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Therapeutic Options for the Treatment of Actinic Keratosis with Scalp and Face Localization

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ABSTRACT Actinic keratosis (AK) is a common skin disease related to ultraviolet chronic exposure, that is now considered a squamous cell carcinoma *in situ*. Primary skin cancer prevention strategies should be recommended for high risk patients. There is a wide spectrum of treatment options available for AKs, and several variables should be taken into account regarding the best therapeutic choice for each patient. The purpose of this article is to review the current treatment strategies for AKs localized on the face and scalp, with a focus on the practical point of view that could be useful for choosing the best therapeutic option. The two main therapeutic approaches will be distinguished first: lesion-directed and field-directed. Afterwards, the treatment based on clinical type and patient comorbidity will be discussed.

INTRODUCTION

Actinic keratosis (AK) is one of the most frequently encountered skin lesions, almost considered a squamous cell carcinoma (SCC) *in situ*. Since there is a low but definite potential of progression into an invasive SCC, early treatment of AK is strongly recommended. This review will only discuss AK treatments of the face and scalp.

Several clinical variants have been described: the most common is the erythematous type, characterized by red skin color and scaling patches or papules surrounded by photo-damaged skin with telangiectasia, dyschromia, and wrinkles (1); other variants include the hyperkeratotic type that may occasionally evolve into a cutaneous horn, and pigmented and lichenoid AK (Figure 1). Finally, actinic cheilitis may resemble the classic form of AK located on the lower lip or can appear like a thicker and more diffuse patch involving the entire lower lip. These clinical subtypes can be distinguished thanks to typical dermoscopic features (Figure 2). Regarding symptoms, tenderness, itchiness, and burning sensation are sometimes reported (2). Ultraviolet (UV) rays are the most important etiologic factor for AK development; they act both directly, inducing mutations of the p53 gene, and indirectly, causing immunosuppression and stromal changes (3-4). Consequently, AKs mainly arise on chronic sun-exposed skin areas, such as the face, ears, neck, scalp, chest, hands, forearms, and lips. The most important risk factors for the development of AK are: fair skin type, prior history of AKs, immunosuppression, genetic predisposition, advanced age, and male gender (5-6). AK may undergo spontaneous

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regression or may persist or progress into an invasive SCC. No clinical and dermoscopic features have been yet described that could help to predict the natural history of AK. The risk of progression has been estimated to range from 0% to 0.53% per lesion per year, thus it is highly variable ranging from 1% to 20% per patients per year, depending on the number of AKs. In addition, the presence of AKs represents the main risk factor for non-melanoma skin cancer development, and up to 80% of invasive SCCs arise from a pre-existing AK, thus an efficacious management is recommended (7-12).

TREATMENT OPTIONS

Treatment options for AKs are classified as lesion-directed or field-directed, but these approaches may be combined (13). A number of factors should be taken into account to determine the best therapeutic choice, including cost, rapidity, efficacy, patient tolerability and compliance, number of lesions to treat, high-risk locations, lesion morphology, symptoms such as pain and bleeding, and previous treatment history (2).

Lesion-directed treatments

Among lesion-directed treatments, cryotherapy and curettage are recommended as first-line treatment for few or isolated lesion, while laser therapy and excisional surgery are indicated as second line treatment in case of recurrence or persistence after therapy or in presence of suspicious lesions.

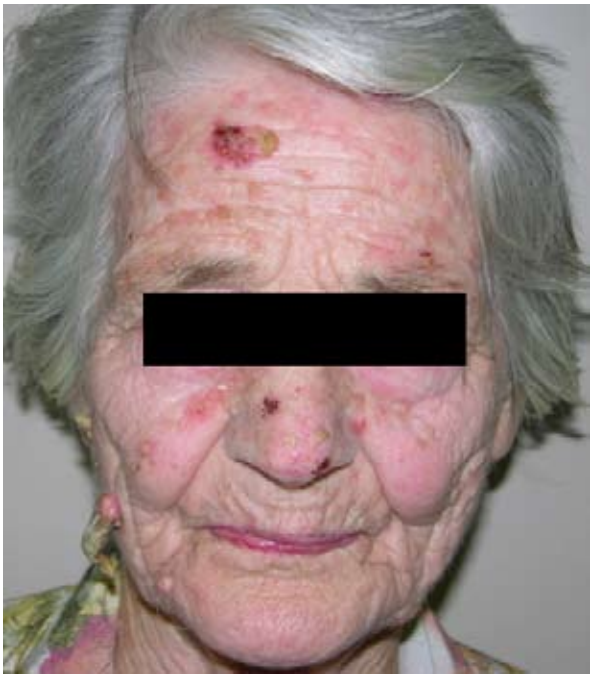

Figure 1. Different clinical variants of actinic keratosis in the same patient.

Cryotherapy

Cryotherapy with liquid nitrogen is a standard first-line treatment for isolated AKs, thanks to its low-cost and invasiveness and easy administration (14). Cryotherapy causes selective tissue necrosis by the reduction of skin temperature with consequent freezing of cells. The strongest indications for cryosurgery are single or few well-demarcated palpable or visible AKs (9). The procedure is highly effective, with reported cure rates between 75% and 99% (15,16). Both spray and contact techniques have been successfully used and only one treatment is usually required; however, significant long-term recurrence rates have been observed due to lack of properly perilesional skin treatment (17,18). Pain, redness, edema, blistering, and hypopigmentation are the common associated side-effects (19).

Laser therapy

Laser therapy is an emerging treatment approach. Ablative laser resurfacing with either the CO2 or erbium-doped:YAG (Er:YAG) lasers employs specific wavelengths to selectively induce thermolysis and destruction of the epidermal layer. Evidence demonstrated that ablative lasers are superior when compared with non-ablative fractional lasers in the treatment of AK, because the latter requires multiple treatments with photothermolysis (20-22). Compared with topical 5-FU, Er:YAG laser resurfacing has shown, despite more side-effects, a significantly higher efficacy with a 91% clearance rate at one-year assessment, associated with a shorter healing period (20). Other studies report cure rates between 58% and 100% (23,24).

Curettage, dermabrasion

Surgical procedures are rarely employed in AK treatment. More frequently curettage is used in combination with electrocautery to destroy atypical keratinocytes that may have been left. Alternatively, dermabrasion can be used to manage superficial AKs, but great expertise is necessary (25-27).

Excisional surgery

Excisional surgery is recommended when the clinical and dermoscopic diagnosis is uncertain or suggests progression into an invasive SCC. The clinical findings include: ulceration, induration/inflammation, bleeding, diameter >1 cm, rapid enlargement, and erythema, while dermoscopic criteria include neovascularization characterized by progressive development of elongated vessels, keratinization, and ulceration. Prospective trials on long-term efficacy of surgical excision are not available in the literature (28).

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Field-directed treatments

Field-directed therapies aim to eradicate both clinically visible and subclinical AKs within the treated area and should be preferred for the management of multiple AKs in individuals with significant sun-damage and fair skin photo-type.

5-fluorouracil

5-fluorouracil (5-FU) is a pyrimidine analog that prevents cellular proliferation and leads to tumor cells death through the irreversible inhibition of thymidylate synthase. It has been used for AK treatment since the 1960s, with different concentrations and schedules (29). The standard treatment regimen differs according to concentrations: 5% 5-FU should be applied once or twice daily for 4 weeks or longer, 0.5% once daily up to 4 weeks, and 1% twice daily for up to 6 weeks. A longer period and frequency of application is recommended if lesions are not located on the head-neck region (30). Treatment with 5-FU can result in severe dermatitis, irritation, rash, xerosis, pruritus, pain, and ulceration, leading to high withdrawal rates. Complete clearance rates range from 16.7% to 57.8% for multiple AKs of the face and from 43% to 100% for multiple AKs of the scalp (31). Goon *et al*. (32) proposed an off-label regimen with topical 5% 5-FU applied in occlusion (chemowraps) that appears to be more effective for large areas of sun-damaged skin, with a low risk of systemic and local toxicity.

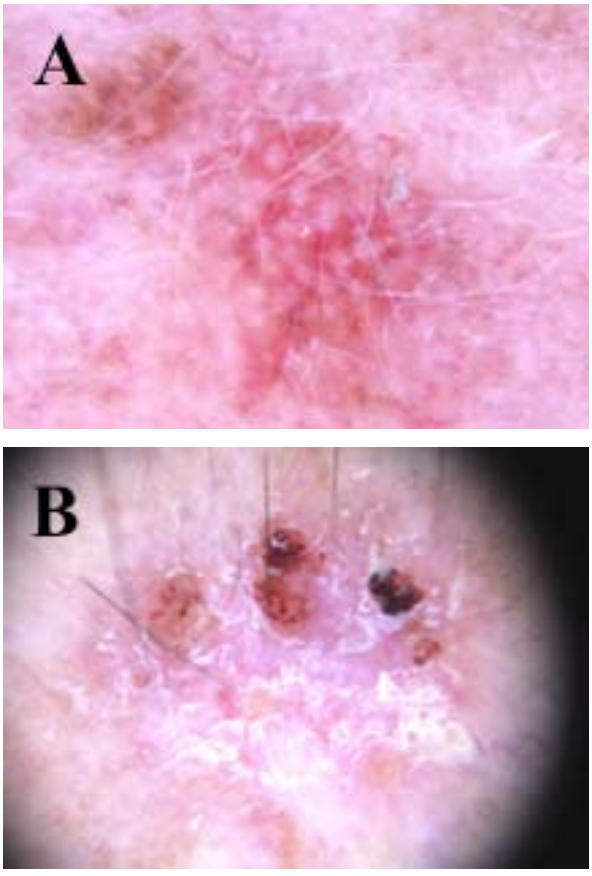

Figure 2. Dermoscopic images of erythematous actinic keratosis: red pseudo-network (A); scaling patch (B) surrounded by photo-damaged skin.

Recently, a new topical combination of 0.5% 5-fluorouracil and 10% salicylic acid (5-FU/SA) applied once daily up to 12 weeks showed a higher complete clinical clearance rate and a lower AK recurrence rate than topical 5-FU alone, with only mild to moderate skin adverse effects (33).

Diclofenac sodium

Diclofenac is a nonsteroidal anti-inflammatory drug; the formulation of 3% diclofenac sodium in 2.5% hyaluronic acid gel has been used for topical treatment of AKs since the 1990s (34). The mechanism of action has not been fully clarified, but cyclo-oxgenase-2 pathway inhibition, inhibition of angiogenesis, and induction of apoptosis are probably involved (35). Diclofenac sodium should be applied twice-daily for up to 90 days; it is generally well-tolerated due to its low irritation power, although it may cause erythema, pruritus, dry skin, and scaly rash. A recent study showed a 75% lesion count reduction in 85% and 91% of patients who applied diclofenac sodium twice daily for 90 days, one month, and one year after the end of treatment, respectively [36].

Imiquimod

Imiquimod is an immune-response modifier approved for the treatment of AK of the head and neck. Its activity is primarily based on activation of toll-like receptor-7 in the epidermis; the stimulation of pro-inflammatory cytokines results in antiviral, antitumor, and immune-regulatory effects (37-39). Three studies investigating different treatment regimens of 5% imiquimod twice per week for 16 weeks (40), 3 times per week for 4 weeks followed by 4 weeks of washout (41), and once per week for 6 months (42) indicated that imiquimod remain effective even at reduced application frequencies or in a cyclical fashion. Side-effects are restricted to the site of application and include erythema, ulceration, edema, and scaling (43). Application of 5% imiquimod 3 times per week for 16 weeks resulted in a complete clearance of 57.1% and partial clearance of 72% of lesions (44,45).

The recently approved a new formulation of 3.75% imiquimod, administered for 2 cycle of 2-week daily treatment separated by a 2-week treatment-free interval, achieved a partial clearance in 59% of cases and a complete clearance in 35%, reaching 59.5%

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when preceded by cryotherapy. An additional week of treatment was not recommended since no additional benefit was shown (46-48).

Ingenol mebutate

Ingenol mebutate gel has been recently approved for the treatment of non-hypertrophic non-hyperkeratotic AKs located on the face, scalp, trunk, and extremities. It has shown a dual mechanism of action, consisting of both chemoablative and immunostimulatory effects (49). Depending on body location, 2 different formulation are recommended: the 0.015% gel formulation that is used once daily on the face or scalp for 3 consecutive days, and the 0.05% gel formulation which is applied once daily on the trunk or extremities for 2 consecutive days. A complete clearance rate of 42% and lesion count reduction of 83% were reported at day 57; after 12 months of treatment a sustained clearance rate of 46% and lesion reduction rate of 87% were also achieved (50-51). Similarly to all topical treatments, local skin responses include erythema, flaking, scaling, and crusting. Moreover, thanks to the lack of phototoxic or photosensitizing properties, ingenol mebutate can be used throughout the year (52).

Since January 16, 2020, EMA has recommended the suspension of ingenol mebutate therapy in European countries (EMA/32231/2020), as a precaution while review of skin cancer risk continues. Nevertheless, the use of ingenol mebutate in all other countries worldwide remains a valid therapeutic option (53).

Photodynamic therapy

Photodynamic therapy (PDT) can be used as both a lesion-direct and a field-direct therapy. Topical photosensitizers are used in PDT, such as 5-aminolevulinic acid (5-ALA) or its ester methyl-aminolevulinate (MAL); these are activated by light, to produce apoptosis and necrosis of abnormal cells with minimal damage to the surrounding normal tissue. 5-ALA is available in 8 mg self-adhesive patch formulation, in 78 mg/g nanoemulsion gel, and in 20% solution, while MAL is disposable as 16.8% cream. After 3 hours from the application of photosensitizer on the tumor surface, a 7-9 minute illumination with a blue or red light emitting lamp (respectively 417 nm and 630 nm of wavelength) is performed. PDT is recommended for non-hyperkeratotic, non-pigmented AKs with efficacy rates that vary from 70% to 90%. The best results are obtained after two sessions (54-58). Despite intense application-site pain, redness, and swelling as frequent photo-toxic reactions, cosmetic results are usually excellent. The activation of the photo-sensitizers obtained with daylight exposure (daylight PDT), achieved similar efficacy rates than conventional PDT, while minimizing pain and local inflammation (59). A new nanoemulsion-based formulation of ALA called BF-200, combined with narrow-spectrum light illumination, has shown a greater clinical efficacy than MAL; in a meta-analysis of 25 trials, BF-200 ALA resulted the treatment with the highest efficacy rate (60,61).

Chemical peels

Chemical peeling represents another suitable option for the treatment of multiple AKs of the face. Trichloroacetic acid is the most commonly used, in concentrations varying from 35% to 70%, and satisfactory results can be achieved with only one treatment session. Alternatively, 70% alpha-hydroxy acid or 88% phenol peels can be used for a deep exfoliation. They can be associated with PDT or cryotherapy, and efficacy rates vary according to the employed acid compound. Trichloroacetic acid has been shown to cause the disappearance of the 75% of visible AKs, although at 1-year follow-up the recurrence rate ranged from 25% to 35%. Treatment with chemical peels are frequently associated with pain, local erythema, and mild desquamation, while scarring and pigmentation changes may rarely occur (62,63).

Retinoids

Both topical and oral retinoids have been used for AK treatment, showing conflicting results. Oral isotretinoin, thanks to its anti-proliferative and anti-apoptotic properties, may avoid new skin cancer development; it may be beneficial in patients with severe actinic damage with multiple and diffuse AKs. In case of recurrence, the combination of low-dose isotretinoin (10 mg/day) and 5-FU may be effective, as a second line therapy, in preventing the appearance of new AKs and in reducing the number of existing lesions. Prolonged use of oral retinoids is limited by their significant adverse effects such as xerosis, cheilitis, conjunctivitis, elevation of transaminases, triglycerides, and cholesterol levels and teratogenicity (64,65).

Combination therapy

Use of two different treatments concurrently or sequentially may improve clearance outcomes and must be encouraged in order to successfully manage AKs, especially in widespread or resistant cases. For example, a field-directed topical cream approach after cryotherapy was shown to be more effective than the use of single therapies alone (66).

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Prevention

Photo-protection remains the best way to prevent the appearance of AKs. Avoidance of sun exposure during the peak hours of UV emission should be recommended. Regular use of high sun protection factor sunscreens can provide protection against damage induced by UVs when solar exposure cannot be avoided. New topical sunscreens containing photolyase, a critical enzyme in DNA repair, have demonstrated a great efficacy in reducing the UV-mediated cell damage. The chronical use of these products may lead to a 40-45% decrease of UV-inducible pyrimidine dimers and p-53 mutations in keratinocytes and can prevent the immunosuppressant effect of UV rays (67,68).

PRACTICAL PARAMETERS FOR TREATMENT CHOICE

Treatment based on anatomic site of lesion

Lesion location is an important variable that can affect response to treatment. It is known that AKs on the scalp tend to be more resistant to therapy than lesions localized on the face, often requiring multiple extended treatments. Sometimes a pre-treatment with 5% salicylic acid is also required (69). The effectiveness of PDT is poor for AK on acral sites, probably due to a higher proportion of thicker lesions on these locations. The area around the eyes and mouth requires the use of a treatment with a minimal skin-irritating effect such as diclofenac, which is also effective for AK of the lip. When the cosmetic outcome must be considered for lesions on the face, either imiquimod or PDT are generally preferable. A network meta-analysis comparing the efficacy of various available treatment for AKs of the face and scalp concluded that BF-200 ALA has the highest absolute complete clearance rate, followed by 0.5% and 5% 5-FU, 5% imiquimod for 16 weeks, 5% imiquimod for 4 weeks, and ALA-PDT patch (70-72). Cryosurgery is contraindicated when the lesions are located in delicate areas such as the central part of the face, hairy scalp, and eyebrows, due to an increased risk for scarring alopecia.

Treatment based on patient comorbidities

In elderly and disabled patients or those with significant comorbidities, adherence to topical field self-administered therapies may be an issue, and thus cryotherapy and PDT are more suitable options in these cases. Immunosuppressed patients such as hematopoietic/solid organ transplant recipients, patients with HIV, or those taking immunosuppressive drugs have a higher risk to develop AKs compared with the general population; additionally, AKs in these patients may turn into invasive SCC more quickly, and close monitoring for early detection of AKs and more rigorous treatment approaches are thus necessary. In immunosuppressed patients, excisional surgery is the first-line therapeutic choice in case of suspicious lesions, while for multiple AKs a combination between an ablative and a topical treatment is the best option. Conversely, in these patients imiquimod must be used with caution and PDT has demonstrated a lower clearance rate compared with immunocompetent patients. Finally, oral retinoids could even be a valuable option in immunosuppressed individuals as well in patients affected by xeroderma pigmentosum and Gorlin-Goltz syndrome (73-76).

Treatment based on clinical type of lesion

Treatment choice primarily depends on clinical presentation of AKs, using focal ablative procedures to treat single lesions and field directed treatments for multiple visible and non-visible lesions over a large sun-damaged area. Both European and Italian guidelines address patient classification into subgroups according to the clinical presentation. "Single lesion" is defined as the presence of one to five palpable or visible AK per field or affected body region, while multiple lesions refer to six or more distinguishable AKs in one body region or field. European recommendations for single AK indicate only cryotherapy as a suitable option, while curettage, 0.5% and 5% 5-FU 5-FU/SA, 3.75%, and 5% imiquimod and 0.015% ingenol mebutate and PDT are weakly recommended. No recommendations are present for 3% diclofenac and laser therapy. Conversely, 0.5% 5-FU, 3.75% imiquimod, 0.015%, and 0.5% ingenol mebutate and PDT are all strongly recommended for multiple AKs (9).

Treatment based on clinical grade

Lesion grade is another key parameter that can affect treatment response. According to Olsen *et al.* (77), AKs are clinically classified into 3 severity degrees: (i) grade 1 (mild): flat pink macule or patch felt better than seen; (ii) grade 2 (moderate): moderately thick pink to red papules or plaques with a rough, hyperkeratotic surface and variable induration that are easily seen and felt; and (iii) grade 3 (severe): very thick red to pigmented indurated plaques on sun-damaged skin. A histological classification was also developed based on the extent of atypical keratinocytes in the epidermis: AK I indicates the presence of atypical keratinocytes in the lower third of the epidermis; in AK II atypical keratinocytes extend over the lower

two-thirds of the epidermis with buds of keratinocytes extending into the upper papillary dermis; and AK III indicates the diffusion of atypical keratinocytes in more than two-thirds of the full thickness of the epidermis, including the epithelia of hair follicles (78). Invasive SCC is believed to develop from the progressive extension of atypical keratinocytes from the epidermidis into the dermis. Interestingly, a recent study questioned the pathway of progression from AK I to AK III and consequently to invasive SCC by demonstrating that invasive carcinoma generally arises from basaloid atypical keratinocytes of AK I; consequently, all grades of AK should be treated (79). Intuitively, thin grade 1 lesions should be more responsive to treatment than grade 3 lesions. Response rates for grade 1 lesions were higher for imiquimod and MAL-PDT (72.13% and 71.64%, respectively) compared with response rates for grade 2 lesions (37.03% and 57.89%, respectively). Due to the limited penetration of the photosensitizer drugs, PDT is not recommended for hyperkeratotic AKs although the removal of overlying crust and scale may improve efficacy. More invasive options are therefore suggested in grade 3 lesions, such as dermoabrasion, curettage, double freeze-cryotherapy, and surgery.

CONCLUSIONS

Although the real risk of progression from AK to invasive SCC is unknown, AK should be considered a SCC *in situ* and consequently treated. Optimal management should take into account the treatment of single lesions as well as the treatment of the entire field of cancerization. Given the large number of treatment options with advantages and disadvantages, proper guidance towards their selection and usage is important. This review provides a global and complete report of main therapeutic approaches currently in use, highlighting their optimal applications in clinical practice.

A gold standard management algorithm is difficult to design due to the large number of variables that should be considered: number of lesions, localization, clinical and histological features, patient age and comorbidities, patient compliance, and clinician's experience. For that reason, the best approach would be sequential or combination therapies evaluated individually, which is known as patient tailored therapy, in order to achieve the best results for each patient.

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