

# Field Cancerization in Dermatology: Updates on Treatment Considerations and Emerging Therapies

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There has been increasing awareness of field cancerization in dermatology and how it relates to actinic damage, actinic keratoses (AKs), and the development of cutaneous squamous cell carcinomas (SCCs). The concept of field cancerization, which was first described in the context of oropharyngeal SCCs, attempted to explain the repeated observation of local recurrences that were instead multiple primary oropharyngeal SCCs occurring within a specific region of tissue. It was hypothesized that the tissue surrounding a malignancy also harbors irreversible oncogenic damage and therefore predisposes the surrounding tissue to developing further malignancy.<sup>1</sup> The development of additional malignant lesions would be considered distinct from a true recurrence of the original malignancy.

Field cancerization may be partially explained by a genetic basis, as mutations in the tumor suppressor gene, *TP53*—the most frequently observed mutation in cutaneous SCCs—also is found in sun-exposed but clinically normal skin.<sup>2,3</sup> The finding of oncogenic mutations in nonlesional skin supports the theory of field cancerization, in which a region contains multiple genetically altered populations, some of which may progress to cancer. Because there currently is no widely accepted clinical definition or validated clinical measurement of field cancerization in dermatology, it may be difficult for dermatologists to recognize which patients may be at risk for developing further malignancy in a potential area of field cancerization. Willenbrink et al<sup>4</sup> updated the definition of field cancerization in dermatology as “multifocal

clinical atypia characterized by AKs or SCCs in situ with or without invasive disease occurring in a field exposed to chronic UV radiation.” Managing patients with field cancerization can be challenging. Herein, we discuss updates to nonsurgical field-directed and lesion-directed therapies as well as other emerging therapies.

## Field-Directed Therapies

Topical 5-fluorouracil (5-FU) and imiquimod cream 5% used as field-directed therapies help reduce the extent of AKs and actinic damage in areas of possible field cancerization.<sup>5</sup> The addition of calcipotriol to topical 5-FU, which theoretically augments the skin’s T-cell antitumor response via the cytokine thymic stromal lymphopoietin, recently has been studied using short treatment courses resulting in an 87.8% reduction in AKs compared to a 26.3% reduction with topical 5-FU alone (when used twice daily for 4 days) and conferred a reduced risk of cutaneous SCCs 3 years after treatment (hazard ratio, 0.215 [95% CI, 0.048-0.972];  $P=.032$ ).<sup>6,7</sup> Chemowraps using topical 5-FU may be considered in more difficult-to-treat areas of field cancerization with multiple AKs or keratinocyte carcinomas of the lower extremities.<sup>8</sup> The routine use of chemowraps—weekly application of 5-FU covered with an occlusive dressing—may be limited by the inability to control the extent of epidermal damage and subsequent systemic absorption. Ingenol mebutate, which was approved for treatment of AKs in 2012, was removed from both the European and US markets in 2020 because the medication may paradoxically increase the long-term incidence of skin cancer.<sup>9</sup>

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Meta-analysis has shown that photodynamic therapy (PDT) with aminolevulinic acid demonstrated complete AK clearance in 75.8% of patients (N=156)(95% CI, 55.4%-96.2%).<sup>10</sup> A more recent method of PDT using natural sunlight as the activation source demonstrated AK clearance of 95.5%, and it appeared to be a less painful alternative to traditional PDT.<sup>11</sup> Tacalcitol, another form of vitamin D, also has been shown to enhance the efficacy of PDT for AKs.<sup>12</sup>

Field-directed treatment with erbium:YAG and CO<sub>2</sub> lasers, which physically remove the actinically damaged epidermis, have been shown to possibly be as efficacious as topical 5-FU and 30% trichloroacetic acid (TCA) but possibly inferior to PDT.<sup>13</sup> There has been growing interest in laser-assisted therapy, in which an ablative fractional laser is used to generate microscopic channels to theoretically enhance the absorption of a topical medication. A meta-analysis of the use of laser-assisted therapy for photosensitizing agents in PDT demonstrated a 33% increased chance of AK clearance compared to PDT alone ( $P < .01$ ).<sup>14</sup>

### Lesion-Directed Therapies

Multiple KAs or cutaneous SCCs may develop in an area of field cancerization, and surgically treating these multiple lesions in a concentrated area may be challenging. Intralesional agents, including methotrexate, 5-FU, bleomycin, and interferon, are known treatments for KAs.<sup>15</sup> Intralesional 5-FU (25 mg once weekly for 3–4 weeks) in particular produced complete resolution in 92% of cutaneous SCCs and may be optimal for multiple or rapidly growing lesions, especially on the extremities.<sup>16</sup>

### Oral Therapies

Oral therapies are considered in high-risk patients with multiple or recurrent cutaneous SCCs or in those who are immunosuppressed. Two trials demonstrated that nicotinamide 500 mg twice daily for 4 and 12 months decreased AKs by 29% to 35% and 13% (average of 3–5 fewer AKs as compared to baseline), respectively.<sup>17,18</sup> A meta-analysis found a reduction of cutaneous SCCs (rate ratio, 0.48 [95% CI, 0.26–0.88];  $I^2 = 67%$ ; 552 patients, 5 trials), and given the favorable safety profile, nicotinamide can be considered for chemoprevention.<sup>19</sup>

Acitretin, shown to reduce AKs by 13.4% to 50%, is the primary oral chemoprevention recommended in transplant recipients.<sup>20</sup> Interestingly, a recent meta-analysis failed to find significant differences between the efficacy of acitretin and nicotinamide.<sup>21</sup> The tolerability of acitretin requires serious consideration, as 52.2% of patients withdrew due to adverse effects in one trial.<sup>22</sup>

Capecitabine (250–1150 mg twice daily), the oral form of 5-FU, decreased the incidence of AKs and cutaneous SCCs in 53% and 72% of transplant recipients, respectively.<sup>23</sup> Although several reports observed paradoxical eruptions of AKs following capecitabine for other malignancies, this actually underscores the efficacy of

capecitabine, as the newly emerged AKs resolved thereafter.<sup>24</sup> Still, the evidence supporting capecitabine does not include any controlled studies.

### Novel Therapies

In 2021, tirbanibulin ointment 1%, a Src tyrosine kinase inhibitor of tubulin polymerization that induces p53 expression and subsequent cell death, was approved by the US Food and Drug Administration for the treatment of AKs.<sup>25</sup> Two trials reported AK clearance rates of 44% and 54% with application of tirbanibulin once daily for 5 days (vs 5% and 13%, respectively, with placebo, each with  $P < .001$ ) at 2 months and a sustained clearance rate of 27% at 1 year. The predominant adverse effects were local skin reactions, including application-site pain, pruritus, mild erythema, or scaling. Unlike in other treatments such as 5-FU or cryotherapy, erosions, dyspigmentation, or scarring were not notably observed.

Intralesional talimogene laherparepvec (T-VEC), an oncolytic, genetically modified herpes simplex virus type 1 that incites antitumor immune responses, received US Food and Drug Administration approval in 2015 for the treatment of cutaneous and lymph node metastases of melanoma that are unable to be surgically resected. More recently, T-VEC has been investigated for oropharyngeal SCC. A phase 1 and phase 2 trial of 17 stage III/IV SCC patients receiving T-VEC and cisplatin demonstrated pathologic remission in 14 of 15 (93%) patients, with 82.4% survival at 29 months.<sup>26</sup> A multicenter phase 1b trial of 36 patients with recurrent or metastatic head and neck SCCs treated with T-VEC and pembrolizumab exhibited a tolerable safety profile, and 5 cases had a partial response.<sup>27</sup> However, phase 3 trials of T-VEC have yet to be pursued. Regarding its potential use for cutaneous SCCs, it has been reportedly used in a liver transplant recipient with metastatic cutaneous SCCs who received 2 doses of T-VEC (1 month apart) and attained remission of disease.<sup>28</sup> There currently is a phase 2 trial examining the effectiveness of T-VEC in patients with cutaneous SCCs (ClinicalTrials.gov identifier NCT03714828).

### Final Thoughts

It is important for dermatologists to bear in mind the possible role of field cancerization in their comprehensive care of patients at risk for multiple skin cancers. Management of areas of field cancerization can be challenging, particularly in patients who develop multiple KAs or cutaneous SCCs in a concentrated area and may need to involve different levels of treatment options, including field-directed therapies and lesion-directed therapies, as well as systemic chemoprevention.

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