Treatment of Actinic Keratoses and Field Cancerization – Croatian perspective

Mirna Šitum[1,2,3], Nika Franceschi[1], Nikola Ferara[*1], Zdenka Šitum Čeprnja[4]

[1] Department of Dermatology and Venereology, Sestre Milosrdnice University Hospital Centre, Zagreb, Croatia
[2] School of Dental Medicine, University of Zagreb, Croatia
[3] Croatian Academy of Sciencies and Arts, Zagreb, Croatia
[4] Department of Dermatology and Venereology, University Hospital Centre Split, Split, Croatia

Abstract

Actinic keratoses (AKs) are the most common premalignant skin lesions, caused by chronic sun damage and accordingly, found on chronically sun-exposed skin, such as face, scalp, neck, hands, and forearms. Clinically, these lesions present as macules, papules or hyperkeratotic plaques on an erythematous background. In Caucasians over 60 years of age, the prevalence of AKs is up to 80%. The diagnosis is based on clinical and dermoscopic examination. The main concern with AKs is the risk of transformation into squamous cell carcinoma (SCC), therefore all lesions should be evaluated for treatment. Treatment options for AKs are divided into lesion-oriented and field-oriented treatments. Lesion-directed treatment modalities commonly involve cryosurgery/liquid nitrogen cryotherapy, surgery (shave, excision), and laser therapy, while field-directed treatments include topical agents, photodynamic therapy, chemical peels, field ablation with dermabrasion and CO_2 laser resurfacing. This review outlines the different types of treatments available, the characteristics, side effects, and benefits of each modality, and highlights the best treatment options, with a reflection on possibilities and limitations in the Republic of Croatia.

Keywords: actinic keratoses, field cancerization, treatment, Croatia

Sažetak:

Liječenje aktiničkih keratoza i zloćudne transformacije – hrvatska perspektiva

Aktiničke keratoze (AKS) najčešće su premaligne kožne lezije uzrokovane kroničnim oštećenjem sunčevih zraka, a prema tome se nalaze na kronično izloženoj suncu, kao što su lice, vlasište, vrat, ruke i nadlaktice. Klinički, te se lezije manifestiraju kao makule, papule ili hiperkeratoze na eritematoznoj pozadini. U Kavkazijaca starijih od 60 godina prevalencija AKS-a iznosi do 80%. Dijagnoza se temelji na kliničkom i dermoskopskom pregledu. Glavni razlog za zabrinutost kod AKS-a je rizik od transformacije u karcinom skvamoznih stanica (SCC), stoga je potrebno procijeniti sve lezije radi liječenja. Opcije liječenja AKS-a podijeljene su na tretmane usmjerene na lezije i terenske tretmane. Načini liječenja usmjereni na lezije obično uključuju kriokirurgiju/krioterapiju tekućim dušikom, kirurgiju (brijanje, eksciziju) i lasersku terapiju, dok terenski tretmani uključuju topikalna sredstva, fotodinamičku terapiju, kemijske pilinge, ablaciju polja dermoabrazijom i CO2 lasersko obnavljanje. U ovom se pregledu opisuju različite vrste dostupnih tretmana, značajke, nuspojave i koristi svakog modaliteta te se ističu najbolje opcije liječenja, s osvrtom na mogućnosti i ograničenja u Republici Hrvatskoj.

Ključne riječi: aktinička keratoza, područna zloćudna transformacija, liječenje, Hrvatska

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Correspondence:
Nikola Ferara
nfera94@gmail.com

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Introduction

Actinic keratoses (AKs) are the most common premalignant skin lesions and the third most common reason for dermatological consultation, after acne and dermatitis (1). They are caused by atypical proliferation of epidermal keratinocytes induced by chronic ultraviolet (UV) radiation. Therefore, in 75% of cases they occur on sun-exposed skin of older, fair-skinned individuals (2,3), predominantly affecting the face, neck, hands and forearms (4). The typical clinical presentation of an AK is an erythematous macule, papule or scaly patch or plaque, usually with poorly defined borders and varying degree of hyperkeratosis, sometimes better identified by touch than visual inspection. Lesions are usually numerous and signs of sun damage such as pallor, wrinkles, hyperpigmentation, telangiectasias and xerosis are visible on adjacent skin. There are several clinical variants of AKs, such as atrophic, classic, hypertrophic, cutaneous horn, pigmented lichenoid and actinic cheilitis (5). Diagnosis is usually based on clinical examination, including palpation, dermoscopic findings and medical history (6). The sensitivity and specificity of dermoscopy in the diagnosis of classic AKs are 98% and 95%, respectively. Classic AKs dermoscopically exhibit a red pseudonetwork, white scales, yellowish keratotic follicular openings, also known as the "strawberry pattern". AKs are premalignant lesions confined to the epidermis and, if left untreated, can progress, invade deeper layers of the skin, and eventually metastasize. The number of AKs that progress to SCCs is unknown and depends on the presence of risk factors but is estimated to occur in 0.075% to 0.096% of per lesions per year (7,8). Dermoscopy is essential in identifying specific dermoscopic patterns associated with different stages of AK development, especially early signs of invasive SCC, such as the presence of coiled/glomerular or polymorphous vessels and white circles (9,10). Biopsy should be considered for rapidly growing lesions, lesions greater than one centimeter in diameter, indurated, ulcerated or tender lesions, and those that do not respond to appropriate local treatment (eg. persisting for 8 to 12 weeks after cryotherapy) (6). As it is impossible to predict the risk of progression to SCC for an individual AK, treatment of AKs is of paramount importance and follow-up is recommended (11). In this review we are going to present all treatment options for AK and FC, with a reflection on possibilities, limitations, and the experience in the Republic of Croatia.

Field cancerization

According to a literature review by a committee of eight expert European dermatologists, field cancerization (FC) is clinically defined as: "an anatomical area with or adjacent to AKs and visibly sun-damaged skin identified by at least two of the following signs: telangiectasia, atrophy, pigmentation disorders and sandpaper. It is unclear if a visible AK is needed for field cancerization " (12). Field cancerization does not have a separate code in the International Classification of Diseases, 10th revision, Clinical Modification, which underlines the fact that it is not considered a separate diagnosis from AK. However, multiple AKs are not always considered field cancerization, as patients with field cancerization have a disease process that behaves differently, more often have broad and hyperkeratotic scaly lesions and a significantly higher risk of invasive SCC compared to patients with AKs only. In this context, a group of US authors proposed an appropriate definition of field cancerization, defined as multifocal clinical atypia characterized by AKs or SCCs in situ with or without invasive disease, occurring in a field exposed to chronic UV radiation (13) , giving a rationale for active treatment of field cancerization.

Treatment – general principles

The goals of ideal treatment of AKs are to eradicate evident and subclinical lesions, prevent progression to SCC and reduce recurrences (11, 14). Treatment of AKs can be either lesion- or field-directed. Lesion-directed treatments target individual AKs, whereas field-directed treatments have the advantage of treating multiple, widespread, and subclinical AKs that may occur within a field of chronic sun damage, commonly referred to as field cancerization (15). Side effects such as erythema, edema, blistering, erosions, crusting, pigment changes, and scarring, as well as sensations such as burning, pain and pruritus are expected with all treatments. Healing may take a few days to weeks, depending on the location and number of lesions treated. More than one treatment is usually required (11). Lesion-directed treatment modalities commonly involve focal ablative procedures of a clinically evident lesion, such as cryosurgery/liquid nitrogen cryotherapy, surgery (shave, excision), and laser therapy (5). On the other hand, field-directed treatments are indicated for the treatment of field cancerization. These treatments can also be used as an alternative to lesion-directed treatments in patients with multiple AKs, poor response to treatment and lesion recurrence (16). Field-directed treatments include topical agents (eg. imiquimod, fluorouracil), photodynamic therapy, chemical peels, field ablation with dermabrasion and CO_2 laser resurfacing (17). Figure 1 summarizes management of AKs and FC.

Cryotherapy

Cryosurgery/liquid nitrogen cryotherapy is a widely available, relatively easy to administer, rapid and effective lesion-directed treatment for AKs. It is recommended as a first-line treatment for one or a few isolated AKs (11,18). However, it should be performed when the clinical diagnosis of AK is certain or after histopathologic confirmation, as this procedure does not produce a specimen for histopathologic confirmation. It is usually performed by applying liquid nitrogen with a cotton-tipped applicator or spray during a single freeze-thaw cycle also including a one millimeter wide margin of normal skin, for a period of 5 to 40 seconds, depending on size of the lesion and keratiniza-

tion (19). The destructive effect of freezing is achieved in two ways: immediate cell destruction or direct effect (osmotic shock, intracellular ice formation, apoptosis, autophagy, necrosis) and delayed cell destruction or indirect effect (avascular necrosis, immune reaction). Cell destruction is greatest near the site of liquid nitrogen application and gradually decreases at the periphery. For maximum effect, it is best to create a temperature of -40 °C at the tumor margin. It is strongly recommended to perform a second freezing after the first thawing (19,20). The large differences in reported clearance rates may be related to differences in cryotherapy administration (freeze time, number of freeze-thaw cycles, contact versus spray technique) (21). Overall, cryosurgery is reported to cure 57% to 98.8% of AKs, followed for three months to 8.5 years (11). Multicentric studies have also shown that cryotherapy is preferable to ablative CO_2 laser for the treatment of isolated AKs of the face and scalp (22). When comparing cryotherapy alone or in combination with other topical treatments (ie, imiquimod, 5-fluorouracil, diclofenac), response rates for cryotherapy alone ranged from 39 to 76% compared to 73 to 89% for combination therapy (23). Side effects following cryotherapy include edema, erythema, pain, blistering (serohemorrhagic blistering develops 12 to 36 hours following the procedure), and changes in skin pigmentation, with hypopigmentation being more common than hyperpigmentation. Scarring is rare, while permanent hair loss may occur if the treatment is performed on the scalp. One of the main drawbacks of cryotherapy is the lack of standardization, so the efficacy is highly dependent on the physician and the chosen protocol (19,21). Cryotherapy is contraindicated in patients with cryoglobulinemia or cold urticaria, and for lesions requiring histopathologic analysis to

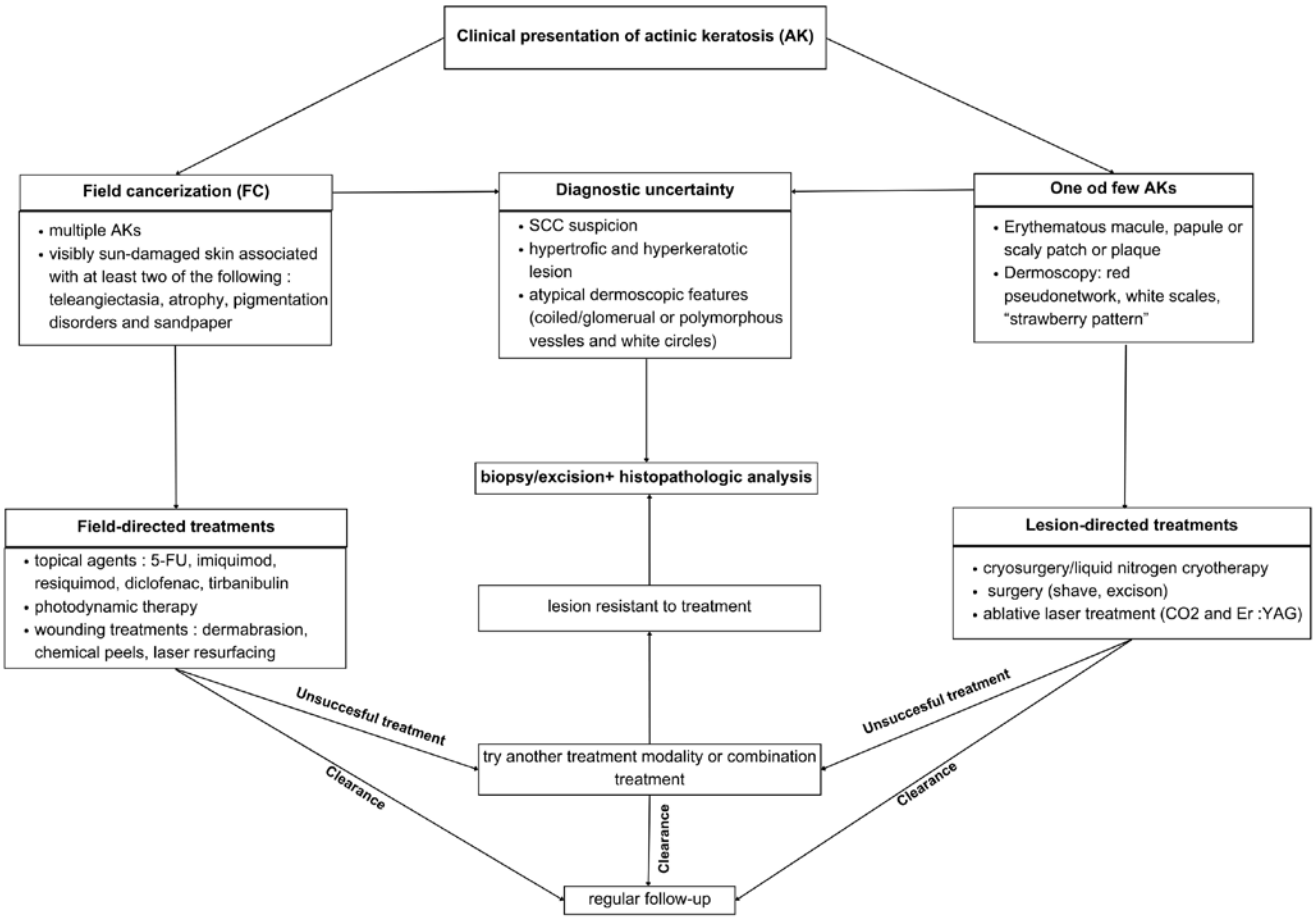

Figure 1. Management of AKs and FC in a practical algorithm.

exclude malignancy (5). Cryotherapy is, by far, the most used method of treating actinic keratoses in the Republic of Croatia. Coming from the personal experience of the authors, the major issue about its use is, the above mentioned, lack of standardization. Physicians often use it in insufficient scope and intensity, which often results in repeated visits for follow-up examinations. The main reason for this is the patient's fear of the cosmetic effect, but also possible uncertainty in diagnosing actinic keratoses. Patient should be given an informative explanation about how the treated area could look and what to expect.

Surgical treatments

Surgical treatment is often used for hyperkeratotic and hypertrophic AKs, those that have not responded to other treatments or in cases where the diagnosis is uncertain, as it allows specimen collection and subsequential histopathologic analysis. This is particularly important if there is high suspicion of SCS (20). These procedures require local anesthesia and can cause bleeding and scarring. Curettage is the most frequently performed surgical procedure in AK management and is best suited for solitary lesions. It can be combined with other destructive procedures, such as cryosurgery (4). Electrodessication following curettage can help with hemostasis and for defining lesion margins (24). However, compared to complete excision, shave excision and curettage followed by other treatments usually do not provide an adequate sample to assess whether a lesion is invasive (4).

Laser therapy

Laser treatment is another effective lesion-directed treatment. However, it can also be used as a field-directed treatment in the form of laser resurfacing. Laser therapy can be ablative or non-ablative, depending on the type of laser used-ablative laser (CO_2 and erbium yttrium aluminum garnet) or non-ablative fractional laser systems. When ablative laser systems are used, the superficial layers of the skin are ablated, including the epidermal and superficial dermal actinic damage. Re-epithelialization occurs from unaffected skin and keratinocytes from follicles. When using CO_2 lasers, the additional positive cosmetic results are due to removal of not only the epidermis, but also part of the dermis, and the thermal effect just below the ablated layer, which induces tissue tightening and collagen shrinkage. The thermal effect is also responsible for the absence of intraoperative bleeding (coagulation) and less pain (ablation of superficial nerves) but poses a risk of scarring. Non-ablative lasers (eg. erbium glass lasers) induce a dermal regeneration response by producing a vertical coagulation column (microthermal zone) located mostly in the dermis, leaving the stratum corneum intact (25). Laser therapy appears to be quite effective with a 90% response rate in treatment of AKs and recurrence rate of 10-15% at 6 months (24). Possible side effects of laser treatment include pain, inflammation, pigment change and delayed skin healing. Laser treatment is generally one of the most effective treatments for AKs, although it is expensive and has a higher learning curve compared to other lesion-directed treatments (20,25). In the Republic of Croatia laser treatment of actinic keratoses and field cancerization is not covered by Croatian Health Insurance Fund and is therefore only present in the settings of private practice. Because of this, there is scarce information about its use and effect in treating AKs and FC.

5-fluorouracil (5-FU)

5-fluorouracil (5-FU), a pyrimidine analogue, is a chemotherapeutic anticancer agent that is associated with inhibition of thymidylate synthase and incorporation into RNA and DNA, which interferes with DNA synthesis, thereby destroying actinic cells. There are various formulations of 5-FU, such as 1% and 5% cream or solution, 2% solution and 0.5% cream. In Europe the most used formulation is 5% 5-FU cream, usually applied twice daily for four weeks (20). 5% 5-FU cream is the only available formulation in Croatia. Based on the available data, 5-FU appears to be the most effective topical agent for the treatment of AKs (26). Its superiority compared to other topical agents was recently confirmed in a large, multicenter, single-blind, randomized, head-to head trial, conducted by a group of Dutch authors and involving 624 patients. At 12 months post-treatment, 5% 5-FU cream was significantly more effective than other agents in patients with multiple lesions on the head, with a cumulative probability of treatment success of 74.7% (95% confidence interval (CI)) for 5-FU, and 53.9% (95% CI), 37.7% (95% CI) and 28.9% (95% CI) for imiquimod, photodynamic therapy and ingenol mebutate, respectively. Another important aspect of this study is the inclusion of grade III or severe lesions (very thick or obvious AKs), which has not been considered in most other studies investigating the efficacy of field-directed treatments (27). Additionally, 5-FU can be combined with other agents, such as calcipotriol and salicylic acid. Topical application of 5-FU/calcipotriol appears to be an effective immunotherapy for AKs, with even better results than 5-FU alone. In a blinded prospective cohort study, a short course treatment with 5-FU/calcipotriol on the face and scalp was associated with induction of robust T-cell immunity and tissue resident memory T-cells against AKs and a significantly lower risk of SCC at 3 years post-treatment (28). This additional carcinoma-preventing property makes it an ideal field-directed treatment. A fixed combination of 0.5% 5-FU and 10% salicylic acid was initially introduced for the treatment of hyperkeratotic AKs of the head and neck, on the rationale that salicylic acid should improve the penetration of 5-FU due to its well-known keratolytic properties. Although the efficacy of this combination therapy has not yet been established, recent reports are promising. One observational study reported complete clearance of 50% of treated lesions and partial clearance of 28% of the treated lesions at week 4; at 12 weeks, these

results were 84% and 8%, respectively. The combination of 5-FU and salicylic acid has been shown to be an effective treatment for mild to moderate AKs (29).
In the Republic of Croatia 5% 5-FU cream belongs to the Basic list of medicines, which means that for the most part, treatment with this agent is covered by health insurance. Because of this, and the substantial clearance rate, 5% 5-FU cream is the most prescribed topical agent in treatment of FC in our country. Also, it is often prescribed for AKs of large surfaces, superficial basal cell carcinomas and Bowen's disease. There is an established procedure for presenting photo documentation of treatment phases to achieve the highest possible adherence to therapy.

Imiquimod and resiquimod

Another field-directed treatment is imiquimod, a synthetic imidazoquinolone that has a potent immune response modifying activity when used topically. It is a toll-like-receptor (TLR) agonist, inducing apoptosis and the release of cytokines and chemokines, such as tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), interleukins, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The release of these pro-inflammatory mediators causes a great influx of inflammatory cells into the lesion, resulting in its destruction by natural killer cells and cytotoxic T lymphocytes (30). The mechanism of action may explain why, in addition to AKs, imiquimod is also used for treating other skin conditions such as genital or perianal warts caused by human papillomavirus (HPV) or basal cells carcinoma (BCC). Imiquimod is available as 2.5%, 3.75% and 5% cream. In Croatia imiquimod is available only as a 5% cream. A 5% concentration should be applied to an area of no more than 25 cm^2 on the face and scalp, three times a week for 4 weeks over a period of 16 weeks. Lower concentrations, 2.5% and 3.5%, can be applied daily in a 6-week regimen: 2 weeks of treatment, followed by 2 weeks off and another 2 weeks of treatment (20). The 5% formulation is preferred for BCCs, while the 3.5% formulation is a reasonable option for AKs and field cancerization, as it can be applied to a larger surface and has fewer side effects than the 5% formulation, while having similar efficacy. The 3.5% imiquimod formulation has a clearance rate of 35.6% and recurrence rate of 20.9% 12 months post-treatment (30). Recently, a small study presented an interesting feature of imiquimod 3.75% cream detecting clinically invisible (subclinical) actinic damage. Experimental application of 3.75% imiquimod cream to chronically UV-exposed skin induced a faint, but visible inflammation, a sign of binding of imiquimod to TLR-7 on monocytes and macrophages, which mediates activation of intrinsic and acquired immunity through activation of cytokines with antineoplastic capabilities. In other words, imiquimod caused a skin reaction at sites of early, clinically invisible, malignant cells (31). In Croatia, 5% imiquimod cream is listed in the Supplementary list of medicines – therefore it is substantially less prescribed for treatment of AKs and FC in comparison to 5-FU.
Resiquimod, just like imiquimod, belongs to the class of imidazoquinolines and is a TLR-7 and TLR-8 agonist that activates myeloid and plasmacytoid dendritic cells. Resiquimod is available in concentrations of 0.01, 0.03, 0.06, or 0.1%, with greatest efficacy observed when used three times a week for four weeks. Given its pharmacodynamic profile, resiquimod may potentially achieve greater efficacy than imiquimod. A recent multi-center, partly placebo-controlled, double-blind clinical trial found that 0.03% and 0.01% resiquimod gel were effective treatments for the AKs of balding scalp, forehead, and face. Additionally, dosing regimens with erosions as a biological endpoint proved to be effective and may be suitable for tailored treatment of AKs (32). Unfortunately, resiquimod is not available in Croatia.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory, analgesic, and antipyretic properties. The likely mechanisms of its anti-tumor effects are inhibition of cyclooxygenase 2 activation, which is overexpressed in SCCs, and inhibition of prostaglandin E2, which is associated with tumor angiogenesis and cell proliferation, as well as binding to the nuclear receptor PPARγ (partial agonist of peroxisome proliferator-activated receptor gamma), whose activation inhibits cancer cell growth (16, 33). It is currently only available in a combination formulation of 3% diclofenac gel in 2.5% hyaluronic acid and is routinely applied twice daily for 60 to 90 days, making it one of the longest treatments for AKs. Although slightly less effective than other topical treatments (e.g., 5-FU or imiquimod) with a 54 to 63% clearance rate, it is very well tolerated and causes only mild skin irritation, making it an alternative to other, more aggressive topical treatments and suitable for the management of AKs (16). In Croatia diclofenac is not available for treatment of AKs and FC. There is only formulation of diclofenac as a pain-relief gel.

Ingenol mebutate

Ingenol mebutate is an active substance isolated from milkweed (Euphorbia peplus), historically known as a home remedy for BCCs, warts and AKs due to its cytotoxic activity and ability to affect cell differentiation. Although the true mechanism of anticancer activity had not been fully elucidated, there are two plausible mechanisms; direct cytotoxic activity (direct tumor cell death resulting in necrosis) and immune-mediated mechanism (antibody-dependent cellular cytotoxicity mediated by neutrophils) (34, 35). Despite being promising treatment agent, it has been proved that ingenol mebutate (in the form of a gel) increased the risk of skin cancer, particularly SCC in the treatment area. As a resul of this, in April 2020, the European Medicines

Agency (EMA) issued a press release clearly stating that the risks of ingenol mebutate outweighed the benefits, suspending it from the market in the European Union (36).

Tirbanibulin

Tirbanibulin is a microtubule-targeting agent that has shown potent anti-proliferative and anti-tumoral effects in-vitro and in-vivo by inducing cell cycle arrest and ultimately apoptotic cell death (37). It works by inhibiting tubulin polymerization and disrupting Src kinase signaling, the two pathways often upregulated in AKs and SCCs (38). Tirbanibulin, available as a 1% ointment, is a novel agent approved by the European Medicines Agency (EMA, 2021) and the Medicines and Healthcare Products Regulatory Agency (MHRA, 2021) for 5-day topical field-directed treatment of non-hyperkeratotic, non-hypertrophic AKs on the face and scalp in adults. A recent review of the efficacy and safety of different AK and FC treatments showed that tirbanibulin is superior to diclofenac in complete clearance rate and has similar efficacy as well-established treatments, such as photodynamic therapy, imiquimod, cryotherapy and 5-fluorouracil, with significantly lower rates of serious local skin reactions. Potential advantages over existing treatments are the short duration of treatment with once-daily application over five days, a good safety profile and efficacy comparable to existing topical treatments (39). Although available in Croatia, there is scarce use of this agent, mostly because of high treatment cost.

Photodynamic therapy

Photodynamic therapy is an effective treatment for AKs and field cancerization. In contrast to some agents used for topical treatment of AKs, it has a clear mechanism of action using visible light to react with photosensitizing chemical compounds, 5-aminolevulinic acid (ALA) and methyl-aminolevulinate (MAL) to generate active oxygen species responsible for the apoptosis of skin cancer cells. This treatment exploits the pathological property of cancer cells to accumulate protoporphyrin IX, the production of which is induced by ALA and MAL (40). One of the most convenient treatment executions is the use of daylight as part of daylight photodynamic therapy, whereby MAL or ALA cream is applied to the affected area and removed after a 2-hour exposure to natural daylight (20). Photodynamic therapy has a clearance rate of 82 to 91% and a recurrence rate of 53 to 64% at 12 months post-treatment, making it as effective as 5-FU or even more effective. The disadvantages of this treatment are the cost, time and severe pain associated with application (16). The use of photodynamic therapy in Croatia has been largely limited by difficulties in import of photosensitizing compunds (ALA and MAL). Additionally, many patients in the past requested cessation of treatment due to unbearable pain.

Wounding treatments

Recently, wounding treatments such as dermabrasion, microneedling, chemical peeling, and fractionated laser resurfacing have been shown to restore IGF-1/IGF-1R (insulin-like growth factor-1/insulin-like growth factor-1 receptor) signaling in geriatric skin and suppress the propagation of damaged keratinocytes. In contrast to well-established topical treatments for AKs and field cancerization, which target already altered cells in precancerous lesions, wounding therapies have the potential of preventing malignant transformation (41).

Chemical peels

Topical exfoliative agents, alone or combined, are used to induce controlled cutaneous injury leading to epidermal turnover and collagen regeneration. In addition to their cosmetic effects, these agents can also be used in the treatment of AKs and field cancerization, because of their ablative nature, which has the potential to ablate premalignant cells (42). Chemical peels can be superficial (only penetrating the epidermis), medium-depth (penetrating the epidermis and papillary dermis) and deep (penetrating into the mid-reticular dermis). Usually, different groups of chemical peels can be combined to achieve the desired treatment goal (43). For example, Jessner's solution, a superficial peel consisting of resorcinol, salicylic acid and lactic acid, and 35% trichloroacetic acid (TCA), as a medium-depth peel. In one small split-face trial, the combination of Jesnner's solution and 35% TCA in a single application was almost as effective in clearing AKs on the face as a 4-week treatment with 5% imiquimod cream (79.1% clearance with chemical peel vs 72.8% with imiquimod). Although both treatments were effective, chemical peels were more effective, easier to apply (shorter treatment duration) and resulted in greater patients' satisfaction (44). In addition to combination chemical peels, there are also sequential peels, in which wounding agents are applied sequentially, for example Jessner's solution followed by TCA. One of the medium-depth peel options for field cancerization treatment is the Brody peel, a sequential peel in which a solid CO_2 slush is followed by 35% TCA (45). In general, chemical peels seem valid field-directed treatments, and in the context of awareness that field cancerization needs to be adequately treated, these treatments are likely to be more widely recognized.

Fractionated laser resurfacing

Fractionated laser resurfacing has been extensively used for the treatment of photoaging, acne scarring and dyschromia. The rationale behind laser resurfacing for the treatment of AKs and field cancerization is based on removing the superficial layers of the skin and allowing re-epithelialization with healthy keratinocytes. According to a recent review regarding the efficacy of laser resurfacing compared to existing treatments for AKs, laser

resurfacing monotherapy has been shown to be at least as effective or more effective than 5-FU as field therapy and as effective as a 30% TCA peel in reducing AKs. However, there are still not enough studies to draw definitive conclusions about its efficacy (46).

Dermabrasion

Dermabrasion is a skin resurfacing technique that has been used in dermatology for more than 100 years to treat various skin conditions (41). It is performed using a portable hand-held dermabrader with either wire brushes, diamond fraises, or serrated wheels for precise treatment. Although dermabrasion is an old technique, a carefully designed study by a group of American authors was the first to demonstrate how it restores a more youthful phenotype and induces a reversible molecular signature that can suppress the characteristic geriatric pro-carcinogenic ultraviolet response (41). Recently, a group of Chinese authors presented dermabrasion combined with photodynamic therapy (D- PDT) as a new option for the treatment of AKs and non-melanoma skin cancers (NMSC) - SCC, nodular BCC, Bowen disease. In their study only two patients with three AKs experienced recurrence after 12 months and 34 out of 40 patients (including those with NMSCs) treated with D-PDT reported excellent or good cosmetic results, proving that pretreatment with dermabrasion enhances the effect of PDT, making it suitable for management of thicker lesions (47). However, over all the effectiveness of dermabrasion depends heavily on the skill of the practitioner, and the cosmetic results can sometimes be unsatisfactory.

Retinoids

Although retinoids are not considered conventional therapy for AK and FC treatment, they can help decrease the number of damaged or precancerous cells due to their effect on oxidative stress and cell differentiation (24). Retinoids can be used both topically and orally, with oral (systemic) retinoids mainly used for skin cancer chemoprevention in immunocompromised patients and are suitable for patients with multiple AKs. Isotretinoin is one of the most used retinoids and can be used as a 0.1% topical agent twice daily for six months or orally at a dose of 20 mg daily for three weeks (30). Combination therapy consisting of oral isotretionin 20 mg and 5-FU once daily, also known as "turbo therapy", has shown good efficacy (24).

Prevention

All patients with AKs should be advised to apply protective measures against UV radiation: wearing appropriate clothing, hats, using sunscreens with a high sun protection factor (SPF > 30), avoiding strong and prolonged exposure to sunlight, sunbed use. Secondary prevention is important in patients at high risk of multiple AKs, field cancerization or immunosuppression, and includes prophylactic treatment with photodynamic therapy, 5-FU or imiquimod. Studies show that treatment with 5% 5-FU cream twice daily for 4 weeks reduces the number of AKs, the need for additional lesion-oriented treatments and leads to a 75% reduction in the risk of developing SCC (48). Several studies have examined the use of systemic chemoprevention in high-risk populations. Investigated agents included oral retinoids, NSAIDs, capecitabine, dietary supplements and vitamins (nicotinamide, β-carotene). Oral nicotinamide (vitamin B3) at a dose of 500 mg twice daily has been shown to reduce the development of SCC by 30% in immunocompetent individuals with confirmed keratinocyte carcinomas in the past five years (49). However, there are still no recommendations for chemoprevention of skin cancers.

Choosing treatment options

There is no standard treatment for AKs. Physicians should decide considering both the lesions (number, distribution, location, histology) and patient characteristics (patient's preferences, age, compliance, immune status, cost). As treatment of these lesions is usually a long-term process for most patients, accompanied by a certain degree of discomfort and difficulty, the decision on the best treatment modality should be made jointly by the physician and patient. In our review, we analyzed possible treatment options based on indications and clinical presentation. Based on a review of the literature and our clinical experience, cryotherapy remains the gold standard for solitary or few AKs. It is a fast, effective, easy to administer and widely available treatment. Surgical treatment is irreplaceable in the assessment of malignancy of a solitary lesion in cases of diagnostic uncertainty, but usually only complete excision provides an adequate histopathological specimen. Biopsy should be considered for rapidly growing lesions, lesions greater than one centimeter in diameter, indurated, ulcerated or tender lesions, and those unresponsive to previous treatment.

All field-directed therapies used showed a short-term reduction in actinic keratosis, with 5-FU and PDT being the most effective methods for short-term clearance. Clearly, further studies with longer follow-up periods are needed to assess the effect of topical therapies on the long-term incidence of skin cancer, as best illustrated by the case of ingenol mebutate, the use of which has been associated with an increased incidence of keratinocyte carcinomas (SCC, Bowen's disease), leading to its withdrawal from the market in the EU. Adverse effects following topical treatment of AKs, and FC are mostly local and are observed for all the treatments used. They include erythema, ulceration, crusting, blistering, pruritus, and others and, in most cases, are mild and transient. Scarring and pigmentation can be irreversible adverse events. Systemic side effects are rare but can occur, for example flu-like symptoms after treatment with imiquimod. Diclofenac can be considered least effective, but it has an extremely good tolerability and high safety profile, with almost no systemic side

effects observed. Imiquimod and 5-FU are more effective, but are usually accompanied by moderate to severe reactions at the site of application, most of which resolve without sequelae (50). An unpleasant adverse event following photodynamic therapy is pain and possible photosensitization of the skin[30]. Further studies are needed to find a treatment that could achieve the best result in clinically visible lesions and a durable result for field cancerization, with fewer side effects and shorter duration to avoid poor patient compliance.

Conclusion

Treatment of AKs and FC in Croatia relies mostly on the use of cryotherapy and 5% 5-FU cream. Just like in other countries, the use of cyrotherapy lacks standardization and is often used with an insufficient intensity, resulting in lower clearance rate and repeated check-ups. 5% 5-FU cream is the most prescribed agent for treatment of FC and an established procedure for presenting photo documentation of treatment phases contributes to high adherence to the therapy. 5% imiquimod cream in our country is not listed on the Basic list of medicines, which is why it is not prescribed as often as 5-FU cream. Following EMA's suspension, ingenol mebutat is no longer available in Croatia. Despite being respectable treatment modality for FC and AKs, photodynamic therapy is not routinely used in Croatia, due to the difficulties in the import of photosensitizing chemical compunds (ALA and MAL). Other treatment modalities, including laser, are not covered by medical insurance and their use is contained in the private practice. From our point of view, there is a great potential in use of chemical peels for treatment of AKs and FC in hospital settings in Croatia, mostly because some of the agents are already being used for cosmetic purposes and the treatment is supervised by an expert physician. From our experience, in some cases, no treatment is also a valid approach, especially in older patients, in whom there would be more harm than benefit from conducting the treatment. However, in these cases more frequent follow-ups are essential to closely monitor for SCC development.

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