Received: 25 May 2020 | Revised: 25 June 2020 | Accepted: 7 July 2020

DOI: 10.1111/dth.13992

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Italian expert consensus paper on the management of patients with actinic keratoses

Elvira Moscarella[1] | Eugenia Veronica Di Brizzi[1] | Alice Casari[2] | Vincenzo De Giorgi[3] | Nicola Di Meo[4] | Maria Concetta Fargnoli[5] | Francesco Lacarrubba[6] | Giuseppe Micali[6] | Giovanni Pellacani[2] | Ketty Peris[7,8] | Stefano Piaserico[9] | Piergiacomo Calzavara-Pinton[10] | Pietro Quaglino[11] | Pietro Sollena[7,8] | Iris Zalaudek[4] | Cristina Zane[10] | Giuseppe Argenziano[1]

[1]Dermatology Unit, University of Campania "L. Vanvitelli", Naples, Italy

[2]Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy

[3]Department of Dermatology, University of Florence, Florence, Italy

[4]Department of Dermatology, University of Trieste, Trieste, Italy

[5]Dermatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

[6]Dermatology Clinic, University of Catania, Catania, Italy

[7]Institute of Dermatology, Università Cattolica, Rome, Italy

[8]Fondazione Policlinico Universitario A. Gemelli –IRCCS, Rome, Italy

[9]Unit of Dermatology, Department of Medicine, University of Padova, Padova, Italy

[10]Department of Dermatology, Spedali Civili, Brescia, Italy

[11]Department of Medical Sciences, Section of Dermatology, University of Turin, Turin, Italy

Correspondence
Elvira Moscarella, MD, Dermatology Unit, University of Campania "L. Vanvitelli," Nuovo Policlinico (edificio 9C), Via Pansini 5, 80131 Naples Italy.
Email: elvira.moscarella@gmail.com

Abstract

Two round tables involving experts were organized in order to reach a consensus on the management of patients with actinic keratosis (AK). In the first, seven clinical questions were selected and analyzed by a systematic literature review, using a Population, Intervention, Control, and Outcomes framework; in the second, the experts discussed relevant evidences and a consensus statement for each question was developed. Consensus was reached among experts on how to best treat AK patients with respect to different clinical scenarios and special populations. Lesion-directed treatments are preferred in patients with few AKs. Patients with multiple AKs are challenging, with more than one treatment usually needed to achieve complete lesion clearance or a high lesion response rate, therapy should be personalized, based on previous treatments, patient, and lesion characteristics. Methyl aminolevulinate-PDT, DL (day light) PDT, and imiquimod cream were demonstrated to have the lowest percentage of new AKs after post treatment follow-up. For IMQ 5% and 3.75%, a higher intensity of skin reactions is associated with higher efficacy. Photodynamic therapy (PDT) is the most studied treatment for AKs on the arms. Regular sunscreen use helps preventing new AKs. Oral nicotinamide 500 mg twice daily, systemic retinoids and regular sunscreen use were demonstrated to reduce the number of new squamous cell carcinomas in patients with AKs. Limited evidence is available for the treatment of AKs in organ transplant recipients. There is no evidence in favor or against the use of any of the available treatments in patients suffering from hematological cancer.

KEYWORDS

0.5% 5-FU (fluoro uracil)-salicylic acid, actinic keratosis, ALA and MAL PDT, cancerization field, imiquimod cream (3.75% and 5%), ingenol mebutate gel, nicotinamide, organ transplant recipients, systemic retinoids, topical treatment

1 | INTRODUCTION

In the last few decades, a number of topical and systemic agents enriched the armamentarium of the dermatologist dealing with patients with actinic keratoses (AKs). Several guidelines and consensus papers on how to manage patients with AKs have been published recently.[1-10] However, given the continuing introduction of new treatments and the rising amount of literature on the topic, updated recommendations are warranted.

The optimal management of patients with AKs is still matter of debate among clinicians and choosing the optimal treatment option for a given patient can be complex.

The main reasons for treating patients with AKs are eradication of the clinically evident lesions, prevention of the evolution into invasive squamous cell carcinoma (iSCC), and reduction the number of relapses.[11-18]

A high total number of AKs is one of the major risk factors for the development of iSCC.[19]

Traditionally, AKs are divided into three clinical groups depending on the degree of hyperkeratosis, with clinical grade I lesions being more felt than visible, and clinical grade III AKs being hyperkeratotic lesions. This clinical grading has a corresponding dermoscopic grading.[20] Both, the total number and the clinical/dermoscopic grading of AKs influence treatment choice. Moreover, the location of the lesions is also influencing treatment response, with lesions located on the limbs being more resistant to the standard treatments.[5] Finally, patients' characteristics are of outmost importance. It is well known that immune-suppressed patients and in particular organ transplant recipients (OTR) are at higher risk of developing AKs and iSCC, thus they represent a special population subgroup.[5,21-24]

Furthermore, AKs are very often a chronic and relapsing disease even after complete patient clearance, and nowadays many patients experience multiple treatment modalities in their life, especially when presenting multiple AKs.

The need for a better standardization of treatment modalities and for an optimal management of special groups of patients has led to this consensus paper that aims to give evidence-based answers to manage the most common clinical scenarios.

2 | METHODS

2.1 | Selection of the expert panel

The Nominal Group Technique (NGT) technique[25] is used in research to achieve a general agreement or convergence of opinions on a specific topic. This method is a highly structured face-to-face group interaction, which enables experts in a certain field to share ideas and opinions, and comprises four key stages:

- *Silent generation*: Participants reflect and record their ideas on specific questions selected in advance
- *Round robin*: Participants can share their opinion with others and new coming ideas can be added during this stage; there is no discussion among participants
- *Clarification*: This step gives the opportunity to group similar ideas together, with the agreement of all the participants, who can also exclude, include, or modify ideas. All ideas are discussed to ensure alignment among participants, enabling them to make an informed decision
- *Voting*: participants are asked to vote or to rank the generated ideas according to a prespecified scale.

The NGT was used to develop a consensus among experts on the management of patients suffering from AK. The experts (all dermatologists) were selected according to one or more of the following criteria: (a) Italian Society of Dermatology and Venereology (SIDeMast) members; (b) Dermato-Oncologic dermatology referral specialists; and (c) Heads of University Departments.

2.2 | Round table 1

The expert panel met to select a list of relevant clinical topics to define statements on the management of patients with AKs.

The following seven questions were identified:

- Which is the best currently available treatment in a patient with few AKs?
- Which is the best currently available treatment in a patient with multiple AKs?
- Which is the best currently available treatment in a patient with multiple AKs on the arms?
- Which is the best currently available treatment preventing iSCC in a patient with AKs?
- Which is the best currently available treatment preventing the development of new Aks in a patient who already experienced AKs?
- In a patient undergoing treatment for AKs is a higher intensity of local side effects correlated to increased efficacy?
- Which is the best care in special groups of patients with AKs (organ transplant patients/patients with immunologic diseases/patients with hematological cancer)?

A comprehensive review of the literature published in English was conducted by searching PubMed for papers about the given questions from inception until March 13, 2019. An update was made on September 2, 2019. Randomized clinical studies, controlled trials, observational, retrospective and prospective studies, meta-analyses, and systematic reviews were taken into consideration. The following MeSH terms were used to perform the research: “actinic keratosis,” “actinic keratoses,” “treatment,” “therapy.” Boolean research tools OR/AND were also used to optimize the research. A total of 2649 publications were retrieved from PubMed. They were individually analyzed and selected according to the requirements of any specific question. This resulted in selecting 64 publications that were considered relevant to all the topics.

The Population, Intervention, Control, and Outcomes (PICO) framework is a widely used methodology to perform systematic

reviews to obtain evidence-based responses to specific and structured questions.[26] The PICO approach was followed to analyze the selected papers. The PICO format consists in a widely known strategy for framing a "foreground" research question. PICO acronym translates to: P: population/disease; I: intervention or variable of interest (drug, surgical or rehabilitative intervention, diagnostic method, etc.); C: comparison (therapeutic or diagnostic intervention); O: outcome (outcome of interest for formulating a recommendation).

2.3 | Round table 2

Based on the PICO analysis, evidences related to each question were discussed by the expert panel. Real life experience was also considered in the debate. A 5-point Likert scale was used to evaluate agreement or disagreement on the items proposed: 1 = absolutely disagree, 2 = disagree, 3 = agree, 4 = more than agree, 5 = absolutely agree. The consensus was reached when the sum of items 1 and 2 (disagree) or 3, 4, and 5 (agree) reached 66%. No consensus was reached when the sum of the responses for a negative consensus (1 and 2) or a positive consensus (3-5, and) was <66%.

3 | RESULTS

Consensus was reached among experts for each of the selected questions.

3.1 | Question 1: Which is the best currently available treatment in a patient with few AKs?

A patient was defined with few AKs when having less than five scattered AKs or less than three AKs in an area of 25 cm^2. The outcomes considered were patient complete clearance and lesion response rate. There is scarce available literature on interventions for patients with few AKs. The majority of recommendations are based on "expert opinions" and recommend a lesion directed intervention. These involve focal ablative procedures, including cryotherapy, laser therapy, surgery, and curettage.[1-10] Cryotherapy is a rapid technique and does not require anesthesia. It is applied with spray during a single freeze-thaw cycle involving also a 1 mm rim of normal skin between 5 and 20 seconds usually. Reported side effects are redness, pain, blistering, and areas of hypochromia. Response rate are high, complete response is about 98%.

Laser therapy includes lasers systems that remove the superficial layers of the skin ablating epidermis and superficial dermis (the most used for treating AKs are CO_2 and erbium yttrium aluminum garnet). They have a high response rate and good cosmetic outcome but are more expensive than other lesion directed treatments. A biopsy is performed usually when histopathological examination in needed, that is, in the differential diagnosis with iSCC or with a melanocytic lesion. It requires anesthesia and results in residual scarring. Curettage is particularly indicated for hyperkeratotic lesions, it may result in residual scarring.

One study fulfilled the research criteria; this was a randomized controlled trial (RCT) including 200 patients with a total number of 543 AKs. Patients were randomized to receive CO_2 laser ablation or cryotherapy. After 90 days, the overall complete remission (CR) rates of patients and lesions were assessed. The CR rates were 78.2% with cryotherapy and 72.4% with CO_2 laser ablation. The authors concluded that cryotherapy is preferable to CO_2 laser for the treatment of isolated AKs, even if a better cosmetic outcome was reported for CO_2 treatment.[27]

Statement 1: There is scarce available literature on interventions for patients with few AKs. Lesion-directed treatments are preferred in patients with few AKs.

3.2 | Question 2: Which is the best currently available treatment in a patient with multiple AKs?

A patient was defined with multiple AKs when having five or more AKs overall, or three or more AKs in an area of 25 cm^2. The outcomes considered were patient complete clearance and lesion response rate.[28-40] In general, field directed treatment are preferred in patients with multiple AKs. Two network meta-analysis and two systematic reviews on the efficacy of currently available interventions for AK have been published.[28-31] In the Cochrane review by Gupta et al[31] also one oral treatment was included (etretinate). All the active treatments included in this review (5-aminolevulinic acid [ALA] and methyl aminolevulinate [MAL]-photodynamic therapy [PDT]; 3.75% and 5% imiquimod [IMQ] cream; ingenol mebutate gel; 5-fluoro uracil with or without salicylic acid; diclofenac gel; cryotherapy; electrocurettage; etretinate) performed significantly better than placebo on the outcome "patient complete clearance" (Table 1).

However, a comparison among drugs was made difficult because of the high variability among studies, in terms of variability in the reporting of outcomes, differences in outcome definitions and variable follow-up assessment timings. The board agreed that patients with multiple AKs are challenging patients, and therapy should be personalized, based on patient and lesion characteristics. More than one treatment is usually needed to achieve complete patient clearance or a high lesion response rate. Since it was not possible to give a univocal answer to the question, the board agreed in providing an expert opinion based on possible clinical scenarios. As a corollary to this question, the experts were faced with three clinical scenarios (Figures 1-3) and were asked to give their opinion on their preferred first- and second-line treatments for the given situation.

Among the available treatments, the panel expressed their preference for the following agents: ALA or MAL PDT; 3.75% and 5% IMQ cream; ingenol mebutate gel; 5-fluoro uracil with or without salicylic acid; diclofenac gel; cryotherapy; systemic retinoids; and oral nicotinamide.

PDT is a field directed treatment based on the interaction between the photosensitizer, appropriate wavelength of light and oxygen. ALA or derivate as MAL are usually used as photosensitizers,

TABLE 1 List of topical agents for field treatment of actinic keratoses

Agent	Mode of action	Dosage	Side effects
ALA-PDT	Combines a dedicated light source of appropriate wavelengths with the application of a photosensitizing cream to produce apoptosis and necrosis of the target tissue	Single or multiple treatments in case of residual lesions	Treatment can be painful Erythema and crusting can occur
MAL-PDT	Same as above	Single or multiple treatments in case of residual lesions	Same as above
5% IMQ cream	Topical immune-response modifier	Once daily application at 2 or 3 d/wk for a time period of 4-16 wk; continuously or intermittent.	Severe erythema, scabbing and crusting, and erosions or ulceration. Flu-like symptoms can also arise
3.75% IMQ cream	Same as above	Once daily application for 2 wk followed by a rest period of 2 wk (one or two treatment cycles)	Severe erythema, scabbing and crusting, and erosions or ulceration. Flu-like symptoms can also arise
5% 5 FU	5-FU works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis. It may also interfere with the formation and function of RNA	Once daily for 1-4 wk	Soreness, redness, and possible crusting
0.5% 5-fluorouracil + 10% salicylic acid	5-FU works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis. It may also interfere with the formation and function of RNA	Once daily application for 6-12 wk	Soreness, redness and possible crusting less intense compared to the 5% 5FU
Diclofenac gel	Mechanism of action for AK is not known, but may be related to inhibition of the cyclooxygenase pathway leading to reduced prostaglandin E2 synthesis	Twice daily application for 60-90 d	Treatment is generally tolerated and reported side effects are mainly pruritus and rash due to a hypersensitivity reaction to the drug

Abbreviations: 5% 5 FU, 5% 5-fluorouracil; ALA, 5-aminolaevulinic acid; IMQ, imiquimod; MAL, methylaminolevulinate; PDT, photodynamic therapy.

they are absorbed by the tissue and subsequently activated by the wavelengths that fall in their specific absorption spectrum. There is the activation of photochemical mechanisms mediated by various prostaglandins and cytokines generating reactive oxygen species ultimately inducing cell death. Recently introduced, daylight PDT involves the application of MAL to the skin without occlusion and subsequent exposure to ambient daylight. A high-SPF sunscreen without mineral filters is applied 15 minutes before the photosensitizing cream. Thirty minutes later, the patient spends 2 hours outdoors.

IMQ is a topical immune-response modifier. It is available as a 5% and a 3.75% cream. The 3.75% cream (@Zyclara) was recently introduced as a local treatment that can reduce the rate of AKs in a field of cancerization extended on face and scalp, being approved for the treatment of a larger surface area of up to 200 cm. The side effects of IMQ include erythema (30.6%), scabbing and crusting (29.9%), and erosions or ulceration (10.2%). Flu-like symptoms can also arise and are more likely if multiple sachets are used at each treatment or if it is being used for superficial BCC with more frequent applications than is typically the case for AK.

5-FU works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis. It may also interfere with the formation and function of RNA. The majority of the data on topical therapies relate to the 5% concentration of 5-FU cream. A 0.5% concentration combined with salicylic acid is also available. Common side effects include irritation associated with erythema, dryness, and burning. It is a widely used, flexible, and low-cost treatment.

Diclofenac 3% in a 25% hyaluronic gel is licensed for application twice daily for 60 to 90 days and can be applied as a lesion- or field-based treatment. Its mechanism of action for AK is not known but may be related to inhibition of the cyclooxygenase pathway leading to reduced prostaglandin E2 synthesis. Diclofenac gel usually causes few if no local skin reaction (LSR) with the exception of the development of a contact allergy to the product.

Ingenol mebutate is a diterpene ester extracted from the plant *Euphorbia peplus*. At a cellular level, it appears to work through the disruption of mitochondrial membranes resulting in damage and death of host cells and promotion of cell-specific antibodies with consequent antibody-dependent, cell-medicated cellular cytotoxicity. It is licensed for the treatment of nonkeratotic, nonhypertrophic AK in adults (grades 1 and 2). It is sold in two strengths, with the weaker one applied 3 days in succession to the chosen area on the face and scalp and the stronger one applied 2 days in succession to other sites. Each

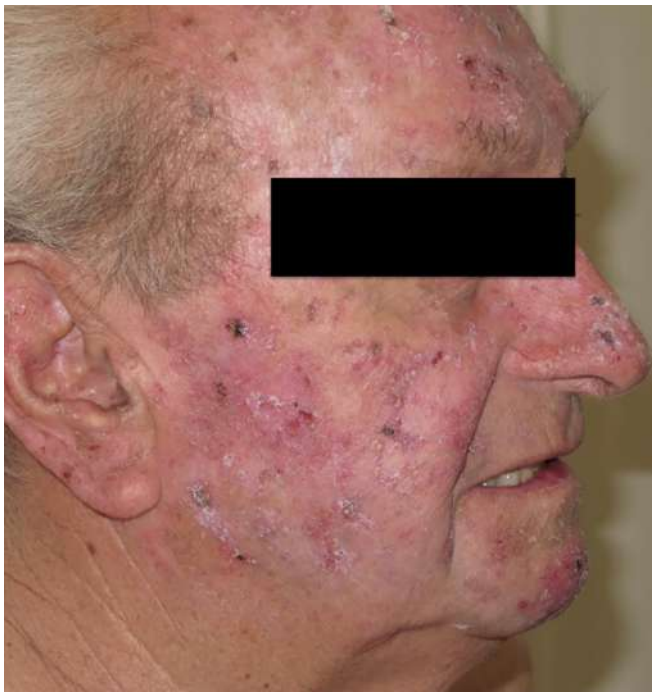

FIGURE 1 Patient 1. Multiple grade II and III actinic keratoses on the face

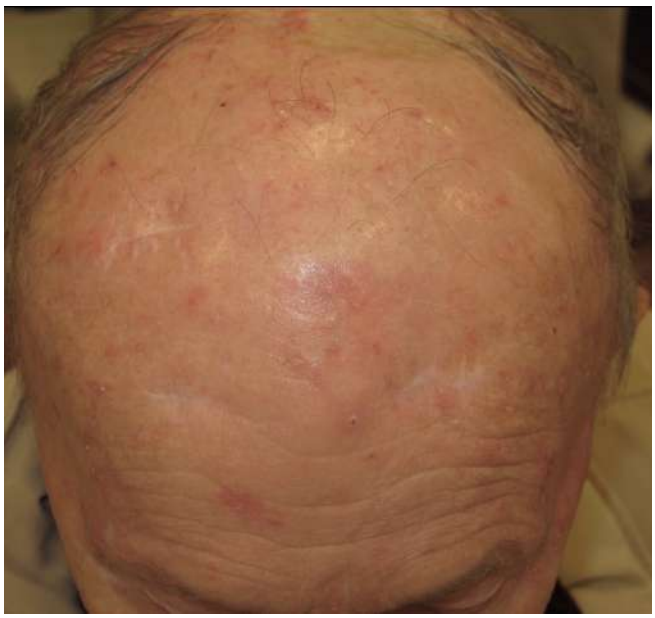

FIGURE 2 Patient 2. Multiple grade I and II actinic keratoses on the face and scalp

application is dispensed as a single tube of cream (three tubes for the face and scalp or two tubes for other sites). During the drafting of this manuscript, EMA (European Medicines Agency) decided to review data on skin cancer in patients using ingenol mebutate. The review was triggered by data from several studies showing a higher number of skin cancer cases, including cases of squamous cell carcinoma, in

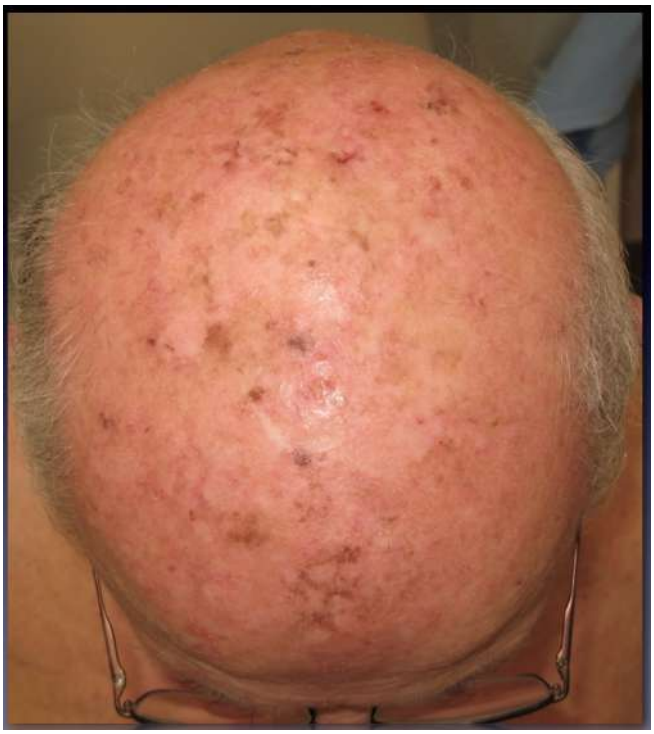

FIGURE 3 Patient 3. Multiple pigmented actinic keratoses on the scalp

patients using ingenol mebutate. An update of the review was published in May 2020 concluding that the medicine may increase the risk of skin cancer and that its risks outweigh its benefits. Ingenol mebutate is no longer authorized in the EU as the marketing authorization was withdrawn on February 11, 2020.

The results of the consensus on this statement are summarized in Table 2.

Statement 2: Patients with multiple AKs are challenging, with more than one treatment usually needed to achieve complete lesion clearance or a high lesion response rate. Therapy should be personalized, based on previous treatments, patient and lesion characteristics.

3.3 | Question 3: In a patient with multiple AKs on the arms, which is the best currently available treatment?

A patient was defined with multiple AKs on the arms when having five or more AKs on the arms, or three or more AKs in an area of 25 cm^2 on the arms. Limited evidence is available on the efficacy of AK treatments for lesions located on the arms that fulfills the inclusion criteria for the present research.[5,41-46] The majority of studies investigated PDT (with ALA or MAL), some of the treatments are off-label for the use on the arms.

One study by Brian Jiang SI et al[42] compared ALA-PDT vs placebo-PDT on the upper extremities. ALA-PDT achieved at week 12 complete patient clearance in 31% of cases (42/135), compared to

TABLE 2 First and second line treatment choices of the expert panel on the three proposed clinical scenarios. Patient 1 presented with multiple actinic keratoses of clinical grade I to III and extensive solar damage. Patient 2 presented with multiple grade I and II AKs of the forehead. Patient 3 presented multiple pigmented AKs on the head/neck area

Clinical scenario	First line treatment	Second line treatment (in case of partial response)
Patient 1 (Figure 1)	PDT+ IMQ +	Cryotherapy[a] IMQ 5FU
Patient 2 (Figure 2)	PDT[b] IMQ	Cryotherapy IMQ PDT[b]
Patient 3 (Figure 3)	PDT[c] IMQ 5FU	Cryotherapy[a] IMQ Diclofenac gel 5FU

Note: PDT (ALA or MAL PDT); IMQ (3.75% or 5% cream); 5FU (5% or 0.5% 5FU+ 10% salicylic acid); diclofenac = 3% diclofenac with HA. +Acitretin and/or oral nicotinamide to be considered in combination with topical treatment.
Abbreviations: 5% 5 FU, 5% 5-fluorouracil; ALA, 5-aminolaevulinic acid; IMQ, imiquimod; MAL, methylaminolevulinate; PDT, photodynamic therapy.
[a]In combination with PDT.
[b]Conventional or day light PDT.
[c]After curettage.

13% in the placebo-PDT group (17/134). Lesion clearance rate in ALA-PDT group was 53% and 69% at weeks 8 and 12, respectively; in VHE (vehicle)-PDT group it was 26% and 30% at weeks 8 and 12, respectively.[42] AK lesion clearance rate up to 80% was achieved when applying occluded ALA-PDT in the study by Schmieder et al.[43] MAL-PDT achieved 67% partial clearance in the study by Miola et al.[44] IMQ 5%, applied 3 times a week for 8 weeks, achieved a complete patient clearance in 6.9% of cases and a partial clearance in 24.1% in the study by Gebauer et al[45] evaluating the effects of dosing frequency on the safety and efficacy of IMQ 5% for AKs on forearms and hands.[45] Sotiriou et al[46] performed an intraindividual, right-left comparison of topical ALA PDT vs 5% IMQ cream for AK on the upper extremities, concluding that ALA-PDT and 5% IMQ cream were both attractive treatment options for upper extremities AKs with comparable efficacy and cosmetic outcomes. (lesion response rate of 65.32% for PDT vs 55.65% for IMQ cream).[46]

Statement 3: Limited evidence is available on the efficacy of AK treatments for lesions located on the arms. The majority of studies investigated PDT, some treatments are off-label if used to treat AKs on the arms.

3.4 | Question 4: In a patient with AKs which is the best currently available treatment preventing iSCC?

Few studies are available on effective therapy for reducing iSCC in patients with AKs.[47-52] Oral nicotinamide 500 mg twice daily was associated with a reduction in the number of SCCs after 12 months treatment in both immune competent patients[47] and OTRs[48] compared to placebo. Regular sunscreen use reduced the number of new SCC in immunosuppressed[49] and immunocompetent patients.[50]

Systemic retinoids (isotretinoin, etretinate, and acitretin) have been shown to be effective agents in reducing the number of iSCCs in studies of patients recipients of organ or bone marrow transplantation.[51-53] In addition, patients who do not have these disorders but who are actively developing large numbers of new skin cancers may also benefit from this approach.[53]

Statement 4: Few studies are available on effective therapy for reducing the incidence of SCC in patients with AKs. Oral nicotinamide 500 mg twice daily, systemic retinoids, and regular sunscreen use were demonstrated to reduce the number of new SCCs.

3.5 | Question 5: In a patient with AKs which is the best currently available treatment preventing new AKs?

Few studies reported on sustained clearance of AK patients after treatment. MAL-PDT, DL PDT, and IMQ 5% were demonstrated to have the lowest percentage of new AKs after posttreatment follow-up.[46,49,54-56] In one study, regular sunscreen use was demonstrated to be useful for preventing new AKs in immunosuppressed[49] and immune competent patients.[57-59]

There might be a role for photolyase-based sunscreens in reducing the number of newly appearing lesions in the follow-up of patients previously treated for AKs.[60,61]

Statement 5: MAL-PDT, DL (day light) PDT, and 5% IMQ cream were demonstrated to have the lowest percentage of new AKs after posttreatment follow-up. Regular sunscreen use helps preventing new AKs.

3.6 | Question 6: In a patient undergoing treatment for AKs is a higher intensity of local side effects correlated to better efficacy?

Topical treatments for AKs often induce a LSR occurring with erythema (mild, moderate, or severe) scaling, crusting, vesiculation, and edema. The frequency and type of LSRs vary depending on the drug. Systemic side effects have been also reported with IMQ 5% and 3.75% cream, due to the immune modulatory effect of this agent.[62]

Whether or not the intensity of LSR is associated with treatment efficacy has been studied for IMQ cream. For IMQ 5% and 3.75%, a higher intensity of skin reactions is associated with higher efficacy.[45,63,64] No difference in efficacy of MAL-PDT with respect to intensity of erythema have been reported.[65] No clear data are available for other treatments.

Statement 6: For IMQ 5% and 3.75%, a higher intensity of skin reactions is associated with higher efficacy.

3.7 | Question 7: In special groups of patients with AKs (organ transplant patients/patients with immunologic diseases/patients with hematological cancer) which is the best care?

Recently, a systematic review including RCT dealing with treatments for AKs in OTR, reported no therapy-related transplant rejections or worsening of graft function in any of the included studies accounting for 242 OTR overall.[64] MAL-PDT is currently the best-studied intervention.[66] A single case of acute renal failure attributed to IMQ 5% cream in a renal transplant patient was reported in 2011.[67] There is no evidence in favor or against the use of any of the available treatments in patients suffering from hematological cancer.

Statement 7: MAL-PDT is currently the best studied intervention for the treatment of AKs in OTRs. There is no evidence in favor or against the use of any of the available treatments in patients suffering from hematological cancer.

4 | DISCUSSION

The present expert consensus aimed to provide evidence-based answers to seven clinical scenarios reflecting different real-life patients. Almost all guidelines and management recommendations distinguish between patients with few and multiple AKs.[1-10] As most RCTs for field-directed therapies included patients with >5 AK lesions, some panelists suggested that this cut-off should be used. For patients with few AKs (less than five scattered AKs or less than three AKs in an area of 25 cm^2) only limited evidence is available, the majority of recommendations are based on expert opinion and suggest using lesion-directed treatments. On the contrary, for patients with multiple AKs (five or more AKs overall, or three or more AKs in an area of 25 cm^2) the literature is vast. Given the difficulty to provide a univocal answer to the second question, a corollary was added to integrate the experts' recommendation. Looking at the answers given by the experts a high variability in the approach to patients with multiple AKs can be noticed. This highlights the interindividual variability characterizing medical advices that are very often influenced by both available evidence and doctors' experience. However, a trend can be observed in considering PDT and IMQ cream (either 3.75% or 5%) as first choice for treating patients with multiple AKs. Second line choices were more heterogeneous, including IMQ cream (either 3.75% or 5%), diclofenac gel, 5FU. Interestingly, many of the experts indicated cryotherapy as second line treatment also in cases of multiple AKs, followed or not by a field directed therapy.

Regarding specific scenarios, the first concerned lesions located on the arms. It is common experience that on this body area, lesions tend to be more difficult to eradicate. Literature suggests PDT for this specific location.[5]

The second specific clinical scenario was related to special groups of patients; on one side OTR, on the other side patients suffering from hematological cancer. OTR are at higher risk of developing both AKs and iSCC. Despite one negative case report on the use of IMQ followed by acute renal failure in an OTR, no transplant rejects or any kind of treatment related side effects emerged from a recently published systematic review.[66,67]

Preventing the development of new AKs and more importantly of new iSCC is one of the most important aims when treating these patients. Based on the available evidences, regular sunscreen use is associated with a reduction in newly appearing AKs and iSCC in both immunocompromised and immunocompetent patients.[49,50] A regular use of sunscreens is recommended by all guidelines and consensus recommendations on this topic.[1-10] Evidence also suggests the chemopreventive effect of nicotinamide and systemic retinoids in high-risk patients.[47,48,51]

Finally, managing adverse events and LSR is a consistent part of patient care when dealing with some of the available topicals. However, knowing that a high intensity of LSR is indicating a higher treatment efficacy may help clinicians in trying to improve patients' compliance when LSR are particularly pronounced.[63,64]

In conclusion, the management of patients with AKs can be challenging. AKs are relapsing and remitting and constitute a chronic disease. Many parameters should be taken into considerations when designing a treatment approach. In all instances, management should entail advice on sun protection and long-term follow-up for the associated increased risk of nonmelanoma skin cancer.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly, and they are in agreement with the content of the manuscript.

ETHICS STATEMENT

The patients involved have given their oral and written informed consent to the use of the images.

ORCID

Elvira Moscarella https://orcid.org/0000-0001-5160-8997
Vincenzo De Giorgi https://orcid.org/0000-0001-6531-7998
Nicola Di Meo https://orcid.org/0000-0002-5987-1375

REFERENCES

1. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis—international league of dermatological societies in cooperation with the European dermatology forum—short version. *J Eur Acad Dermatol Venereol*. 2015;29:2069-2079.
2. National Institute for Health and Care Excellence. Improving outcomes for people with skin tumours including melanoma; 2016. https://www.nice.org.uk/guidance/csg8. September 16, 2016.
3. Chetty P, Choi F, Mitchell T. Primary care review of actinic ker- atosis and its therapeutic options: a global perspective. *Dermatol Ther*. 2015; 5:19-35.
4. Peserico A, Neri L, CalzavaraPinton P, et al. Key opinion leader (KOL) consensus for actinic keratosis management in Italy: the AKTUAL work-shop. *G Ital Dermatol Venereol*. 2013;148:515-524.

5. Richard MA, Amici JM, Basset-Seguin N, Claudel JP, Cribier B, Dreno B. Management of actinic keratosis at specific body sites in patients at high risk of carcinoma lesions: expert consensus from the AKTeam™ of expert clinicians. *J Eur Acad Dermatol Venereol*. 2018;32(3):339-346.
6. Fleming P, Zhou S, Bobotsis R, Lynde C. Comparison of the treatment guidelines for actinic keratosis: a critical appraisal and review. *J Cutan Med Surg*. 2017;21:408-417.
7. Calzavara-Pinton P, Hædersdal M, Barber K, et al. Structured expert consensus on actinic keratosis: treatment algorithm focusing on daylight PDT. *J Cutan Med Surg*. 2017;21(1_suppl):3S-16S.
8. Berman B, Ablon GR, Bhatia ND, et al. Expert consensus on cosmetic outcomes after treatment of actinic keratosis. *J Drugs Dermatol*. 2017;16(3):260-264.
9. de Berker D, McGregor JM, MohdMustapa MF, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol*. 2017;176(1):20-43. https://doi.org/10.1111/bjd.15107.
10. Peris K, Calzavara-Pinton PG, Neri L, et al. Italianexpertconsensus for the management of actinickeratosis in immunocompetentpatients. *J Eur Acad Dermatol Venereol*. 2016;30(7):1077-1084.
11. Rowert-Huber J, Patel MJ, Forschner T, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. *Br J Dermatol*. 2007;156(Suppl 3):S8-S12.
12. Huerta-Brogeras M, Olmos O, Borbujo J, et al. Validation of dermoscopy as a real-time noninvasive diagnostic imaging technique for actinic keratosis. *Arch Dermatol*. 2012;148:1159-1164.
13. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Klowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. *Int J Dermatol*. 1998;37:677-681.
14. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF. Actinic keratoses: natural history and risk of malignant transformation in the veterans affairs topical tretinoin chemoprevention trial. *Cancer*. 2012;115:2523-2530.
15. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. *Br J Dermatol*. 2007;157(Suppl 2):21-24.
16. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. *An Bras Dermatol*. 2013;88:775-786.
17. Vanharanta S, Massague J. Field cancerization: something new under the sun. *Cell*. 2012;149:1179-1181.
18. Fernandez-Figueras MT, Carrato C, Saenz X, et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. *J Eur Acad Dermatol Venereol*. 2015;29:991-997.
19. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient- oriented perspective. *Arch Dermatol*. 1991;127:1029-1031.
20. Zalaudek I, Piana S, Moscarella E, et al. Morphologic grading and treatment of facial actinic keratosis. *Clin Dermatol*. 2014;32:80-87.
21. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47:1e20.
22. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *New Engl J Med*. 2003;348:1681e91.
23. Euvrard S, Kanitakis J, Pouteil-Noble C, et al. Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. *J Am Acad Dermatol*. 1995;33:222e9.
24. Fortina AB, Caforio AL, Piaserico S, et al. Skin cancer in heart transplant recipients: frequency and risk factor analysis. *J Heart Lung Transplant*. 2000;19:249e55.
25. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi technique. *Int J Clin Pharmacol*. 2016;38:655-662.
26. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med*. 1997;127(5):380-387.
27. Zane C, Facchinetti E, Rossi MT, Specchia C, Ortel B, Calzavara-Pinton P. Cryotherapy is preferable to ablative CO2 laser for the treatment of isolated actinic keratoses of the face and scalp: a randomized clinical trial. *Br J Dermatol*. 2014;170(5):1114-1121.
28. Vegter S, Tolley K. A network meta-analysis of the relative efficacy of treatments for actinic keratosisof the face or scalp in Europe. *PLoS One*. 2014;9(6):e96829.
29. Stockfleth E, Sibbring GC, Alarcon I. New topical treatment options for actinic keratosis: a systematic review. *Acta Derm Venereol*. 2016;96(1):17-22.
30. Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in non-immunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol*. 2013;169:250-259.
31. Gupta AK, Paquet M, Villanueva E, et al. Interventions for actinic keratoses. *Cochrane Database Syst Rev*. 2012;12(12):CD004415.
32. Stockfleth E, von Kiedrowski R, Dominicus R, et al. Efficacy and safety of 5-fluorouracil 0.5%/salicylic acid 10% in the field-directed treatment of actinic keratosis: a phase III, randomized, double-blind, vehicle-controlled trial. *Dermatol Ther*. 2017;7(1):81-96.
33. Stockfleth E, Harwood CA, Serra-Guillén C, Larsson T, Østerdal ML, Skov T. Phase IV head-to-head randomized controlled trial comparing ingenol mebutate 0·015% gel with diclofenac sodium 3% gel for the treatment of actinic keratosis on the face or scalp. *Br J Dermatol*. 2018;178(2):433-442.
34. Sotiriou E, Evangelou G, Papadavid E, et al. Conventional vs. daylight photodynamic therapy for patients with actinic keratosis on face and scalp: 12-month follow-up results of a randomized, intra-individual comparative analysis. *J Eur Acad Dermatol Venereol*. 2018;32(4):595-600.
35. Zane C, Fabiano A, Arisi M, Calzavara-Pinton P. A rrandomized split-face clinical trial of photodynamic therapy with methyl aminolevulinate versus ingenol mebutate gel for the treatment of multiple actinic keratoses of the face and scalp. *Dermatology*. 2016;232(4):472-477.
36. Moggio E, Arisi M, Zane C, Calzavara-Pinton I, Calzavara-Pinton P. A randomized split-face clinical trial analyzing daylight photodynamic therapy with methyl aminolaevulinate vs ingenol mebutate gel for the treatment of multiple actinic keratoses of the face and the scalp. *Photodiag Photodyn Ther*. 2016;16:161-165.
37. Genovese G, Fai D, Fai C, Mavilia L, Mercuri SR. Daylight methylaminolevulinate photodynamic therapy versus ingenol mebutate for the treatment of actinic keratoses: an intraindividual comparative analysis. *Dermatol Ther*. 2016;29(3):191-196.
38. Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol*. 2012;132(5):1497-1500.
39. Hanke CW, Swanson N, Bruce S, Berman B, Kulp J, Levy S. Complete clearance is sustained for at least 12 months after treatment of actinic keratoses of the face or balding scalp via daily dosing with imiquimod 3.75% or 2.5% cream. *J Drugs Dermatol*. 2011;10(2):165-170.
40. Foley P, Merlin K, Cumming S, et al. A comparison of cryotherapy and imiquimod for treatment of actinic keratoses: lesion clearance, safety, and skin quality outcomes. *J Drugs Dermatol*. 2011;10(12):1432-1438.
41. Mei X, Wang L, Zhang R, Zhong S. Daylight versus conventional photodynamic therapy for the treatment of actinic keratosis: a meta-analysis of randomized controlled trials. *Photodiag Photodyn Ther*. 2019;25:23-28.
42. Brian Jiang SI, Kempers S, Rich P, et al. A randomized, vehicle-controlled phase 3 study of aminolevulinic acid photodynamic therapy for the treatment of actinic keratoses on the upper extremities. *Dermatol Surg*. 2019;45(7):890-897.

43. Schmieder GJ, Huang EY, Jarratt M. A multicenter, randomized, vehicle-controlled phase 2 study of blue light photodynamic therapy with aminolevulinic acid HCl 20% topical solution for the treatment of actinic keratoses on the upper extremities: the effect of occlusion during the drug incubation period. *J Drugs Dermatol*. 2012;11(12):1483-1489.
44. Miola AC, Ferreira ER, Lima TRR, Schmitt JV, Abbade LPF, Miot HA. Effectiveness and safety of 0·5% colchicine cream vs. photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratosis and skin field cancerization of the forearms: a randomized controlled trial. *Br J Dermatol*. 2018;179(5):1081-1087.
45. Gebauer K, Shumack S, Cowen PS. Effect of dosing frequency on the safety and efficacy of imiquimod 5% cream for treatment of actinic keratosis on the forearms and hands: a phase II, randomized placebo-controlled trial. *Br J Dermatol*. 2009;161(4):897-903.
46. Sotiriou E, Apalla Z, Maliamani F, Zaparas N, Panagiotidou D, Ioannides D. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol*. 2009;23(9):1061-1065.
47. Chen AC, Martin AJ, Damian DL. Nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2016;374(8):790.
48. Drago F, Ciccarese G, Cogorno L, Calvi C, Marsano LA, Parodi A. Prevention of non-melanoma skincancers with nicotinamide in transplantrecipients: a case-control study. *Eur J Dermatol*. 2017;27(4):382-385.
49. Ulrich C, Jürgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. *Br J Dermatol*. 2009;161(Suppl 3):78-84.
50. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2546-2548. Epub 2006 Nov 28.
51. Collins L, Asfour L, Stephany M, Lear JT, Stasko T. Management of non-melanoma skin cancer in transplant recipients. *Clin Oncol (R Coll Radiol)*. 2019;31(11):779-788. https://doi.org/10.1016/j.clon.2019.08.005.
52. Kim C, Cheng J, Colegio OR. Cutaneous squamous cell carcinomas in solid organ transplant recipients: emerging strategies for surveillance, staging, and treatment. *Semin Oncol*. 2016;43(3):390-394. https://doi.org/10.1053/j.seminoncol.2016.02.019.
53. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther*. 2006;19(5):306-314.
54. Liew YCC, de Souza NNA, Sultana RG, Oh CC. Photodynamic therapy for the prevention and treatment of actinic keratosis/squamous cell carcinoma in solid organ transplant recipients: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2019;34(2):251-259. https://doi.org/10.1111/jdv.15852.
55. Dirschka T, Ekanayake-Bohlig S, Dominicus R, et al. A randomized, intraindividual, non-inferiority, phase III study comparing daylight photodynamic therapy with BF-200 ALA gel and MAL cream for the treatment of actinic keratosis. *J Eur Acad Dermatol Venereol*. 2019;33(2):288-297.
56. Sotiriou E, Apalla Z, Vrani F, et al. Daylight photodynamic therapy vs. conventional photodynamic therapy as skin cancer preventive treatment in patients with face and scalp cancerization: an intra-individual comparison study. *J Eur Acad Dermatol Venereol*. 2017;31(8):1303-1307.
57. Naylar MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol*. 1995;131:170-175.
58. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratosis. *Arch Dermatol*. 2003;139:451-455.
59. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *New Engl J Med*. 1993;329:1147-1151.
60. Moscarella E, Argenziano G, Longo C, Aladren S. Management of cancerization field with a medical device containing photolyase: a randomized, double-blind, parallel-group pilot study. *J Eur Acad Dermatol Venereol*. 2017;31(9):e401-e403.
61. Eibenschutz L, Silipo V, de Simone P, et al. A 9-month, randomized, assessor-blinded, parallel-group study to evaluate clinical effects of film-forming medical devices containing photolyase and sun filters in the treatment of field cancerization compared with sunscreen in patients after successful photodynamic therapy for actinic keratosis. *Br J Dermatol*. 2016;175(6):1391-1393.
62. Cantisani C, Lazic T, Richetta AG, Clerico R, Mattozzi C, Calvieri S. Imiquimod 5% cream use in dermatology, side effects and recent patents. *Recent Pat Inflamm Allergy Drug Discov*. 2012;6(1):65-69.
63. Stockfleth E, Ulrich C, Lange-Asschenfeldt B, et al. Treatment of multiple, multiform actinic keratoses on the head with imiquimod 5% cream. *Eur J Dermatol*. 2009;19(4):355-359. https://doi.org/10.1684/ejd.2009.0692.
64. del Rosso J, Swanson N, Berman B, Martin GM, Lin T, Rosen T. Imiquimod 2.5% and 3.75% cream for the treatment of photodamage: a meta-analysis of efficacy and tolerability in 969 randomized patients. *J Clin Aesthet Dermatol*. 2018;11(9):28-31.
65. Räsänen JE, Neittaanmäki N, Ylitalo L, et al. 5-Aminolaevulinic acid nanoemulsion is more effective than methyl-5-aminolaevulinate in daylight photodynamic therapy for actinic keratosis: a nonsponsored randomized double-blind multicentre trial. *Br J Dermatol*. 2019;181(2):265-274.
66. Heppt MV, Steeb T, Niesert AC, et al. Local interventions for actinic keratosis in organ transplant recipients: a systematic review. *Br J Dermatol*. 2019;180(1):43-50.
67. Santos-Juanes J, Esteve A, Mas-Vidal A, et al. Acute renal failure caused by imiquimod 5% cream in a renal transplant patient: review of the literature on side effects of imiquimod. *Dermatology*. 2011;222(2):109-112.

How to cite this article: Moscarella E, Di Brizzi EV, Casari A, et al. Italian expert consensus paper on the management of patients with actinic keratoses. *Dermatologic Therapy*. 2020;33:e13992. https://doi.org/10.1111/dth.13992