

Field Cancerization Therapies for Management of Actinic Keratosis: A Narrative Review

Nathan Jetter¹ · Neha Chandan¹ · Stephanie Wang² · Maria Tsoukas²

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Abstract Actinic keratoses (AKs) are atypical, precancerous proliferations of keratinocytes that develop because of chronic exposure to ultraviolet (UV) radiation. Treatment of AK can be lesion-directed or field-directed. Field cancerization theory postulates that the skin surrounding AK is also at increased risk for possible malignant transformation since it has been exposed to the same chronic UV light. Field-directed therapies thus have the potential to address subclinical damage, reduce AK recurrence rates, and potentially reduce the risk of squamous cell carcinoma (SCC) development. Published clinical studies have found lesion clearance rates ranging from 81 to 91% for photodynamic therapy (PDT) with either aminolevulinic acid (ALA) or methylaminolevulinate (MAL). Clinical studies have also been published on various topical treatments. Complete clinical clearance (CCC) was significantly higher in patients treated with a combination of 5-fluorouracil and salicylic acid (5-FU-SA) than in the vehicle group across multiple studies, and CCC ranged between 46 and 48% following treatment with imiquimod. Additionally,

treatment with diclofenac sodium (DFS) found reduction in lesion sizes to range from 67 to 75%. Reported results have been similar for another non-steroidal anti-inflammatory drug (NSAID), piroxicam, which has more cyclooxygenase (COX)-1 activity than DFS. Active treatments with ingenol mebutate were also significantly more effective than vehicle at clearing AK lesions. All treatments resulted in mild, localized skin reactions. PDT using conventional light sources was associated with increased severity of pain and/or discomfort, while PDT using daylight as the light source was associated with less pain and occasionally no pain at all. Though no widely accepted algorithm for the treatment of AKs exists, field-directed therapy can be particularly useful for treating photo-exposed areas containing multiple AKs. Additional research with more direct comparisons between these field-directed therapies will help clinicians determine the best therapeutic approach. Here, we provide a balanced and comprehensive narrative review of the literature, considering both light-based and topical therapies with a focus on their field-therapy aspects, and propose a therapeutic algorithm for selecting an appropriate treatment in the clinical setting.

✉ Maria Tsoukas
tsoukasm@uic.edu

Nathan Jetter
Njette2@uic.edu

Neha Chandan
Nchand8@uic.edu

Stephanie Wang
Swang36@uic.edu

¹ University of Illinois College of Medicine, 808 S. Wood St. R380 MC624, Chicago, IL 60612, USA

² Department of Dermatology, University of Illinois College of Medicine, 808 S. Wood St., Suite 380, Chicago, IL 60612, USA

Key Points

The important role of field-directed therapies in the treatment of actinic keratoses (AKs) is becoming ever clearer given the need to address subclinical damage, reduce AK recurrence rates, and potentially reduce the risk of squamous cell carcinoma (SCC) development.

Currently, no widely accepted algorithm exists for the treatment of AK in the USA, though the evidence leans towards field-directed treatment of photo-exposed areas containing multiple AKs.

Deciding between the various light-based and topical therapies requires an understanding of the outcomes, adverse effects, and costs of each therapy and how those relate to the patient preferences.

1 Introduction

The emerging science of field cancerization is changing the paradigm for treating cutaneous malignancies by targeting entire skin regions. The concept was first proposed by Slaughter et al. in 1953 to describe histologically abnormal tissue surrounding primary oral squamous cell carcinoma (SCC) and to explain the development of multiple primary tumors and locally recurrent cancers within the field. Since that time, modern molecular techniques have established a genetic basis for this model in various types of cancers, including cutaneous malignancies. The field begins from a singular cell, which accumulates genetic mutations after carcinogen exposure and subsequently divides to create a field of monoclonal pre-malignant cells. Eventually, transformative events may occur, resulting in cells with invasive and metastatic properties, thus forming a carcinoma. In terms of cutaneous malignancies, ultraviolet (UV) radiation (UVA/UVB) is the most common source of carcinogenesis. The concept of field cancerization suggests that, because the skin surrounding cutaneous malignancies has been exposed to the same chronic UV light as the initial lesion, it is at increased risk for genetic abnormalities and thus possible malignant transformation.

Actinic keratoses (AKs) are intraepithelial atypical proliferations of keratinocytes that are generally regarded as precancerous and typically develop because of chronic exposure to UV radiation. The prevalence of AKs was

estimated to be 40 million in the USA in 2004 [1]. In Australia, 11–40% of white people were estimated to have AKs in 1989 [2]. The visible clinical lesions are the initial manifestation of a multi-step carcinogenesis process or disease continuum that can progress from initial subclinical keratinocyte dysplasia into invasive SCC. Field cancerization develops because UV light causes neoplastic changes across the entire sun-exposed field of skin. Thus, areas of subclinical, or non-visible, sun damage in the periphery of visible AKs contain the same genetic changes as those found in the lesions themselves and are known as areas of field cancerization. Within the cancerous field, all stages of AKs may coexist, including individual UV-damaged keratinocytes, subclinical (non-visible, non-palpable) lesions, early clinical lesions, late clinical lesions, and possibly eventually invasive SCCs.

The consequence of this pathophysiology is that the treatment of cutaneous malignancies should focus not only on the tumor but also on the field from which it developed. In terms of AKs, this means that all lesions on the entire sun-exposed field should be targeted and eliminated to provide long-term disease remission and prevent disease recurrence. This concept provides a rationale for field therapy, in which the entire field, rather than individual lesions, is treated. The goals of field therapy are to eliminate clinically visible as well as subclinical lesions and to prevent the development of invasive SCC.

Although broadly applied and effective in clearing visible AKs, lesion-directed therapies such as cryotherapy do not address field cancerization and can lead to high recurrence rates. Field-directed therapies address subclinical damage, reduce AK recurrence rates, and potentially reduce the risk of SCC development [3, 4]. Emerging preclinical evidence indicates that field-directed therapy may have preventive effects and delay recurrence of non-melanoma skin cancers (NMSCs). Thus, field therapy for specialized patient groups, including organ transplant recipients (OTRs) and individuals with a history of chronic sun exposure, are promising developments, as these therapies may confer a preventive potential.

The purpose of this article is to discuss the range of field-directed therapies that are currently available, including photodynamic therapy (PDT) with aminolevulinic acid (ALA) or methylaminolevulinate (MAL), and various topical therapies such as 5-fluorouracil (5-FU) cream (5, 1, 0.5%), imiquimod cream (5, 3.75, 2.5%), diclofenac 3% gel, piroxicam gel (1 and 0.8%), and ingenol mebutate gel (5 and 3.75%). We examine the literature and critically evaluate the role of these treatments as field-directed therapies.

2 Light-Based Minimally Invasive Field Cancerization Therapies

PDT involves the topical application of the precursor molecules ALA or its derivatives (i.e., MAL), which are enzymatically converted through the heme pathway into the active endogenous photosensitizer protoporphyrin IX (PpIX). When an appropriate light source illuminates PpIX, it generates reactive oxygen species (ROS) such as highly cytotoxic singlet oxygen. Cell death follows, driven by direct ROS damage to cell membranes and lipid peroxidation. A reactive inflammatory response is also involved. PpIX preferentially accumulates in pre-malignant and malignant cells, likely due to both enhanced cellular uptake of the precursor molecules and increased heme pathway enzymatic activity. PpIX has several absorption peaks in the visible spectrum, and the 410 nm (blue light) and 635 nm (red light) wavelengths have been broadly applied and received US FDA approval to activate the photodynamic effect. As pre-malignant cells concentrate PpIX even when not clinically visible, PDT represents a field therapy for AKs since an entire area of actinically damaged skin can be treated [5–9].

2.1 Efficacy and Outcomes

The FDA approved PDT with ALA photosensitization and blue light for the treatment of AK in September 2000 [10, 11]. FDA approval for ALA photosensitization and red light followed in 2016 [12, 13]. Initial phase II/phase III trials by Jeffes et al. [14] on face and scalp AKs demonstrated 66% clearance of individual AKs at 8 weeks. A phase III trial by Piacquadio et al. [15] demonstrated individual AK lesion clearance of 83% at 8 weeks, with 66% of patients experiencing complete response rates, that is, 100% AK clearance (Table 1). Both trials gave a second treatment for persistent AKs, finding 85% clearance at 16 weeks and 91% clearance at 12 weeks, respectively. Further studies have investigated PDT with ALA or MAL compared with PDT plus placebo, most recently a double-blind, placebo-controlled multicenter randomized controlled trial (RCT) in 2016 that used red light [12]. These studies have found lesion complete clearance rates of 81–99% for PDT–ALA–MAL versus 22–37.1% for PDT plus placebo after a maximum of two treatments [12, 16, 17]. Jerjes et al. [18] conducted a longer-term follow-up retrospective evaluation of outcome study in 62 patients at a large tertiary center in the UK. At 3-year follow-up, 96.8% of patients and 98.3% of lesions had complete response.

PDT field therapy has been shown to help prevent AK development. For facial AK, PDT with ALA delayed the

Table 1 Efficacy of photodynamic light therapy treatments

Study	Study type	Tx photo-sensitizer	Tx light source	Pts (N)	Follow-up duration	Efficacy/outcomes	AEs
Dirschka et al. [17]	MC, RAN, PC, observer-blind phase III inter-individual	BF-200 ALA, a registered MAL cream, and PL	Aktilite CL 128, Omnilux PDTTM, PhotoDyn 750/505 Waldmann PDT 1200 L	600	3 mo	Lesion complete clearance rate 94% (BF-200 ALA) vs. 37.1% (PL)	At least one local skin reaction event: 80.6% (BF-200 ALA), 80.1% (MAL), 46.1% (PL). At least one discomfort AE: 89.1% (BF-200)
Piacquadio et al. [15]	MC, RAN, PC, investigator-blind, uneven PG phase III inter-individual	ALA (20% wt/vol) and PL vehicle	Visible blue light (Blu-U)	243	8 wk	ALA individual AK lesion clearance: 83%	90% of pts treated with ALA reported moderate-severe discomfort, 3% of pts discontinued tx due to pain
Szeimies et al. [16]	MC, RAN, PC, DB, phase III inter-individual	BF-200 ALA and PL	Aktilite CL 128 (590–670 nm) and PhotoDyn 750 (580–1400 nm)	122	3 mo	Lesion complete clearance rates of 81% (ALA) vs. 22% (PL)	Incidence of pain, itching, burning higher in pts treated with Aktilite CL 128 vs. PhotoDyn 750

Table presents the largest three trials cited by number of pts in descending order

AK actinic keratosis, AE adverse effect, ALA 5-aminolevulinic acid, MAL methylaminolevulinic acid, MC multicenter, PC placebo-controlled, PG parallel-group, PL placebo, *pt(s)* patient(s), RAN randomized, *tx* treatment, *vol* volume, *wt* weight

development of new AKs by 6 months compared with control [19]. Though not a primary outcome of the 2016 study by Reinhold et al. [12], they did note that—while one patient in the placebo group displayed a new lesion after PDT—no patients in the PDT–ALA group developed new lesions despite the group being twice as large. The ability to reduce the incidence of new AKs may be particularly useful in immunocompromised patients who are at increased risk for new AKs and malignant transformation [20]. Wennberg et al. [20] found that PDT–MAL resulted in a 46% reduction in new AKs at 3 months in transplant patients receiving immunosuppressive therapy. In a longer study, 62% of areas receiving PDT were free from new lesions compared with 35% in control areas 12 months after PDT with MAL in renal transplant patients [21].

Both lesion-targeted PDT and field therapy PDT have been shown to have good outcomes in secondary endpoints. In the early pivotal studies by Jeffes [10], investigators assessed cosmetic results and rated 92% of lesions as appearing “good” or “excellent” after treatment. That same year, investigators in a study by Szeimes et al. [22] graded 96% of cosmetic outcomes for patients treated with PDT as “good” or “excellent” versus 81% for patients treated with cryotherapy. In a comparison study against topical diclofenac, PDT–MAL had significantly greater investigator-reported cosmetic outcomes and never resulted in scarring or pigmentation changes [23].

Daylight is among the light sources that can activate the FDA-approved photosensitizers ALA and MAL. Three split-face/scalp studies, also called intra-individual studies, investigated the efficacy of daylight PDT (d-PDT) compared with conventional PDT (c-PDT) for lesion-targeted treatment. In Italy, Fagnoli et al. [24] showed that d-PDT with MAL had equivalent results to c-PDT with MAL for AK grade I but was not as effective as c-PDT with MAL for AK grades II and III. Two phase III multicenter RCTs demonstrated non-inferiority of d-PDT compared with c-PDT. In the Australian trial, 89.2% of mild AKs treated with d-PDT with MAL had resolved versus 92.8% treated with c-PDT at 12 weeks [25]. In the European trial, 70% of mild AKs treated with d-PDT with MAL had resolved versus 74% treated with c-PDT at 12 weeks [26]. Furthermore, non-inferiority of d-PDT compared with c-PDT for the prevention of new lesions was recently demonstrated. In a split-face/scalp study, there was no statistically significant difference in the development of new lesions at any follow-up point between the d-PDT and c-PDT sides [27]. Interestingly, in two studies of d-PDT, efficacy was maintained regardless of sunny or cloudy weather conditions [26, 27].

2.2 Patient Satisfaction and Preference

We found two surveys of patient satisfaction in the literature. A 2011 telephone survey of Australian patients receiving lesion-targeted therapy found 50% thought PDT–MAL was very effective, and 66% stated they would recommend the therapy. All these patients had previously received cryotherapy for earlier AKs, and patients reported equivalent recovery times [28]. An earlier mailer survey to patients of a hospital in Michigan found patients reported a faster recovery time than with cryotherapy and surgical excision. In this survey, patients had equal preference for PDT, cryotherapy, and trichloroacetic acid destruction and preferred PDT over 5-FU and imiquimod [29]. In an early trial, 98% of patients reported their outcome with PDT as “better than” or “equal to” their results from previous treatments with cryotherapy or 5-FU [22]. Additionally, patients have reported satisfaction with PDT over other therapies such as diclofenac [23]. In a study looking at antihistamine use for side effect prophylaxis, 77.8% of those receiving standard PDT–ALA reported feeling “extremely satisfied” on day 30. On day 180, that number had decreased to 62.5%, with 25% being “slightly satisfied” [30]. Satisfaction is also high with d-PDT. In the European split-face intra-patient trial comparing d-PDT with c-PDT, 64.8% of patients reported being “very satisfied” with the d-PDT treatment side compared with only 18.9% for the c-PDT side [26].

Patient-reported satisfaction with cosmetic outcomes with PDT therapy has been positive. Recently, Tanaka et al. [31] found 83% of patients indicated excellent cosmetic outcome. Of note, despite 88% of patients treated with PDT at a UK tertiary hospital reporting “excellent” cosmetic outcomes, data as of 2015 showed only 15–20% of patients elected PDT over topical or surgical therapies [18]. See Table 2 for a summary of patient satisfaction with PDT.

2.3 Adverse Effects

Pain during the procedure is the primary adverse effect of conventional PDT with ALA or MAL, whether for lesion-targeted therapy or field therapy (Table 3). In the telephone survey by Tran et al. [28], 58% of patients reported severe pain during PDT–MAL illumination, and 42% reported moderate pain. Additionally, 20% of patients required nerve block for pain to continue therapy [28]. A study of 14 patients found that six (43%) required an intermission in the therapy session because of severe pain [32].

Pain reduction approaches can be categorized as pain mitigation or pain control. Pain mitigation approaches optimize treatment variables to minimize pain. Multiple studies have investigated the relative pain caused by

Table 2 Patient satisfaction following photodynamic light therapy treatments

Study	Study type	Tx photo-sensitizer	Tx light source	Pts (N)	Follow-up duration	Satisfaction/preference	AEs
Szeimies et al. [22]	RAN, two-arm, inter-individual	MAL 160 mg/g, 3-h application time	Red light (75 J/cm ²)	122	3 mo	98% of pts reported outcome with PDT as “better than” or “equal to” results from previous cryotherapy or 5-FU	Local adverse reactions reported by 43% for MAL vs. 26% for cryotherapy. 3 pts discontinued tx due to pain
Lacour et al. [26]	MC, RAN, two-arm, investigator-blind phase III intra-individual split-face	MAL	Daylight vs. red light illumination (37 J/cm ²)	100	3 mo	64.8% of pts reported being “very satisfied” with the d-PDT tx side vs. 18.9% for c-PDT side	Mean pain score on 0–10 scale: 0.7 for daylight; 4.4 for red light
Jerjes et al. [18]	Retrospective evaluation of outcome	MAL 16%, 3-h application time	Single-channel 628-nm diode laser	62	3 years	15–20% of pts elect PDT over topical or surgical therapies	7 pts had long-term side effects, including pigmentation changes, altered sensation

Table presents the largest three trials cited by number of pts in descending order

5-FU 5-fluorouracil, AE adverse effect, c-PDT conventional PDT, d-PDT daylight PDT, MAL methylaminolevulinate, MC multicenter, pt(s) patient(s), RAN randomized, tx treatment

Table 3 Adverse effects associated with photodynamic light therapy txs

Study	Study type	Tx photo-sensitizer	Tx light source	Pts (N)	Follow-up duration	Efficacy/outcomes	AEs
Steinbauer et al. [35]	Retrospective assessment	ALA vs. MAL	Metal halide lamp (580–750 nm)	224	NA	NA	PDT–ALA more painful than PDT–MAL
Artis et al. [36]	Prospective cohort study	ALA 20% 4-h incubation or MAL 16% 3-h incubation	PDT 1200 L (580–750 nm) or Aktilite (630 nm)	108	NA	NA	PDT–ALA more painful than PDT–MAL, although statistical significance disappeared after adjustment for other pain-related factors
Rubel et al. [25]	MC, RAN, two-arm, investigator-blind intra-individual split-face	MAL	Daylight vs. Aktilite lamp	100	3 mo	Lesion complete clearance 89.2% for daylight vs. 92.8% for lamp	Pain reported on 10-point VAS: 0.8 (daylight); 5.7 (Aktilite lamp)

Table presents the largest three trials cited by number of pts in descending order

AE adverse effect, ALA 5-aminolevulinic acid, MAL methylaminolevulinate, MC multicenter, NA not applicable, PDT photodynamic therapy, pt(s) patient(s), RAN randomized, tx treatment, VAS visual analogue scale

various photosensitizers. Six studies found PDT–ALA to be more painful than PDT–MAL [33–37]. In the most striking result, 14% of patients reported severe pain with PDT–MAL compared with 54% with PDT–ALA [33]. At least three of the studies identified showed no statistical difference in pain between ALA and MAL photosensitizers [32, 38, 39]. A study using d-PDT examined pain when

using a nano-emulsified preparation of ALA (BF-200 ALA) and found no statistically significant difference between MAL and BF-200 ALA [40]. One complicating factor regarding photosensitizers is the lack of standardized incubation time, with ALA generally receiving a longer incubation time than MAL in the cited studies. Martin [41] attempted to elucidate the incubation question and found

that, for ALA, a 15-min incubation time resulted in significantly less pain reported than a 75-min incubation time.

Alternative light sources have also been investigated for pain mitigation. A large study looked at four different light sources used across 688 separate treatments for 483 unique lesions and reported the percentage of treatments for each light source that caused severe pain: xenon (2%), metal halide (16%), halogen (16%), and laser (21%) [42]. d-PDT has received attention because of several studies that reported no pain for many of the patients receiving the treatment, including 17 of 18 patients in a 2012 Swiss study [43]. Three studies investigated d-PDT–MAL compared with c-PDT–MAL and found pain reductions on the 10-point visual analog scale (VAS) of 4.7, 4.9, and 2.2 [24, 25, 44]. Neittaanmäki-Perttu et al. [45] also found that d-PDT–MAL resulted in less pain than c-PDT–MAL. A comparison of light sources is complicated by the lack of standardized irradiation strengths. In one study, low-irradiance c-PDT (7 mW/cm²) delivered over a longer period was shown to be less painful than high-irradiance c-PDT (80 mW/cm²), with similar clearance rates [46].

While pain mitigation approaches have strong potential, especially daylight and low-irradiance/long-exposure protocols, strategies for controlling pain are associated with c-PDT. A review by Ang et al. [47] identified published studies on the following pain-control techniques: nerve block, oral analgesia, intravenous analgesia, subcutaneous infiltration analgesia, inhaled analgesia, cold air, and cold water spray. All four studies of nerve block for pain control during c-PDT found patients given nerve block reported low pain scores [48–51].

Localized side effects are prominent in PDT regardless of pain reduction. A study of 22 patients receiving one treatment of c-DPT–ALA to the complete face found various side effects in the following percentages of patients: erythema 100%, burning 90.9%, edema 90.9%, itching 86.4%, scaling 81.8%, pustules 59.1%, hypo/hyper-pigmentation 0% [39]. Alternatively, Jerjes et al. [18] found 4.8% of patients in their study had hypoesthesia and 6.5% had hypopigmentation. d-PDT evoked less severe local skin reactions than c-PDT, with statistically significant reductions in erythema (86 vs. 97%), pustular eruption (6 vs. 17%), and crusting (74 vs. 83%) [24].

Gholam et al. [39] pursued a holistic view of the adverse effects of PDT by examining patients' quality of life as represented by the Dermatology Life Quality Index (DLQI). DLQI score increased from baseline pretreatment (1.6) to a high immediately post-treatment (7.3) and declined steadily (4.4 on day 14), eventually settling better than pre-treatment (0.1 at 4 weeks). A trial of antihistamine prophylaxis for localized adverse effects of PDT measured lifestyle disruption and found no statistical difference between groups. In the antihistamine group, 11.1% of

patients reported moderate or severe lifestyle disruption on day 7 versus 20% for PDT without antihistamine. Notably, on day 30, no patients in either group reported “moderate” or “severe” lifestyle disruption [30].

2.4 Cost

Kirby et al. [52] estimated average annual patient costs based on utilization for various therapies for AK: ingenol mebutate \$US847, imiquimod \$US823, PDT with ALA or MAL \$US532, diclofenac \$US414, 5-FU \$US311, cryotherapy for >15 lesions \$US299 (cryotherapy for one lesion \$US129). Multiple studies have directly compared c-PDT and specific topical therapies, with somewhat conflicting results. Over 1 year, imiquimod was £174 less costly than PDT–MAL therapy from the perspective of the UK National Health Service, although PDT resulted in an additional 0.005 quality-adjusted life-years (QALYs) gained. The incremental cost-effectiveness ratio (ICER) for PDT–MAL versus imiquimod was £34,576 [53]. Imiquimod and PDT–MAL both generated higher total costs than diclofenac [54]. Conversely, a cost-effectiveness analysis found a higher per-patient cost for PDT–MAL but a lower cost per patient with complete response than for diclofenac at both 2 and 12 months. PDT had a significantly better lesion complete clearance rate of 85.9 versus 51.8% for diclofenac; thus, PDT–MAL was more expensive but was also more cost effective [55]. Using data from Finland, Soini et al. [56] investigated PDT–MAL compared with cryosurgery, imiquimod, diclofenac, and ingenol mebutate. PDT–MAL was the most effective treatment but cost more than all other treatments, with an ICER of €82,706 versus ingenol mebutate, which was the most cost-effective treatment. See Table 4 for a summary of costs.

It may be useful to note that major policies in the USA preferentially reimburse procedural therapies above pharmacologic treatments, tending to favor cryotherapy over PDT [57]. Most economic studies do not include costs of adverse effects or recurrence. Importantly, the preventive aspect of PDT field therapy has not yet been included in the economic cost-effectiveness literature.

3 Topical Therapies

3.1 5-Fluorouracil

Field-directed therapy with topical 5-FU is a common modality for AKs because of its well-understood mechanism and efficacy (Table 5). This anti-metabolic drug inhibits thymidylate synthetase, an enzyme required for DNA synthesis, preventing cell proliferation and resulting in cell death [58]. Considered a gold standard for topical

Table 4 Associated costs of photodynamic light therapy treatment

Study	Study type	Tx	Number of pts/claims	Result
Kirby et al. [52]	Cohort cost-identification	PDT, cryotherapy, 5-FU, imiquimod, DFS, IM	111,129 claims	IM \$US847, imiquimod \$US823, PDT-ALA or PDT-MAL \$US532, DFS \$US414, 5-FU \$US311, cryotherapy > 15 lesions \$US299 (one lesion \$US129)
Zane et al. [55]	RAN, two-arm, observer-blinded inter-individual	PDT-MAL vs. DFS	200 pts	Cost-effectiveness analysis at 3 mo: PDT-MAL €566.7; DFS €595.2
Soini et al. [56]	Probabilistic 2-year decision tree model	PDT-MAL, cryosurgery, imiquimod, DFS, IM	NA	PDT-MAL ICER €82,706 vs. IM, which was most cost-effective tx

Table presents the largest three trials cited by number of pts in descending order

5-FU 5-fluorouracil, ALA 5-aminolevulinic acid, DFS diclofenac sodium, ICER incremental cost-effectiveness ratio, ICER incremental cost-effectiveness ratio, IM ingenol mebutate, MAL methylaminolevulinic acid, NA not applicable, PDT photodynamic therapy, *pt(s)* patient(s), RAN randomized, *tx* treatment

Table 5 Efficacy and adverse effects of 5-fluorouracil treatment

Study	Study type	AKs severity	Tx	Pts (N)	Duration	Efficacy	AEs
Szeimies et al. [59]	Prospective non-interventional	Grade I/II	5-FU 0.5%/SA 10%	1051	Applied once daily for 12 wk	Decrease in mean no. of lesions by 70%, decrease in mean size by 80%; efficacy rated as “very good” or “good” in 89% of pts	Tolerability rated as “very good” or “good” in 87% of pts
Stockfleth et al. [61]	MC, RAN, PC, DB, PG inter-individual	Grade I/II	5-FU 0.5%/SA 10% and DFS 3% in HA	470	5-FU applied OD for 12 wk; DFS HC BID for 12 wk	8 wk post tx: significantly more lesions cleared with 5-FU/SA (74.5%) vs. DFS HA (54.6%; $p < 0.001$) or vehicle (35.5%; $p < 0.001$)	Burning and inflammation more frequent with 5-FU—mild to moderate intensity
Stockfleth et al. [60]	MC, RAN, DB, vehicle-controlled inter-individual	Grade I/II	5-FU 0.5%/SA 10%	166 (55 control)	Applied OD for 12 wk	8 wk post tx: CCC significantly higher in tx group (49.5 vs. 18.2%; $p = 0.0006$)	TEAEs more common with 5-FU than vehicle (99.1 vs. 83.6%)

Table presents the largest three trials cited by number of pts in descending order

5-FU 5-fluorouracil, AE adverse effect, AK actinic keratosis, BID twice daily, CCC complete clinical clearance, DB double-blind, DFS diclofenac sodium, HA hyaluronic acid, IM ingenol mebutate, MC multicenter, *no.* number, OD once daily, PC placebo-controlled, PG parallel-group, *pt(s)* patient(s), RAN randomized, SA salicylic acid, TEAE treatment-emergent AE, *tx* treatment, *wk* week

treatment of AKs, 5-FU is available in creams and solutions of 0.5, 1, 2 and 5%. Destruction of lesions results in inflammation following treatment, with possible local skin reactions including erythema, blistering, scabbing, and itching on treatment sites. Studies have found a combination of 0.5% 5-FU and 10% salicylic acid (5-FU-SA) to be associated with greater efficacy and fewer adverse effects in the management of AKs. 5-FU-SA should be applied once daily for up to 12 weeks, with responses noticeable 4–8 weeks following treatment [58]. Szeimies et al. [59] showed that 5-FU-SA treatment led to a 70% decrease in

the mean number of lesions and a 90% decrease in the mean size of AKs. A 2017 study found that complete clinical clearance (CCC) was significantly higher ($p = 0.0006$) in patients treated with 5-FU-SA than in patients receiving vehicle (49.5 vs. 18.2%, respectively) [60]. Similar studies by Stockfleth and colleagues [60–62] found significantly more lesions cleared with 5-FU-SA than with vehicle (74.5 vs. 35.5%; $p < 0.001$), and 85.8% of the lesions did not recur in the 5-FU-SA group. In these same three randomized, double-blind, vehicle-controlled studies, mild to moderate treatment-emergent adverse

events were more common with 5-FU than with a vehicle gel but did not lead to therapy discontinuation. Treatment tolerability was rated as “very good” or “good” in 87% of patients, making 5-FU–SA a favorable option for long-term management of AKs [59].

3.2 Diclofenac Sodium

Diclofenac sodium (DFS) is a nonsteroidal anti-inflammatory drug (NSAID) that targets AKs through the induction of apoptosis and the inhibition of angiogenesis. It inhibits both cyclooxygenase (COX)-2, of which AKs have increased activity, and the upregulation of the arachidonic acid cascade, preventing the production of prostaglandins and thus the formation of UV-induced skin cancers [63]. Its common application includes diclofenac 3 in 2.5% hyaluronic acid gel applied twice daily for 60–90 days. In one study, 41% of patients experienced CCC following 16 weeks of treatment [64]. In another study, DFS resulted in reduction of lesion size by 64.7% compared with 34.3% in the vehicle group [65]. Additionally, a significantly higher proportion of patients treated with DFS had a total lesion number score (TLNS) of 0 compared with the vehicle group (50 vs. 20%; $p < 0.001$) [66]. This treatment regimen appears to be better tolerated than once-daily application of 5-FU–SA, with patients expressing significant satisfaction and reporting fewer adverse effects [61]. In two different studies, patients observed no significant side effects and reported treatment to be well tolerated [65, 66]. Another study showed adverse effects to be

limited to mild erythema and mild–moderate swelling of treated areas [64]. Similarly, one study reported that only 24% of patients experienced irritant-type contact dermatitis confined to the treatment site [67]. Despite being better tolerated, DFS is less effective than 5-FU–SA, with the latter demonstrating higher histological and clinical clearance rates [61]. See Table 6 for a summary.

3.3 Piroxicam

Piroxicam is an NSAID that has received attention as an alternative to diclofenac for both lesional and field-directed AK therapy (Table 7). Piroxicam appears to have more potent COX-1 inhibitory action than diclofenac [68]. It is hypothesized that the synergistic co-treatment of COX-1 and COX-2 results in a significant inhibition of vascular epidermal growth factor (VEGF), a growth factor important in tumor proliferation [69]. In a study in 2010 [70], ten patients (31 lesions) applied a preparation of piroxicam 1% gel twice daily for 12 weeks. Complete response was observed in 15 lesions (48%) [70]. More recent studies have used a novel topical preparation that includes both piroxicam 0.8% and a 50+ sun protection factor (SPF) sunscreen. Puviani et al. [71] reported a 55% reduction in the number of AKs in areas treated twice daily for 12 weeks. The use of a piroxicam plus sunscreen preparation limits the ability to make direct comparisons between piroxicam and other topical treatments such as diclofenac. However, it is worth noting that daily application of a separate sunscreen product is a component of

Table 6 Efficacy and adverse effects of diclofenac sodium treatment

Study	Study type	AKs severity	Tx	Pts (N)	Duration	Efficacy	AEs
Wolf et al. [66]	RAN, DB, PC inter-individual	5 + lesions contained in 5-cm ² blocks	DFS 3% in 2.5% HA gel	96	3 mo	Significantly higher proportion of pts in tx group had TLNS 0 vs. PL group (50 vs. 20%; $p < 0.001$). 47% of pts in tx group had CLNS 0 vs. 19% in PL group ($p < 0.001$)	Tx well tolerated
Ulrich et al. [90]	RAN, PC inter-individual	≥3 AK lesions in a contiguous 50-cm ² area	DFS 3% in 2.5% HA gel	32 (8 control)—OTRs	BID for 16 wk	4 mo post tx: 41% CCC vs. 0% vehicle	Mild erythema and mild–moderate swelling of treated areas
Rivers et al. [67]	OL prospective assessment of outcome	Clinical diagnosis of ≥1 AK	DFS 3 in 2.5% HA gel	29	Applied BID for 180 days	30 days post tx: 81% CCC, 15% PC	24% irritant-type contact dermatitis confined to tx site

Table presents the largest three trials cited by number of pts in descending order

AE adverse effect, AK actinic keratosis, BID twice daily, CCC complete clinical clearance, CLNS complete lesion number score, DB double-blind, DFS diclofenac sodium, HA hyaluronic acid, mo month(s), OL open-label, OTR organ transplant recipient, PC placebo-controlled, PL placebo, pt(s) patient(s), RAN randomized, TLNS total lesion number score, tx treatment

Table 7 Efficacy and adverse effects of piroxicam treatment

Study	Study type	AKs severity	Tx	Pts (N)	Duration	Efficacy	AEs
Puviani et al. [71]	MC, assessor-blinded	140 grade 1 lesions, 296 grade 2 lesions, 49 grade 3 lesions	Piroxicam 0.8% plus sunscreen SPF 50+	70	3 mo	55% reduction in number of AKs	No SAEs reported during trial; 3 pts reported mild-moderate transient skin rash after application
Campione et al. [70]	Preliminary, OL	Mean AKESA score 7.6	Piroxicam 1% gel	10	3 mo	CR in 48% of lesions	Pruritus (25% of pts), mild erythema (25%), dry skin (10%), rash (2%)
Garofalo et al. [72]	Case series	44 grade 1–2 lesions, 7 grade 3 lesions	Piroxicam 0.8% plus sunscreen SPF 50+	10	4 mo	3 pts showed complete clearance (30%); additional 4 pts had marked ($\geq 75\%$ lesion count reduction) improvement	Limited to mild local irritation; no systemic side effects reported

Table presents the largest three trials cited by number of pts in descending order

AE adverse effect, AK actinic keratosis, AKESA actinic keratosis erythema, scale, and atrophy, CR complete response, MC multicenter, mo month(s), OL open-label, *pt(s)* patient(s), SAE serious adverse event, SPF sun protection factor, tx treatment, wk week

the treatment regimen in many topical studies. A treatment plus sunscreen preparation may be particularly useful when treating OTRs, a population for whom treating existing field-cancerization and preventing additional photodamage are both essential. In a case series of ten OTR patients treated for 16 weeks with a piroxicam plus sunscreen preparation, three patients (30%) experienced complete clearance, and an additional four patients (40%) had marked ($\geq 75\%$ lesion count reduction) improvement in their overall AK lesion count [72]. In the 2010 study by Campione et al. [70], adverse effects included pruritus (25% of patients), mild erythema (25%), dry skin (10%), and rash (2%); none of these required treatment suspension.

3.4 Imiquimod

Imiquimod, of the imidazoquinoline family, is a synthetic nucleoside analog that activates Toll-like receptors (TLRs)-7/8, resulting in the activation of the innate immune response and enhancement of interferon (IFN), tumor necrosis factor (TNF), and interleukins (IL)-1 and -12, which then results in an acquired immune response [73]. Specifically, topical imiquimod induces IFN α within AK lesions, triggering both innate and adaptive immune responses [74]. Its common application includes 2.5, 3.75 and 5% creams. In one study, patients applied imiquimod 5% three times weekly for 16 weeks; 48.3% of patients reported CCC and 64.0% reported partial clearance (PC) compared with vehicle-treated patients (7.2 and 13.6%, respectively; $p < 0.001$) [75]. In another study, 46% of patients experienced CCC, and 35% experienced PC [76]. When response rates were linked to adverse events, a

significant trend ($p = 0.001$) was found, showing a higher percentage of adverse events in the CCC group than in the PC group (74 vs. 39%, respectively) [76]. In a different study, application site reactions were reported by 38.8% of patients ($p < 0.001$), fever by 2.9% ($p = 0.04$), and post-operative pain by 3.7% ($p = 0.03$) [75]. Local erythema has also been reported as an adverse side effect [77]. Overall, imiquimod was well tolerated and led to few treatment-related discontinuations [78, 79], but satisfaction was only 55–60% in imiquimod-treated patients [76]. A pharmacoeconomic analysis of management of AKs assumed standard costs of procedures and office visits and two treatment courses and found imiquimod to be the most expensive treatment compared with 5-FU, DFS, and PDT-ALA [80]. The total cost for each was \$US725.17 for PDT-ALA, \$US845.07 for diclofenac, \$US942.13 for 5-FU, and \$US1473.39 for imiquimod, with costs of imiquimod and DFS increasing because of lower efficacy and the need for additional treatments to reach 100% clearance [80]. See Table 8 for a summary of imiquimod efficacy and adverse effects.

3.5 Ingenol Mebutate

Ingenol mebutate (IM) acts as a protein kinase C (PKC) agonist, stimulating neutrophil-mediated antibody-dependent cellular cytotoxicity and activating necrosis of dysplastic AKs [81]. Approved in 2012 by the FDA for the treatment of AKs, IM is commonly used in gels of 0.015, 0.025 and 0.05% (Table 9). A study assessing the efficacy of IM 0.015% applied once daily for 3 consecutive days observed CCC in 46.7% of patients versus 18.4% in the vehicle group ($p < 0.001$) [82]. Similarly, a study

Table 8 Efficacy and adverse effects of imiquimod treatment

Study	Study type	AKs severity	Tx	Pts (N)	Duration	Efficacy	AEs
Korman et al. [75]	MC, RAN, DB, vehicle-controlled, PG, inter-individual phase III	4–8 lesions in a 25-cm ² area	Imiquimod 5% cream	492 (250 control)	Applied TIW for 16 wk	8 wk post tx: CCC and PC for imiquimod-treated pts (48.3 and 64.0%, respectively) clinically and statistically significantly higher than for vehicle-treated pts (7.2 and 13.6%, respectively); $p < 0.001$	Application site reactions reported by 38.8% of imiquimod-treated pts vs. 7.2% of vehicle-treated pts ($p < 0.001$); fever 2.9 vs. 0.04%, $p = 0.04$; postoperative pain 3.7 vs. 0.8%, $p = 0.03$
Hanke et al. [77]	RAN, DB, PL-controlled, PG inter-individual	5–20 lesions in a 25-cm ² area	Imiquimod 2.5 and 3.75% cream	490	Applied OD for two 3-wk intervals	8 wk post tx: 2.5%: 25.0% CCC, 42.7% PC; 3.75%: 34.0% CCC, 53.7% PC PL: 5.5% CCC, 12.8% PC $p < 0.001$, each imiquimod vs. PL; $p = 0.034$, 3.75 vs. 2.5% for PC	Local events including erythema
Swanson et al. [79]	MC, RAN, DB, PL-controlled, inter-individual phase III	5–20 lesions in a 25-cm ² area	Imiquimod 2.5% and 3.75% cream	479	Applied OD for two 2-wk intervals	CCC and PC ($\geq 75%$ lesion reduction) rates 6.3% and 22.6% for PL, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75%, respectively ($p < 0.001$ vs. PL, each; $p = 0.047$, 3.75 vs. 2.5% for PC)	Few tx-related discontinuations

Table presents the largest three trials cited by number of pts in descending order

AE adverse effect, AK actinic keratosis, CCC complete clinical clearance, DB double-blind, MC multicenter, OD once daily, PC partial clearance, PG parallel-group, PL placebo, *pt(s)* patient(s), RAN randomized, TIW three times weekly, tx treatment, wk week

measuring short-term clearance rates of AKs at week 11 found CCC to be higher in the IM group (60.5%) than in the vehicle group (49.4%) [83]. Another study using IM 0.025% and IM 0.05% gel found that both active treatments were significantly more effective than the vehicle at clearing AK lesions [84]. IM appears to be generally well tolerated, with one study stating that 90% of patients reported a “good” or “excellent” treatment experience [85]. Adverse effects tend to be limited to transient local skin responses, such as erythema, crusting, and flaking, with no evidence of treatment-related scarring [84]. A study comparing the cost of DFS versus IM in the treatment of AKs over a period of 12 months, with costs defined as the cost of treatment and the direct costs of the first consultation with the dermatologist, found IM to be more expensive than DFS [86]. Patients treated with IM also reported an overall lower quality of life than those treated with DFS (469.5 vs. 478 QALYs), although statistical analysis showed this to be non-significant [86]. Thus, treatment with IM is associated with higher treatment costs than, but the same efficacy as, DFS.

4 Conclusion

There is no widely accepted algorithm for the treatment of AKs and the management of generalized actinic skin damage. Treatment comprises a variety of lesion-directed or field-directed therapies, or a combination of both, in conjunction with additional therapies tailored to patient needs. Determining the appropriate treatment of AK should be individualized to account for both lesion-related (morphology, duration) and patient-related factors (age, immune status, cosmesis, pain tolerance). Factors related to the treatment modalities, including clearance rates, treatment duration, tolerability profiles, adherence rates, and costs, all need to be considered when selecting a treatment. Some therapies may be more appropriate than others for certain anatomical sites. In general, therapies with shorter and simpler treatment courses and temporary mild-to-moderate skin reactions are associated with better adherence than are treatments with longer courses.

We propose the therapeutic algorithm shown in Fig. 1 for selecting an appropriate treatment in the evaluation of a patient with AK in the clinical setting. One must first

Table 9 Efficacy and adverse effects of ingenol mebutate treatment

Study	Study type	AKs severity	Tx	Pts (N)	Duration	Efficacy	AEs
Garbe et al. [82]	RAN, DB, PC, inter-individual phase III	4–8 clinically visible AKs within a contiguous 25-cm ² tx area	IM 0.015% gel	450	OD for 3 consecutive days	8 wk post tx: CCC 46.7 vs. 18.4% vehicle; <i>p</i> < 0.001	Well tolerated
Berman et al. [83]	MC, RAN, DB, vehicle-controlled inter-individual phase III	4–8 clinically typical, visible, discrete AKs within a contiguous 25-cm ² tx area	IM 0.015%	329	OD for 3 consecutive days	CCC rates greater with tx than vehicle (wk 11: 60.5 vs. 49.4%; <i>p</i> = 0.04; mo 12: 30.5 vs. 18.5%; <i>p</i> = 0.01)	IM 0.015% gel well tolerated; no unexpected AEs; all AEs resolved within 2 wk of starting tx
Anderson et al. [84]	RAN, DB, double-dummy, vehicle-controlled inter-individual	4–8 clinically typical, visible, discrete AKs within a contiguous 25-cm ² tx area	IM gel 0.025% and IM gel 0.05%	200	Applied OD for 2 or 3 days	Both active txs were significantly more effective than vehicle at clearing AK lesions	Transient local skin response: erythema, flaking/scaling, crusting. Tx tolerated in all dosages; no evidence of tx-related scarring

Table presents the largest three trials cited by number of pts in descending order

AE adverse effect, AK actinic keratosis, CCC complete clinical clearance, DB double-blind, IM ingenol mebutate, MC multicenter, mo month(s), OD once daily, PC placebo-controlled, *pt(s)* patient(s), RAN randomized, tx treatment, wk week

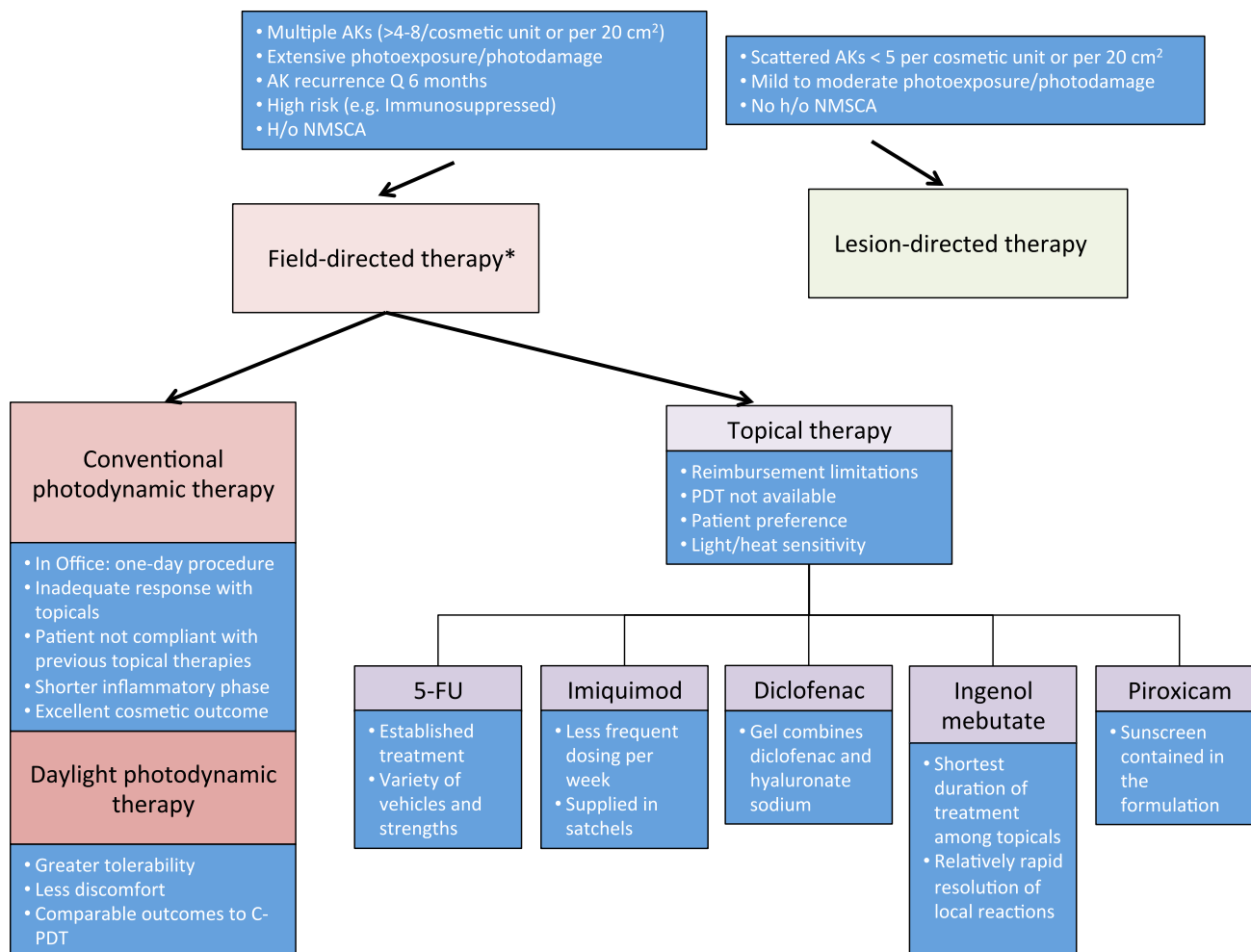
consider whether a lesion-directed therapy or field-directed approach is more suitable. The authors recommend lesion-directed therapies, such as cryotherapy, for patients with few well-defined lesions. Field-directed therapy is recommended for any surface with multiple (more than four to eight) AKs, for example, the face, scalp, forearm, etc., with the appropriateness of field-directed therapy increasing further when the AKs occur in photo-exposed areas and the patient has a history of significant sun exposure, recurrent AKs, history of chronic immunosuppression, and history of NMSC [4]. In the near-term, it is likely that field-directed therapy will become the best practice for high-risk patients such as OTRs [20, 21].

Once the decision to pursue field-directed therapy is made, deciding between PDT and topical therapy requires consideration of multiple patient- and clinician-related factors. The advantages of PDT are that the procedure can be performed within 1 day by a physician in an office-based setting, has high cure rates and excellent cosmetic results after one to two sessions, and has a shorter period of therapy-induced inflammation than long-term application of topical therapies such as imiquimod, 5-FU, diclofenac, or piroxicam [10–12, 16–18, 22, 23, 60–62, 70, 76, 78, 79, 84]. PDT is generally more successful than topical therapy when adherence by the patient is in question, especially given the months-long daily application required by some topicals [23]. Poor results after previous attempts at treatment with

topicals is another reason to consider PDT [18]. Additionally, patient-reported satisfaction seems to support somewhat of a patient preference for PDT over topical therapy [22, 23, 29]. One disadvantage of PDT is pain during illumination, although more widespread adoptions of “slow” or “fractionated” PDT and d-PDT may ameliorate this concern [24, 25, 28, 32, 41, 43–45]. PDT is therefore an appropriate treatment option for patients with multiple AKs because of its high response rate, limited downtime, and excellent aesthetic outcome.

Current reimbursement policies can sometimes dissuade the clinician from using PDT [57]. In the authors’ experience, procedure-based reimbursement for cryotherapy can be equivalent to, and even better than PDT, despite the greater time required by the clinician and/or support staff for PDT. Similarly, topical field therapy places less demand on the clinician’s time than PDT as the topical treatment is applied by the patient at home. Furthermore, the existence in the literature of many different PDT regimens, most of which are not FDA approved, including d-PDT, can make it difficult for a clinician without previous experience to start using PDT [10, 12, 14–26, 87]. More large, high-quality studies comparing modalities of PDT will be helpful.

Topical therapies are a non-procedural form of field cancerization therapy. Several topical therapies are available for the treatment of AKs, including 5-FU cream (5%, 1%, 0.5%), imiquimod 5% cream (5% and 3.75%),



*Treatment can also be comprised of a combination of both photodynamic therapy and topical treatments

Fig. 1 Treatment can also be comprised of a combination of both photodynamic therapy and topical treatments. 5-FU 5-fluorouracil, AKs actinic keratoses, h/o history of, c-PDT conventional photodynamic therapy, NMSCA non-melanoma skin cancer, PDT photodynamic therapy

diclofenac 3% gel, piroxicam 1% gel, and IM gel (5% and 3.75%). Studies have shown similar efficacy for these topicals, but their associated adverse events and cosmetic outcomes differ. Topical therapies in preparations that include sunscreen are advantageous given the importance of regular sunscreen use in AK management [88–90]. Disadvantages of topical field-directed therapies include a more prolonged treatment course (up to 16 weeks) and adverse effects such as photosensitivity, which reduces patients' ability to tolerate treatment. These disadvantages can decrease patient adherence and ultimately result in suboptimal effectiveness. Better adherence in a real-world setting would be expected for IM given the shorter treatment duration and transient local skin reactions. Further research with more direct comparisons between these procedural and non-procedural field-directed therapies are necessary to determine the best therapeutic approach.

Compliance with Ethical Standards

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