Field cancerization: Treatment

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Learning objectives
After completing this learning activity, participants should be able to discuss therapeutic options for the management of field cancerization; explain the utility of a multimodal treatment approach; and define the role of lesion-directed, field, and oral treatment in field cancerization management.

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The goal of field cancerization treatment is to reduce the risk of developing keratinocyte carcinoma. Selecting the appropriate therapy depends on the degree of field cancerization and the number of invasive cutaneous squamous cell carcinomas. Other considerations include treatment efficacy, cost, side effects, and patient preference. Field therapies are preferred because they address clinically visible disease and subclinical atypia. However, lesion-directed therapies are useful for lesions that are more difficult to treat or those where a histologic diagnosis is required. Patients with extensive field cancerization benefit from a combination of field-directed and lesion-directed treatments. The second article in this continuing medical education series provides a framework to guide evidence-based decision making for field cancerization treatment. (J Am Acad Dermatol 2020;83:719-30.)

Key words: actinic keratoses; cutaneous squamous cell carcinoma; field cancerization; keratinocyte carcinoma; solid organ transplant recipient.

The goal of field cancerization (FC) treatment is to reduce the risk of developing keratinocyte carcinoma (KC). Selecting the appropriate therapy depends on the degree of FC and the number of invasive cutaneous squamous cell carcinomas (CSCCs).[1,2] Other considerations include treatment efficacy, cost, side effects, and patient preference.

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Abbreviations used:

5-FU:	5-fluorouracil
AK:	actinic keratosis
BCC:	basal cell carcinoma
c-PDT:	conventional photodynamic therapy
CRR:	complete response rate
CSCC:	cutaneous squamous cell carcinoma
FC:	field cancerization
FDA:	US Food and Drug Administration
IL:	intralesional
KC:	keratinocyte carcinoma
RCT:	randomized controlled trial
SCCis:	squamous cell carcinoma in situ
SOTR:	solid organ transplant recipient

FIELD TREATMENTS

Key points

- **Field-directed treatments reduce cutaneous squamous cell carcinoma formation**
- **5-fluorouracil is the most effective field therapy**
- **Combination 5-fluorouracil and calcipotriol reduces treatment duration and has synergistic effects on field disease**
- **Daylight photodynamic therapy has comparable efficacy to conventional photodynamic therapy, but less treatment-associated discomfort**

Field-directed therapy reduces actinic keratosis (AK) burden as well as the number of new cutaneous squamous cell carcinomas (CSCCs).[3-6] Although there is substantial literature to support various field therapies, comparing different modalities is difficult because of heterogenous study endpoints and the lack of standardized, objective methods for assessing field disease. While many studies report short-term response rates, long-term responses are critical given the chronic nature of FC. Nevertheless, patients with FC often require multiple courses of field-directed treatment. The choice of treatment is largely dictated by patient and physician preferences; however, increasing evidence from randomized trials with long-term follow-up and direct comparison between treatments will allow physicians to make evidence-based recommendations (Table I).[25]

5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine analogue approved by the US Food and Drug Administration (FDA) for the treatment of AKs and superficial basal cell carcinomas (BCCs). Local inflammatory reactions are expected (Fig 1), although patients may experience fewer adverse effects with repeat courses due to improvement in keratinocyte dysplasia in the previously treated field.[5]

The Veterans Affairs Keratinocyte Carcinoma Chemoprevention trial demonstrated that 2 to 4 weeks of 5-FU therapy reduced AK counts and lesion-directed treatments for >2 years.[4] Additional data published from the trial showed a 75% reduction in the risk of SCC at 1 year.[5] No differences were seen between the placebo group and the 5-FU group at 4 years, underscoring the chronic and relapsing nature of FC and the importance of repeated treatment for continued chemopreventive effect.[5] Although the literature on 5-FU for the treatment of squamous cell carcinoma in situ (SCCis) is less robust, response rates of 48% to 85% have been reported.[8,26,27]

A recent multicenter, single-blind, randomized controlled trial (RCT) of 624 patients found that 5-FU 5% is superior to imiquimod cream 5%, methyl aminolevulinate photodynamic therapy, and ingenol mebutate gel 0.015% for the treatment of AKs at 12 months.[25] Similar findings were reported in 2 metaanalyses.[28,29]

Imiquimod

Imiquimod is a topical immune response modifier that is approved by the FDA for the treatment of nonhypertrophic AKs on the face and scalp and low-risk, superficial BCCs in immunocompetent adults. The most common adverse events are local erythema, scabbing or crusting, flaking, erosion, edema, and weeping.[9] Imiquimod in solid organ transplant recipients (SOTRs) has been shown to be safe with no observed effects on systemic immunity.[30]

A metaanalysis of 5 RCTs (n = 1293) reported complete AK clearance in 50% of patients treated with imiquimod cream 5%.[9] Lower concentrations may have reduced clinical efficacy.[31] Imiquimod is beneficial for the off-label treatment of SCCis, with complete response rates (CRRs) of 75% to 93%.[10,32,33]

5-Fluorouracil/calcipotriol

Combination therapy with calcipotriol (also known as calcipotriene) plus 5-FU has been shown to have a synergistic effect in the treatment of AKs by inducing a $CD4^+$ T cell—mediated immune response.[6,11] A RCT with 130 subjects receiving either a twice-daily 4-day regimen of 5-FU 5% plus calcipotriol ointment 0.005% or 5-FU 5% plus petroleum jelly showed a mean AK reduction of 88% vs 26% and CRR of 27% vs 0%, respectively.[11] The combination regimen was also associated with a reduced long-term risk of CSCC, which may be related to the induction of a long-lasting T cell immunity in the skin.[6]

Table I. Field-directed therapies

Therapy	Indications and recommended application	Mechanism of action	Level of evidence*
5-FU[7,8]	AKs 5% cream: twice daily ×2-4 weeks 0.5% cream: daily for up to 4 weeks SCCis (off-label) 5% cream: twice daily ×3-6 weeks; treatment can be continued for ≤12 weeks	Inhibition of TS and DNA and RNA misincorporation, leading to cell death of atypical and rapidly proliferating keratinocytes	AK: IA; SCCis: IB
Imiquimod[9,10]	AKs 5% cream: twice weekly ×16 weeks (limit treatment area to ≤25 cm^2) 2.75% cream and 3.5% cream: daily ×2 weeks for 2 treatment cycles separated by a 2-week rest period SCCis (off-label) 5% cream: daily ×16 weeks	Stimulation of innate and adaptive immune response pathways resulting in antitumor and antiviral activity	AK: IA; SCCis: IB
5-FU plus calcipotriol[11]	AKs (off label): twice daily ×4 days	Induction of thymic stromal lymphopoietin and robust $CD4^+$ T cell immunity against AKs	IB
Chemowraps with 5-FU[12-15]	AKs and SCCis of the extremities (off-label): apply weekly ×4 weeks or until desired clinical response		III
Ingenol mebutate[16]	AKs Face or scalp: apply 0.015% gel once daily to affected area for 3 consecutive days (limit treatment area to ≤25 cm^2) Trunk or extremities: apply 0.05% gel once daily to affected area for 2 consecutive days (limit treatment area to ≤25 cm^2)	Mitochondrial disruption leading to necrosis and localized inflammatory response via activation of protein kinase C pathway and apoptosis[17]	IB
PDT[18,19]	c-PDT ALA 20% solution/blue light (BLU-U 400 nm) ALA 10% nanoemulsion/red light (BF-RhodoLED 635 nm) MAL 16.8% cream†/red light dl-PDT: MAL or ALA 10% nanoemulsion/ambient light[20] Protocols used by the authors: 1. Instruct patients sit in a shady area on a nonrainy day ≥60°F within 60 min of ALA application for a total duration of 2.5 hours[21] 2. 10-min ALA incubation activated by exposure to blue light (16 min, 40 sec) followed by daylight (45 min) (manuscript under review) 3. Sequential treatment with removal of hyperkeratotic material, application of 5% 5-FU twice daily (5 days on the face and scalp or 7 days on the arms), and c-PDT with 1-hour incubation time‡[22]	Photochemical reaction following exposure of topically administered precursors of photoactive porphyrins (ALA or MAL) to light of appropriate wavelength and energy; preferential accumulation of photoactive porphyrins in both malignant and pre-malignant cells leads to selective destruction of atypical keratinocytes[23]	IB

5-FU, 5-Fluorouracil; *AK*, actinic keratosis; *ALA*, aminolevulinic acid; *c-PDT*, conventional photodynamic therapy; *dl-PDT*, daylight photodynamic therapy; *MAL*, methyl aminolevulinate; *PDT*, photodynamic therapy; *SCCis*, squamous cell carcinoma in situ; *TS*, thymidylate synthase.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

†Not available in the United States.

‡Sequential 5-FU and PDT have been shown to improve AK clearance through enhanced photosensitizer accumulation and expression of p53.[24]

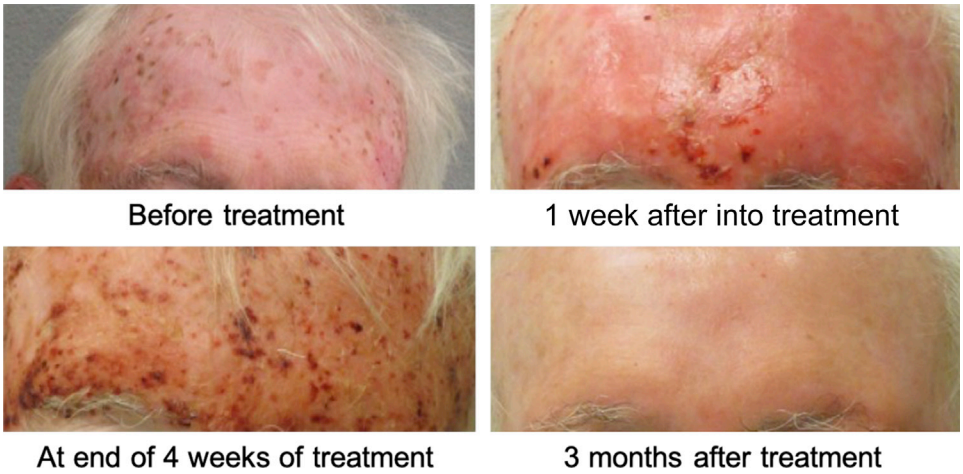

Fig 1. Field cancerization treatment. Local inflammatory reaction and response to 5-fluorouracil at different time points.

Treatment with calcipotriol plus 5-FU is associated with more inflammation than 5-FU alone and peaks approximately 10 days after the initiation of therapy and usually resolves by 2 weeks.[11] The addition of calcipotriol may result in better patient compliance because of the shorter treatment duration. However, the regimen may be more expensive because it requires 2 separate prescriptions or ordering through a compounding pharmacy. In our experience, some patients require a treatment course that is longer than 4 days to induce an adequate response and other patients develop an exuberant reaction with only 4 days of treatment.

Chemowraps

Weekly wraps with 5-FU occluded with zinc-impregnated gauze (Unna wrap) covered by a compression wrap and gauze bandages is effective for FC involving the extremities.[12-15] Treatment is typically continued for 4 weeks, with the wraps changed weekly.[21] Given the mode of application, patient compliance is high; however, some patients are reluctant to undergo a treatment that prohibits bathing for a week. Patients can cut the wrap off and shower before the weekly visit. An alternative to traditional wraps is 5-FU twice daily for 4 weeks with occlusion overnight via a plastic or compression wrap.[21] This approach allows daily bathing and obviates the need for weekly visits.

A retrospective study of 25 patients with multiple AKs treated with chemowraps noted an AK response rate of 60%, with 20% CRR after an average of 9.6 sessions (range 1-64 sessions).[14] As an adjuvant to surgery, chemowraps may help define tumor borders and minimize the extent of surgery required in patients with significant FC.[13-15] Chemowraps are also an option for palliative management of lower leg CSCCs on patients who are poor surgical candidates or refuse surgery.[13,15]

Ingenol mebutate

Ingenol mebutate is approved by the FDA for the treatment of nonhyperkeratotic AKs. Several RCTs have demonstrated 8-week CCRs of 34% to 41% for the trunk and extremities and 42% to 62% for the face and scalp.[16,34,35] In patients who achieved complete clearance at 8 weeks, around half had sustained clearance at 12 months.[16] Local skin reactions are generally mild to moderate and peak at days 4 to 8.[16] Although treatment is indicated for areas $\leq$25 cm^2 of contiguous, AK-affected skin, acceptable tolerability without quantifiable systemic exposure was seen in patients treated with 0.05% gel to areas $\leq$100 cm^2.[36]

Photodynamic therapy

Conventional photodynamic therapy (c-PDT) is approved by the FDA in 3 drug/light combinations for the treatment of nonhyperkeratotic AKs (Table I). PDT can be performed in 1 treatment, with 1 to 2 optional repeat treatments 4 to 8 weeks apart. FC patients who have failed or cannot perform other field-directed therapies benefit from cyclic PDT.[37] There are many PDT regimens, including variations on pretreatment (curettage, microneedling, laser-assisted, etc), photosensitizer incubation time, and light source. Thermally modulated PDT has been used to improve AK clearance rates on the extremities.[38,39] Daylight PDT uses ambient visible light to activate the photosensitizer. This approach minimizes pain and allows for exposure of large fields,

2 limiting factors of c-PDT. Daylight PDT has similar AK reduction rates compared with c-PDT.[40-45] After treatment the photosensitizer is removed with soap and water and patients are instructed to wear sun-protective clothing and to apply zinc- or titanium-based sunscreen to all exposed areas for 48 hours.

Other therapies

There is a paucity of data to support laser or chemical peel resurfacing techniques as monotherapy for field disease. Evidence appears to favor ablative lasers as an adjunct to current therapies, particularly for more difficult-to-treat AKs (such as hyperkeratotic or acral lesions) because they may facilitate the delivery of topical agents.[46] Other novel therapies are being investigated in clinical trials (Table II).[52]

LESION-DIRECTED THERAPIES

Key points

- **Lesion-directed therapies are recommended for KCs that are dermally invasive on clinical examination, focal hyperkeratotic AK, or AK failing field treatments**
- **Cryotherapy of isolated AKs can be highly effective if performed correctly**
- **Surgery or shave removal is indicated for lesions requiring histologic confirmation of margin clearance**

Cryotherapy

Cryotherapy is the mainstay of treatment for isolated AKs because of its ease of use and good tolerability. In a RCT of cryotherapy, 5-FU, and imiquimod 5%, cryotherapy was associated with a 68% initial AK clearance rate, but only a 28% sustained clearance rate at 12 months.[53] Freeze time is an important determinant of treatment efficacy with CRRs of 83%, 69%, and 39% at 3 months with freeze times >20 seconds, 5-20 seconds, and <5 seconds, respectively.[54] Despite higher efficacy, longer freeze durations may result in greater discomfort and localized cutaneous reactions, including hypopigmentation and scarring. Combining cryotherapy of hypertrophic AKs with field-directed therapy can improve response rates.[55,56] Cryotherapy may also be used after field therapy to treat persistent AKs.

Surgical management

Shave removal of persistent hyperkeratotic lesions is diagnostic and therapeutic. Surgical excision of invasive KCs arising within areas of field damage remains the standard of care. Surgical removal with an appropriate margin of clinically normal skin can be a challenge in FC patients and it is often not feasible to surgically remove extensive areas of in situ disease. Patients benefit from pre- or postoperative field treatment. Complete circumferential peripheral and deep margin control with Mohs micrographic surgery is recommended for high-risk CSCCs unless the wound can be closed primarily or reconstruction delayed until clear margins are confirmed.[57,58]

Intralesional 5-FU

Intralesional 5-FU (IL 5-FU) is an effective treatment for eruptive squamous atypia (also termed eruptive keratoacanthoma) and is a noninvasive option for low-risk CSCC, particularly in patients who are poor candidates for surgery. Data supporting IL 5-FU for CSCC treatment are largely derived from case reports and 1 prospective trial, which reported a 96% cure rate of well-differentiated CSCC in 25 patients treated with a proprietary injectable 5-FU gel.[59-62]

IL 5-FU is quick and easy to administer.[63-66] Side effects are generally mild and include erythema, dyspigmentation, crusting, and shallow erosions or ulcerations, which typically heal within 2 to 4 weeks.[65,66] There are no reported cases of systemic adverse events. Drawbacks include the lack of histologic confirmation of clear margins, a risk of significant recurrence if undiagnosed aggressive CSCC fails treatment, and the need for multiple injection visits. Thus, we prefer shave excision for small low-risk CSCCs arising in FC and reserve IL 5-FU for eruptive squamous atypia or lower extremity low-risk CSCC who decline excision because of the risk of poor wound healing.

There is no standard guideline for the administration of IL 5-FU and the dose varies by tumor size (Table III). Smaller (<1.5 cm) and thinner lesions are more likely to respond. Any lesions that grow or that do not respond should be removed surgically. Adjuvant therapies such as topical 5-FU under occlusion, cryotherapy, and oral acitretin can help achieve clearance.[66]

ORAL TREATMENTS

Key points

- **Nicotinamide is a low-cost chemopreventive agent that reduces AKs and CSCCs and requires no monitoring**
- **Oral retinoids may be added for patients who continue to form multiple CSCCs despite comprehensive treatment of FC**
- **Long-term acitretin is required for chemoprevention given the risk of renewed CSCC formation after treatment cessation**

Table II. Investigational agents with recent or ongoing clinical trials in the United States for treatment of actinic keratoses

Investigational agents	Proposed mechanism of action	Study identifier
SR-T100: antiproliferative agent (contains solamargine, solasodine, and solasonine)	Induces apoptosis via death receptors and the mitochondrial pathway[47]	NCT01516515
KX2-391: Src tyrosine kinase inhibitor	Inhibits Src tyrosine kinase and tubulin polymerization, reducing downstream signaling and proliferation of tumor cells overexpressing Src[48]	NCT02838628 NCT03285477 NCT03285490
SOR007: uncoated nanoparticulate paclitaxel ointment	Binds to tubulin and inhibits the disassembly of microtubules, leading to inhibition of cell division and halting the proliferation of rapidly dividing tumor cells[49]	NCT03083470
VDA-1102: antineoplastic agent	Prevents glycolysis and triggers apoptosis in voltage-dependent anion channel/hexokinase 2—expressing tumor cells[50]	NCT03538951
Cold atmospheric plasma device	Increases oxidative stress via reactive oxygen species, leading to DNA damage and cell cycle arrest of malignant proliferative cells[51]	NCT02759900

Table III. Examples of protocols used by the authors for injections of intralesional 5-fluorouracil 50 mg/mL for treatment of eruptive squamous atypia and cutaneous squamous cell carcinoma

Dose	Frequency	Notes
1 mL total to a lesion >1 cm OR distributed amongst a few smaller lesions (up to approximately 1-2 cm^2)	Twice weekly ×2 weeks, then weekly ×3 weeks OR weekly ×7 weeks (up to 7 injections total)	Treat until ulceration, which is typically achieved within 4-5 injections for larger lesions
0.1-2 mL per lesion for a maximum total dose per session of 250 mg	Reinject persistent lesions at 2- to 4-week intervals	Surgical removal is recommended for lesions that do not respond to 2 injections

- **Oral capecitabine may be considered for patients with significant FC and high rates of CSCC formation, or who failed other treatments of extensive FC**

Nicotinamide

Nicotinamide (also known as niacinamide), a water-soluble vitamin B_3 derivative, has modest effects on AK and KC reduction.[67-69] Nicotinamide reduces ultraviolet-associated immunosuppression and ultraviolet-induced depletion of nicotinamide adenine dinucleotide and adenosine triphosphate, which provide the cellular energy required for repair of ultraviolet-induced DNA damage.[70-72] Nicotinamide is well-tolerated at pharmacologic doses, but can cause liver failure at high doses (>3 g/day).[73,74] Increased insulin resistance and flushing, which can occur with nicotinic acid, are not seen in nicotinamide.[75] No safety concerns have been identified in SORTs receiving up to 1 g daily.[68,76]

A phase 3, double-blind RCT showed that nicotinamide 500 mg twice daily reduced the rate of new SCCs by 30% ($P = .05$) and number of AKs compared with baseline by 13% ($P = .001$) at 12 months.[67] No significant difference in KC rates were seen upon discontinuation, suggesting that nicotinamide must be continued to maintain its chemoprotective effect.

The evidence of nicotinamide's chemoprotective effect in immunocompromised patients is limited. A phase 2 RCT of nicotinamide 500 mg twice daily for 6 months in 22 renal transplant recipients found no significant reduction in AKs or new CSCCs, but this may be related to the small sample size.[76] In a case-control trial involving 38 SOTRs, reduced AK size and complete AK regression was seen in 88% and 42% of patients receiving nicotinamide 500 mg daily, respectively.[68] No new AKs or skin cancers were seen in the nicotinamide group at 6 months. In contrast, 91% of the control group showed an increase in AKs and 7 preexisting AKs progressed to CSCCs.

While the benefits of nicotinamide are promising, there is a lack of long-term prospective studies documenting its effects on skin cancer prevention. Given nicotinamide's low cost and favorable safety profile at doses <3 g daily, it is reasonable to offer nicotinamide to patients with FC or who have had >1 CSCC.[21]

Acitretin

Acitretin is an oral retinoid that is used for chemoprevention.[77-81] Continuous treatment appears to be required to maintain a chemotherapeutic effect.[77,81,82] Though it is not expected to alter the course of existing KC, acitretin decreases the likelihood of new primary tumors. A systematic review showed a 60% reduction in CSCC formation.[83] Acitretin has also been shown to reduce AKs by ≤50%.[80]

Acitretin may be considered in patients with ≥5 KCs over the course of 2 to 3 years, significant field disease with diffuse AKs/SCCis despite treatment, high-risk KC, or metastatic KC.[21,84] It can also be considered in high-risk SOTRs with FC before first KC. Though acitretin typically does not cross-react with transplant immunosuppression, initiation should be done in conjunction with the transplant team. The minimal effective dose varies.[85] The typical practice is to start at a low dose, such as 10 mg daily or every other day, and gradually escalate to goal dose of 20 to 30 mg daily.[86] This slow increase minimizes adverse effects and identifies the best dose tolerated. One of the more common adverse effects is hypetriglyceridemia. Other adverse effects are dose-related and include headache, musculoskeletal complaints, mucocutaneous dryness, and alopecia, as well as abnormalities in liver function tests.[82,86,87] Effective management of side effects and dosage modification often allows for continuation of treatment. A limitation to acitretin utilization in the United States is its high cost.[83]

Capecitabine

Oral capecitabine, a prodrug of 5-FU, can be useful for patients with FC with high rates of CSCC despite optimization of risk factors and other chemopreventive and field-directed agents. We initiate treatment at 500 mg twice daily every other week for 1 to 3 months and then increase to 1000 mg twice daily for 2 weeks with 1 week off drug between the 2 weeks of treatment. Case reports and small case series have shown capecitabine to reduce both CSCCs and AKs in SOTRs.[88-91] Although these results are promising, larger studies in other patient populations with long-term follow-up are needed.

The side effects of capecitabine are largely dose-related and include fatigue, diarrhea, hand–foot syndrome, neutropenic fever, and stomatitis. In the literature, treatment-limiting side effects may be observed in ≤30% of patients.[84] However, in our experience, there are minimal side effects even at higher doses. Before initiating treatment, patients should be screened for dihydropyrimidine dehydrogenase deficiency and renal function impairment. During treatment, renal function and hemoglobin should be monitored monthly.

Treatment algorithms

Our approach to FC treatment is based on the degree of field disease and the risk of subsequent KC formation (Fig 2). Other factors, including tolerability, cost, and the patient's motivation for treatment, may also influence treatment choice. Patients with a higher degree of FC benefit from a combination of lesion- and field-directed therapies, as well as oral chemoprophylaxis.[22] These patients require repeated cycles of field-directed therapy, ranging from every few months to every few years.[92] All patients should be counseled on rigorous ultraviolet light protection. For patients receiving oral chemoprophylaxis, nicotinamide and acitretin are safe in combination. The concurrent use of acitretin and capecitabine has not been studied; however, in our experience the 2 medications can also be administered concurrently.

Clinical visits

The frequency of clinical visits is dictated by individual patient risk factors, such as history of skin cancers, degree of FC, and history of SOTR (Table IV). More frequent screenings may lessen morbidity associated with skin cancer and improve overall quality of life.[94,95] Patients undergoing field treatment should have close follow-up to confirm that the desired clinical endpoint has been reached.

FIELD CANCERIZATION IN HIGHER-RISK POPULATIONS

Key points

- **SOTR and patients with chronic lymphocytic leukemia have an increased risk of AK and KC**
- **Higher-risk populations benefit from earlier and more aggressive field-directed therapy**

Solid organ transplant recipients

Compared with immunocompetent patients, SOTRs are more likely to present with field disease and have higher rates of AK recurrence and progression and a lower rate of spontaneous AK regression.[96-98] Lesion-directed therapies may not be

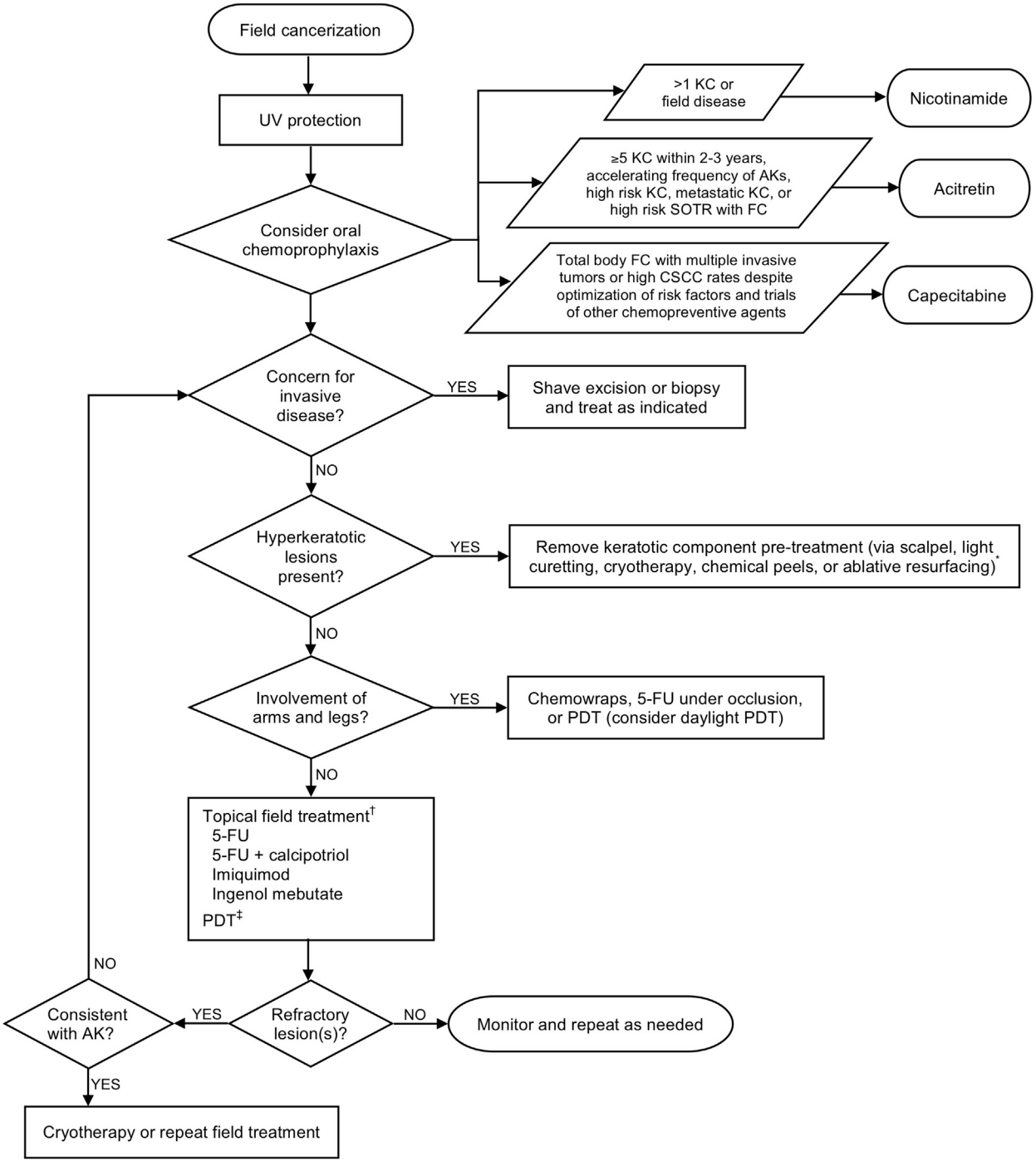

Fig 2. Field cancerization treatment algorithm.*There is a paucity of data supporting the use of ablative resurfacing or chemical peels for field-directed treatment.†Contraindications to topical therapies in general include patient noncompliance and inadequate response to topicals.‡Contraindications to PDT include known hypersensitivity to any components of the topical photosensitizer, known hypersensitivity to porphyrins, porphyria, or photodermatoses.*5-FU*, 5-Fluorouracil, *AK*, actinic keratosis; *CSCC*, cutaneous squamous cell carcinoma; *FC*, field cancerization; *KC*, keratinocyte carcinoma; *PDT*, photodynamic therapy; *SOTR*, solid organ transplant recipient; *UV*, ultraviolet.

Table IV. Recommended frequency of clinic visits based on severity of field cancerization and keratinocyte carcinoma history*

	Interval (months)	
Risk factors	**Immunocompetent**	**SOTR/ CLL**
Degree of field cancerization		
Mild (photodamage with no AKs)	—	12
Moderate (discrete AKs)	12	6
Severe (confluent AKs or SCCis)	4-6	3-6
Keratinocyte carcinoma history†		
Low-risk CSCC	6[21]	3-6[93]
Multiple KC	3-6	3[93]
High-risk CSCC	4[21]	3[93]
Metastatic CSCC	1-3	1-2[93]

AK, Actinic keratosis; *CLL*, chronic lymphocytic leukemia; *CSCC*, cutaneous squamous cell carcinoma; *KC*, keratinocyte carcinoma; *SCCis*, squamous cell carcinoma in situ; *SOTR*, solid organ transplant recipient.

*The suggested frequencies are largely based on the authors' expert opinions and not official guidelines (except those stated as National Comprehensive Cancer Network guidelines) and the clinician should always consider the individual patient when the frequency of clinic visits.

†For patients with local CSCC, National Comprehensive Cancer Network guidelines suggest follow-up every 3 to 6 months for 2 years, then every 6 to 12 months for 3 years, then annually for life. For regional disease, suggested follow-up is every 1 to 3 months for 1 year, every 2 to 4 months for the second year, every 4 to 6 months for the third year, and then every 6 to 12 months for life.[57]

sufficient to achieve disease control, which often requires cyclical use of field-directed therapies. The evidence on efficacy of specific treatments to prevent skin cancers among SOTRs is limited.[99,100]

A recent systematic review of nonsystemic interventions for AKs in 242 SOTRs found PDT to have the highest lesional clearance rates (46-100%), followed by 5-FU (79%), imiquimod (61-73.7%), and diclofenac (53%).[98] Overall, the efficacy of treatments in SOTRs appears to be lower than in immunocompetent patients. While PDT is a highly effective approach in SOTRs, cross-trial comparisons should be interpreted cautiously given their small sample sizes and the heterogeneity of the participants and outcomes. For instance, 6 of the 8 included studies investigated some type of PDT, while 5-FU was investigated in only 1 study involving 8 SOTRs.

Depending on FC severity, initiation of oral chemopreventive agents and revision of the immunosuppression regimen should be considered. Adjustment of immunosuppression is considered in SOTRs with high-risk CSCC, metastatic CSCC, or those that develop >5 to 10 CSCCs per year.[84] Typical approaches include reduction of dosage or number of immunosuppressive medications and early conversion to mammalian target of rapamycin inhibitors.[84,101-105] Recent data also suggest that conversion of calcineurin inhibitor–based immunosuppression to belatacept, a cytotoxic T-lymphocyte-associated antigen 4 fusion antibody, may reduce the risk of CSCC.[106,107] However, because belatacept works to suppress T cell responses in a way opposite to ipilimumab, further work remains to determine belatacept's overall impact on skin cancer risk and outcomes. Alteration of immunosuppression should be done in collaboration with the patient's transplant team.

Chronic lymphocytic leukemia

Patients with chronic lymphocytic leukemia have a 5- to 8.6-fold increased incidence of CSCC compared with the general population.[108,109] Patients with chronic lymphocytic leukemia with skin cancer have worse outcomes, as evidenced by higher rates of local recurrence, regional metastasis, and death.[110,111] Aggressive management of FC is critical in this population.

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