of actinic keratosis: a systematic review. Br J Dermatol, 169 (2013), pp. 502-518*
7. *Neugebauer R, Levandoski KA, Zhu Z, et al. A real-world, community-based cohort study comparing the effectiveness of topical fluorouracil versus topical imiquimod for the treatment of actinic keratosis. J Am Acad Dermatol. 2018;78:710-716.*
8. *Pomerantz H, Hogan D, Eilers D, et al. Long-term efficacy of topical fluorouracil cream, 5%, for treating actinic keratosis: a randomized clinical trial. JAMA Dermatol. 2015;151:952-960.*
9. *Steeb T, Wessely A, Schmitz L, et al. Interventions for Actinic Keratosis in Nonscalp and Nonface Localizations: Results from a Systematic Review with Network Meta-Analysis. J Invest Dermatol. 2021;141(2):345-354.e8.*
10. *Eisen DB, Asgari MM, Bennett DD et al. Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol. 2021 Oct 1;85(4):e209-33.*
11. *Askew DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis a systematic review of randomized controlled trials. Int J Dermatol. 2009;48:453-463.*
12. *Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, Schmults CD, Arron ST, Ruiz ES. Field cancerization: Treatment. J Am Acad Dermatol. 2020 Sep;83(3):719-730.*
13. *Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. J Clin Invest. 2017;127(1):106-116. doi:10.1172/JCI89820*
14. *Mohney L, Singh R, Grada A, Feldman S. Use of Topical Calcipotriol Plus 5-Fluorouracil in the Treatment of Actinic Keratosis: A Systematic Review. J Drugs Dermatol. 2022;21(1):60-65. doi:10.36849/JDD.2022.6632*
15. *Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. J Invest Dermatol. 2006 Jun;126(6):1251-5.*
16. *Henderson BW, Dougherty TJ. How does photodynamic therapy work?. Photochem Photobiol. 1992;55(1):145-157.*
17. *Galderma Canada Inc. Metvix (methyl aminolevulinate topical cream) [product monograph]. Health Canada website. https://pdf.hres.ca/dpd_pm/00038693.PDF . Revised March 30, 2017. Accessed September 22, 2022.*
18. *Clarion Medical Technologies Inc. Levulan Kerastick [product monograph]. Health Canada website. https://pdf.hres.ca/dpd_pm/00027478.PDF. Revised September 30, 2014. Accessed September 22, 2022.*
19. *Tschen EH, Wong DS, Pariser DM, et al. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. Br J Dermatol. 2006;155(6):1262-1269.*
20. *Basset-Seguin N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol. 2008;18(5):547-553.*
21. *Ibbotson SH, Wong TH, Morton CA, et al. Adverse effects of topical photodynamic therapy: a consensus review and approach to management. Br J Dermatol. 2019;180(4):715-729.*
22. *Lacour JP, Ulrich C, Gilaberte Y, et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe. J Eur Acad Dermatol Venereol. 2015;29(12):2342-2348.*
23. *Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. Br J Dermatol. 2002 Jan;146(1):94-100.*
24. *Miller AC, Adjei S, Temiz LA, Tyring SK. Tirbanibulin for the Treatment of Actinic Keratosis: A Review. Skin Therapy Lett. 2022;27(4):4-7.*
25. *Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of tirbanibulin ointment for actinic keratosis. N Engl J Med. 2021 Feb 11;384(6):512-20.*