Actinic keratoses — a systemic review

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Mainly elderly people with pale skin are affected by actinic keratoses (AK). Due to the demographic change, the prevalence of AK increased over the last years. An established risk factor is chronic UV-exposure (outdoor workers) inducing mutations of the tumor suppressor gene TP53 and the oncogene *H-Ras*. This leads to an intraepidermal proliferation of atypical keratinocytes. The term "field cancerization" characterises the presentation of multiple AK in UV-exposed areas. AK are also termed squamous cell carcinoma (SCC) in situ. The risk for AK turning into a SCC is 6—10%. In order to avoid invasive growth, an early treatment is recommended. During the last years multiple therapeutic options have been established. Depending on the clinical extent, lesion- or field-directed therapies with excellent clinical response and cosmetic results are available.

Ключевые слова: **actinic keratosis — UV-exposition — SCC in situ — atypical keratinocytes — photodynamic therapy.**

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The disease pattern of actinic keratoses (AK) was first described by Freudenthal in 1926. In 1958, the term „actinic keratoses" was mentioned by Pinkus for the first time [1]. Chronic UV radiation leads to a proliferation of atypical keratinocytes in the basal layer of the epidermis, wherefore AK are also termed squamous cell carcinoma (SCC) *in situ*. The incidence of AK increased significantly over the last years. In the daily routine of a dermatologist the treatment of AK is one of the most frequent tasks.

Epidemiology

AK are predominantly found in patients with pale skin, blue eyes and red hair (Fitzpatrick skin types I/II). The risk of getting AK is significantly (40%) increased in patients who sunburn more easily than in individuals with brown hair and eyes [2, 3, 4]. The prevalence of AK reaches 6—15% in the European population over the age of 40. There is gender predominance; men are significantly more often affected. The prevalence is also age-related, it increases with higher age and represents 20% in 60 year-old individuals and 52% by the age of 70 [2]. In summary, a significant increase of AK during the last 10 years was noticed. Cause of this increment is the demographic change with many elderly people [3]. Outdoor workers with high UV exposure demonstrate significantly more AK than people working in an office [5—7]. Other risk factors include organ transplantation and/or chronic immunosuppression. After 20 years of immunosuppression the risk of getting AK is 40—60% with a high tendency to malignant transformation into squamous cell carcinoma [8].

Pathogenesis

The prevalence of AK is linked to chronic UV exposure, especially UVB radiation [5—11]. UV radiation leads to a mutation of the tumor suppressor gene TP53. This gene is located at chromosome 17p13.1 coding for the protein p53. p53 is an important regulator of the cell cycle, inducing apoptosis of mutated cells. UV-radiation causes the „UV-typical" signature change from cytidine to thymidine in TP53. This leads to an inactivation of TP53, which results in an uncontrolled proliferation of genetically unstable keratinocytes and development of AK [9—11].

Furthermore, UV radiation leads to a mutation in codon 12 of the Ras-oncogene *H-Ras*, which is an important regulator of the Erk1/Erk2-pathway, regulating the prolifer-

ation of cells. As a consequence of the mutation, the pathway is permanently activated, also resulting in an uncontrolled cell proliferation. This mutation was also detected in non melanoma skin cancers (NMSC) like AK and SCC (figure 1) [12, 13]. In melanoma patients with metastatic disease and therapeutic intervention with the so-called BRAF-inhibitors, a significant side effect is the development of NMSC, based on the iatrogenic imbalance in the generation of those tumors via an activation of the H-Ras pathway [14].

Repeatedly discussed is an association of AK respectively SCC and infections with human papilloma virus (HPV). Zaravinos et al. detected HPV-DNA by PCR in 31% of the investigated AK and in 33% of the investigated SCC [15]. Other analyses showed significantly higher levels of viral load in AK compared to SCC and normal skin. [16]. In conflict with these results are observations showing that HPV-DNA is also detected on normal skin and in hair follicles and therefore should probably only be seen as a coincidal connection [17].

Clinical aspects

AK are often detected in sun exposed areas of elderly people like the scalp, forehead, bridge, ear helices, cheek, forearm and dorsum of the hand. In many cases more AK are observed in the left face, probably due to UV transmission of window glass of the side windows in cars. AK become clinically manifest as isolated, about 0,1—2,5 cm sized circumscribed, skin-coloured, erythematous, occasionally pigmented, scaly and rough plaques, sometimes with crusting and hyperkeratoses (figure 2). Usually AK are symptomless. In rare cases they appeare with itching and burning [9]. AK localised in the area of the lower lip are rare and termed „Cheilitis actinica“. “Field cancerisation” is a confluence of isolated AK in different stages. [18]. Due to the variable clinical appearance of AK, 4 clinical subtypes are defined:

- erythematous type
- keratotic type
- pigmented type
- Lichen-planus type

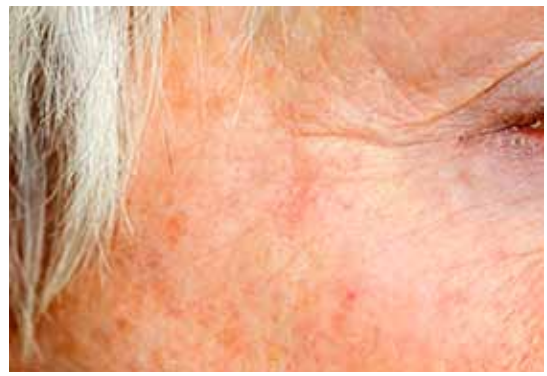

Fig. 2. Typical AK at the right temple in a 72-year old patient: not sharply defined edges, erythematous, nonhyperkeratotic plaque

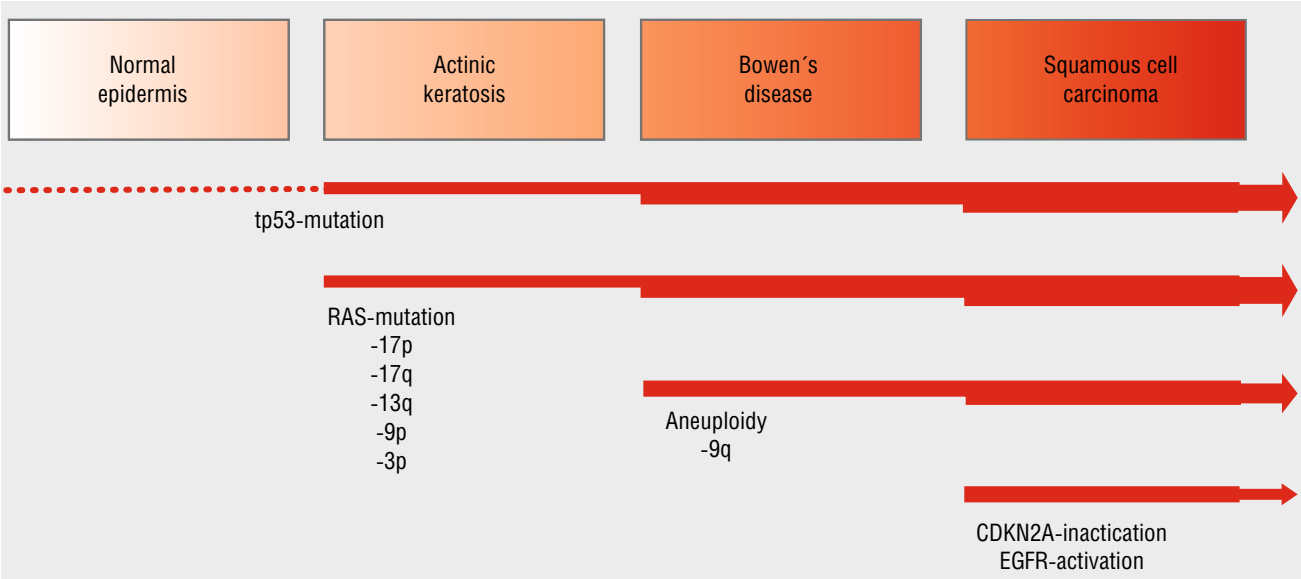

Fig. 1. Step-by-step model of the molecular pathogenesis of squamous cell carcinoma

Diagnosis

AKs are diagnosed due to the clinical appearance and the tactile result. Dermatoscopy or confocal scanning laser microscopy (CSLM) can be helpful in unclear cases or in pigmented lesions. In case of very hyperkeratotic AK, a biopsy is recommended to exclude the presence of a SCC [9, 19].

Differential Diagnoses

Differential diagnoses of AK are skin tumors like superficial basal cell carcinoma, Bowen's disease, SCC, lentigo maligna and seborrhoeic keratoses as well as dermatoses like psoriasis vulgaris, tinea corporis, seborrhoeic eczema and lichen planus. Another important differential diagnosis of AK mainly in the area of the lower leg is porokeratosis and has to be excluded by biopsy.

Histopathology

The histological picture is characterized by a change of ortho- and parakeratosis. The epidermis may appear akanthotic widened or atrophic. In addition, atypical pleomorphic keratinocytes with large cell nuclei and little cytoplasm are found in the lower part of the epidermis. These atypical keratinocytes can be found throughout the whole epidermis during the developmental stages of an AK. Furthermore, mitotic figures and dyskeratotic cells are observed. This picture is often accompanied by solar elastosis and occasionally by a dense infiltration of lymphocytes (figure 3). Depending on the degree of severity of the epidermal changes, AK can be divided into three histological grades (AK I—III), analogous to the classification of cervical intraepithelial neoplasia (table) [20]. Furthermore, several histological subtypes of AK also exist, and there is a differentiation between pigmented, akantholytic, bowenoid, lichenoid and hypertrophic actinic keratoses. Since there are no cytological differences between AK and SCC, AK can also be considered as squamous cell carcinoma *in situ*. [21]. If there is infiltration or penetration of the basal layer of the epidermis by atypical keratinocytes, the lesion is called squamous cell carcinoma [9, 22, 23].

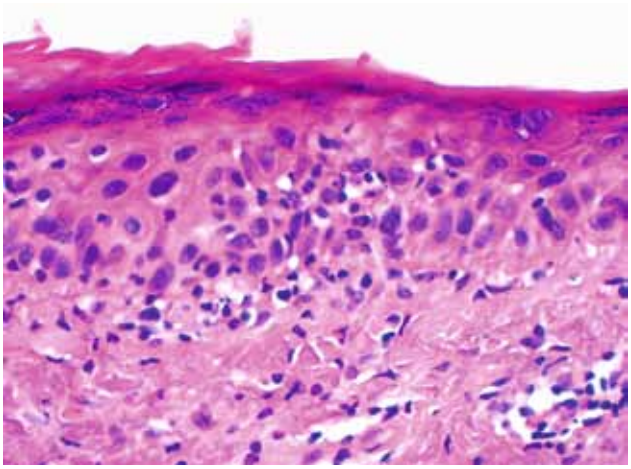

Fig. 3. Histopathological findings: atrophy of the epidermis, pleomorphic keratinocytes in the lower 2/3 of the epidermis (equivalent to a AK II), subepidermal lymphocytic inflammatory infiltration as well as pronounced solar elastosis

Prognosis

Data about the progress of SCC from AK vary widely and are specified with 0 — 0.53% per year [24]. According to Marks et al., the risk for an isolated AK turning into a squamous cell carcinoma is 0.24%. Since most patients have many actinic keratoses, the risk of developing at least one SCC within 10 years is estimated with 6.1 — 10% [25, 26]. Further investigations, however, expect an average progression within 2 years. Age and gender differences as well as localization of AK play no role regarding the progress of SCC [27]. However, the risk of progression is significantly higher in immunocompromised patients after organ transplantion (8). In contrast, in approximately 15 — 63% cases a spontaneous remission of the AK can be seen, which also accounts for high clearance rates of AK in placebo groups in randomized controlled trials [24, 25].

Therapy

Due to the risk of progress into SCC, treatment of AK is recommended in every case. A variety of therapeutic options are available and the optimal therapeutic approach must be individually adapted to the patient. In principle, there is a choice between a lesion-directed therapy as treatment for isolated AK and a field-directed approach. The latter includes the treatment of multiple lesions and large areas (field-cancerization) [28]. In addition, physical therapy (see below) can be distinguished from immuno-

Table Histological degrees of severity of actinic keratoses (after Röwert-Huber [20])

AK I	Atypical keratinocytes in the lower third of epidermis
AK II	Atypical keratinocytes in the lower 2/3 of the epidermis
AK III	Full enforcement of the whole epidermis with atypical keratinocytes

modulating and chemical therapies (figure 4). Combinations of therapies are also well established, especially in refractory cases. In addition to an adequate therapy patients should be informed of the positive effect of a consistent UV protection. A study could show that regular application of sunscreen in organ transplant patients reduced the formation of new AK lesions as well as the progression of AK to squamous cell carcinoma [29].

Lesion-directed therapeutic options

Physical Therapy

One domain of the treatment of isolated AK are physical therapy options like cryosurgery, excision and curettage, which can be applied quickly and easily. However, these procedures seem to be less effective than drug therapies. This circumstance is based on the fact that only a few studies exist for the above mentioned therapies. Due to the high cost for the planning and conduct of a clinical trial no sponsor will be interested in the evaluation of these old procedures. One exception is cryosurgery. This procedure is often used as a comparator in numerous controlled, randomized studies, because a lot of information regarding effectivity, sustained yield and cosmetic outcome are known [30].

Cryosurgery

Cryosurgery represents a simple, effective, and economic therapeutic option for isolated, thin AK. The treatment with liquid nitrogen, either as a spray or as contact procedure, leads to an intracellular ice crystal formation followed by destruction of the cell organelles. In consequence, tissue destruction also induces inflammatory and immunological responses [31]. Since the implementation of cryosurgery, with respect to temperature, duration, repetition, and distance, is not standardized, success rates depend on the experience of the performing physician [18, 31]. Thai et al. showed that the freezing time correlates directly with the effectiveness. Only 39% of AK displayed a complete clinical healing after 5 seconds of treatment, while freezing times > 20 seconds led to a complete remission in 83% of the lesions [32]. Data on response rates differ in the literature because of the many treatment-related variables and range between 39 to 88% [31—34]. Main disadvantages are the painfulness of the procedure, local inflammatory reactions and permanent hypopigmentation due to the concomitant destruction of melanocytes [31—34]. Therefore cryosurgery is suitable only for lesion-directed therapy of isolated mild to moderate AK lesions. Both the cosmetic results after

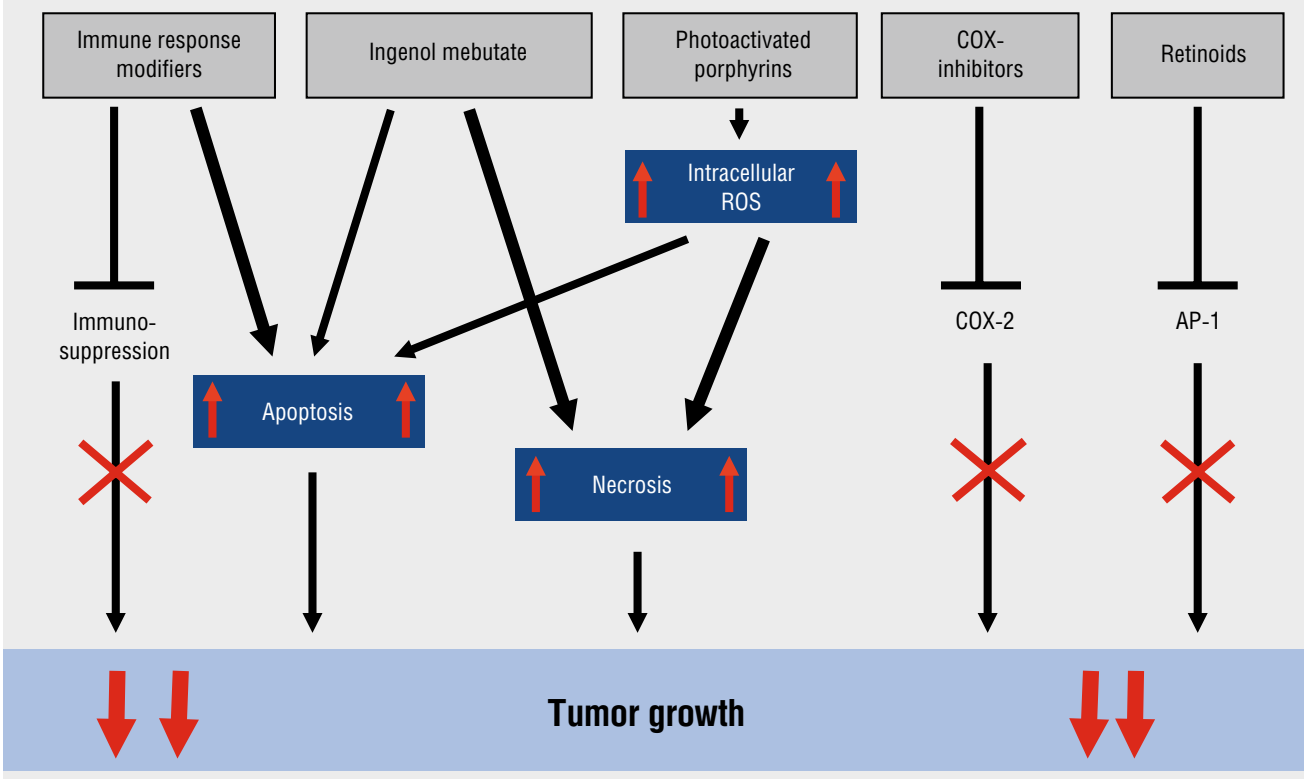

Fig. 4. Pathogenesis-oriented therapeutic approaches in AK

cryosurgery and the patient satisfaction are inferior to the results of photodynamic therapy [34].

Laser ablation

Ablative laser procedures with the CO_2 or Er:YAG laser are alternative therapeutic options for mild and moderate isolated AK. The therapeutic options are related with a temporary complete clinical healing of 90% [35]. Furthermore, there are only a few studies with small numbers of patients, so that the statement is restricted [18]. Atypic keratinocytes in adnexal structures are not caught by laser ablation and are the origin of clinical relapse. Disadvantages of this treatment are again the tenderness, risk of infection and possible scarring in cases of aggressive ablation. Additionally, laser treatment does not have the possibility of a dermatohistopathological report, so that laser ablation can be considered to be in an inferior position compared to surgical intervention in unclear cases [9, 18, 35].

Classical excision, curettage/shave biopsy

In addition to the classical excision, curettage and shave biopsy represent further treatment options, especially in cases of hypertrophic AK with the risk of already existing invasion in the corium. The advantage of this method is the possibility of a dermatohistopathologic evaluation and should be preferred to conservative treatment options in uncertain cases [9]. A statement regarding the effectiveness of surgical procedures cannot be established because there are no studies available also not with comparison to topical medication procedures [18]. Disadvantage of this treatment is also the need for a local anesthesia, as well as the risk of possible infections, scarring and hypo- or hyperpigmentation [9].

5-Fluorouracil + salicylic acid

A combination of 0.5 % 5-fluorouracil and 10% salicylic acid (5-FU/SA) in the form of a laquer (Actikerall®) is approved since 2011 for the treatment of mild to moderately thick, hyperkeratotic AK [18]. 5-Fluorouracil inhibits as cytostatic agent DNA synthesis and thus the cell division [9, 36]. Salicylic acid acts as keratolytic, therefore the combined formulation is considered to be superior to other therapeutic options, in particularly in the treatment of hyperkeratotic AK [36]. The treatment should be given once daily for 6—12 weeks. Because of the application with the help of the brush a targeted treatment of individual AK is possible. A complete clinical response could be reached in 55.4%, while 70% of these targeted areas showed a complete histological response [36]. Side effects like itching and burning of the treatment area as well as mild to moderate local inflammatory reactions appeared 6 weeks after start of treatment in >70% of the patients. These are usually limited to the application site, so that the therapy is overall well tolerated by the patients [36].

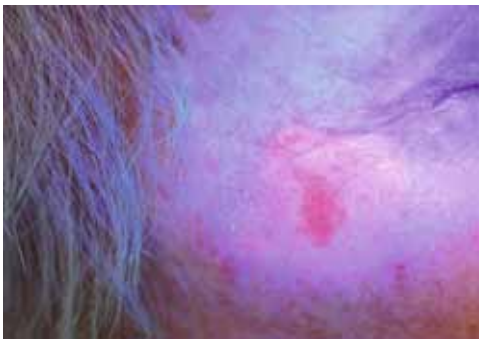

Fig. 5. Same patient as in Figure 2. Fluorescence diagnostics after 4-hour incubation with 5-ALA-containing patch before light exposure. Increased fluorescence in the AK-area as an indicator for the preferential protoporphyrin-IX synthesis

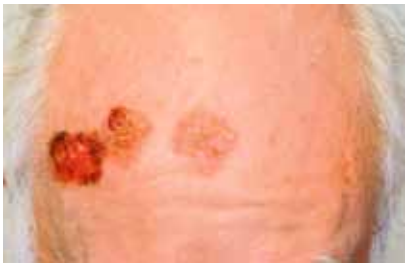

Fig. 6. 76-year-old patient. Side effects 2 days after PDT with the 5-ALA-containing patch. Redness and crusting are limited to the applied patch localization

Lesion-directed photodynamic therapy

The treatment of AK by photodynamic therapy (PDT) with a 5-aminolevulinic acid containing solution (Levulan® Kerastick, DUSA) is approved in the USA since 2002 [9, 18]. Since 2003, 5-ALA methyl ester (Metvix®, Galderma) as a cream is commercially available for the treatment of AK, nodular and superficial basal cell carcinomas, and Bowen's disease. A 5-ALA-containing gel (Ameluz®, Biofrontera) is registered since 2012 for the treatment of AK. The above mentioned preparations are suitable for the treatment of single AK and field-cancerisation. Since 2010, there is also an adhesive patch (Alacare®, Galderma) available, which contains 8 mg 5-aminolevulinic acid. With a size of 4 cm^2 it is particularly suitable for treatment of individual lesions. Without any pre-treatment the patch

is directly applied to the lesions. The incubation period of 4 hours is followed by illumination with red light (630 nm, 37 J/cm^2 [18, 37, 38]. In a double-blind comparative clinical trial it could be shown that the effect of a patch-PDT is significantly superior to cryosurgery (clinical response rates after 12 weeks: 82—89% vs. 77%) and results in significantly better cosmetical outcomes. In particular, postinflammatory hyperpigmentation was hardly observed after PDT [38]. Further advantage is the possibility of a targeted treatment with significantly less pain during the exposure time. Side effects, such as redness, blisters and crusting occur in usually 1—2 days later and are limited to the applied patch localization (figure 5 and 6) [22, 37, 38].

Field-directed therapy

UV-induced mutations of keratinocytes exist in the whole UV-exposed area and are not strictly limited to visible AK lesions. Therefore development into AK also in this areas is very likely, although exact figures cannot be given. So the use of preparations or procedures which already target incipient AK would be beneficial to avoid the development of new AK at least for a certain amount of time. This concept is confirmed by multiple field-directed therapy options.

Hyaluronic acid gel diclofenac sodium

The product Solaraze® (Almirall) contains 3% diclofenac sodium and hyaluronic acid in a gel matrix and is registered for the use in AK since 2001. The exact mechanism of action is not completely understood. It is assumed that an inhibition of the arachidonic acid pathway occurs by inhibition of the enzyme cyclooxygenase I and II (COX I and II). This results in an inhibition of cell proliferation and angiogenesis [9, 18]. Applied twice daily for 90 days, the treatment leads to a remission rate of 40% [39]. Adverse reactions such as itching, burning, redness, and flaking are usually rare, so this therapy can be considered as being well tolerated by the patients [9, 40]. The treatment period of 3 months is relatively long. However, an extension of the treatment period up to 6 months does not lead to an improvement of the effectiveness [9, 39].

Imiquimod

Imiquimod as an immunomodulator and strong interferon-inducer is now available in three different concentrations for the treatment of AK. Information respecting the response rates of the 5% preparation (Aldara®, Meda) in mild to moderate AK differs, depending on the regimen between 45% and 55% [41—43]. Currently, a treatment 3x/week for 4 weeks is recommended. After a 4-week interval a second cycle can be performed [41]. In the lower concentration of 3.75% (Zyclara®, Meda) Imiquimod is applied once daily for 2 weeks and is followed by another 2-week-cycle after a 2-week treatment-free interval. The response rates are approximately 35% [44]. Studies have shown that a longer application interval does not lead to a better response rate [45]. A further 2.5% concentration of Imiquimod is marketed under the same name in the US. Two well-controlled studies showed a similar response rate of the 2.5% formulation in comparison to the 3.75% cream (complete clearance 30.6% vs. 35.6%). Both imiquimod creams (2.5% and 3.75%) were significantly more effective than placebo [46]. Side effects such as redness, erosion and crusting occur in almost all cases, but are more likely to be seen in the higher concentrations of imiquimod. It may also come to flu-like symptoms in all concentrations [45]. Due to the concentration-dependent adverse reactions, imiquimod 5% should be applied only in a maximum of 25 cm^2 large area while imiquimod 3.75% is approved for the treatment of the entire scalp. However, the negative impact of the treatment is in particular the partly pronounced local reactions with the systemic side effects (figure 7). Therefore, a detailed investigation of the patients is essential to avoid discontinuation of treatment. The use of imiquimod in patients with autoimmune disease and transplant recipients under constant immunosuppression should be avoided due to the risk of immunological effects induced by the interferons.

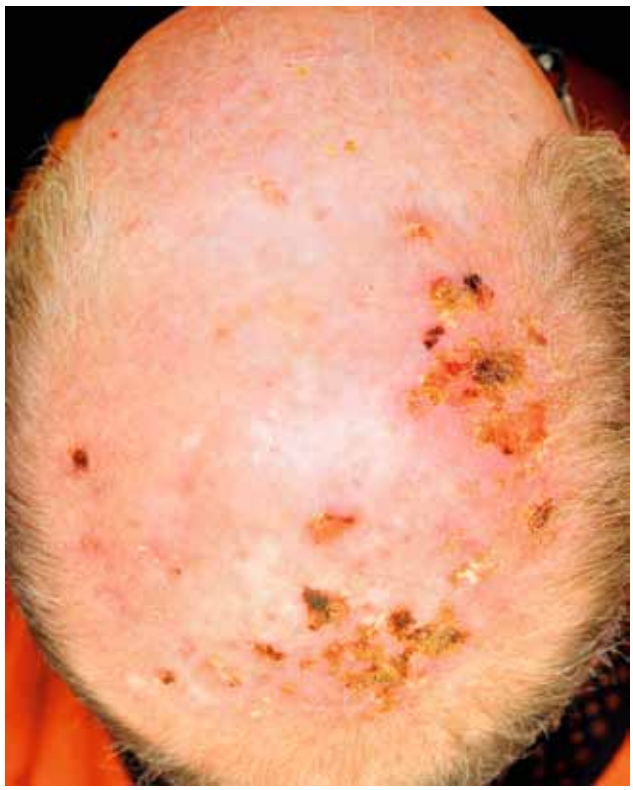

Fig. 7. 72-year old patient. Haemorrhagic-encrusted local reaction restricted in areas with existing AK after application with Imiquimod 5%

Ingenol mebutate

Ingenol mebutate, a tri-terpene isolated from the sap of *Euphorbia peplus*, is registered in Europe since 2013 for the treatment of AK in an area of 25 cm^2. In the face and scalp, a treatment for 3 consecutive days with 0.015% ingenol mebutate gel is recommended, while in the area of the trunk and the extremities the treatment should be performed on 2 consecutive days with a higher gel concentration of 0.05%. Placebo-controlled studies demonstrated response rates (complete clinical remission) of 42.2% in the face and scalp and 34.1% on the trunk, as well as the extremities after 8 weeks. A partial response was reached in 63.9% in the face and scalp and in 49.1% in the trunk and the extremities [47]. Over a follow up period of 12 months, 87% showed a persistent clinical clearance [47, 48]. Side effects like local skin reactions, characterized by erythema, edema, blisters, crusts and pustules appeared 4 days after treatment start. In addition, patients complain about itching, burning and pain. Typically, the side effects subside within 2 weeks. In some rare cases hyperpigmentations can persist over months [47]. Advantage of the treatment with ingenol mebutate is the very short treatment period of 2 or 3 consecutive days with a subsequent, although pronounced, but time-limited inflammatory response. The currently available data relate to a treatment area of 25 cm^2. Due to the time lag of the local reaction, a good education of the patient is required. At the moment, other clinical trials comparing ingenol mebutate with other therapies are in progress. Ingenol mebutate 0,015%, applied 3 weeks following cryosurgery for 3 consecutive days, leads to a higher AK clearance rate than cryosurgery alone after 11 weeks and reduces the appearance of new AK lesions after 12 months [49, 50].

5-Fluorouracil

In a concentration of 5% is 5-fluorouracil (Efudex®) approved since 1968 for NMSC treatment in large areas including AK. A controversial issue is the application interval of 5% fluorouracil. Jury et al. were able to show that an application twice daily for 3 weeks leads to a much better response than a once weekly application for 12 weeks [51]. Remission rates after 4 weeks application were 43% [52]. Currently, a 2—4 week application is recommended. Because of the short duration of the treatment and the associated time-limited side effects, this regimen is usually well tolerated by the patients [51]. However, the sometimes very pronounced side effects (severe crusting and hemorrhage) after treatment of a large area can be a severe limitation. In the 90ies, Plewig and coworkers inaugurated a combination therapy with isotretinoin, which included the daily application of 5-FU in combination with oral isotretinoin 20mg/day for 21 days. The clinical response rates were very good, however often severe erosions and hemorrhagic crusts appeared which required hospitalization of the patients [53].

Photodynamic therapy

For the implementation of field-directed PDT in mild to moderate AK, the two photosensitizers 5-aminolevulinic acid-methyl ester (MAL) Metvix® and 5-ALA nanoemulsion Ameluz® are available. In both cases the 3-hour incubation period is followed by the exposure with red light (630 nm, 37 J/cm^2). For PDT with MAL, response rates of 71—91% are specified, whereas a better overall effect is achieved with thin lesions [34, 54]. Clinical trials of the effectiveness of PDT with the 5-ALA nanoemulsion show response rates of 80—91% 12 weeks after therapy [55]. A long-term follow-up demonstrated a slightly better outcome for patients who have been treated with 5-ALA in comparison to MAL after 12 weeks, the differences were not significant, however [56]. Advantage of PDT is the fact that the treatment — in the sense of an «office-based therapy" — can be carried out in one day under complete observation and, if necessary, can be repeated indefinitely. Due to the field-directed treatment even so far clinically incipient lesions are treated. This leads to a reduction of occurrence of further AK for a period of 6 months in immunocompetent patients [9, 56, 57]. Furthermore, the cosmetic results after PDT are excellent. In comparison with cryotherapy, PDT showed a much better cosmetical outcome 3 months after treatment, which is also reflected by the patient satisfaction [34]. Overall, it appears that PDT in patients with sun damaged skin leads to a smoother skin appearance with less redness, pigmentation spots and teleangiectases [56]. However, in some cases pain during illumination represents a significant problem. Patients with AK lesions on the face and scalp, severe sun damage, Fitzpatrick skin type I, and male gender are more likely to experience pain during illumination. Therefore it may make sense to limit the treatment area to smaller size and to perform PDT sessions stepwise in order to ameliorate pain. Also the use of cooling during illumination or in large areas the application of nerve blocks is advisable [58]. In addition, 1—2 days after treatment appear side effects like redness, swelling, and pustules and crusts in the treated area [56]. A much more gentle procedure is the possibility of the so-called natural daylight-PDT (NDL-PDT) in which patients stay for a time of 2 hours in the sun 30 minutes after application of MAL. First results show similar good response rates for the treatment of mild-to-moderate AK by a favorable adverse event profile in comparison to the classic red light-PDT [59, 60]. Just recently, the Australian Therapeutic Goods Administration (TGA) has registered MAL in combination with daylight for the treatment of AK.

Combination procedures

The application of combination procedures can be useful in cases of refractory AK-lesions. It is also assumed that combination procedures with different mechanism of action lead to a better long-term effects [61]

First and foremost, there is the implementation of a fractional CO_2 laser treatment followed by PDT. The pre-

treatment with a laser or also microneedling results in an increased penetration of ALA or MAL, which then leads to a higher concentration of protoporphyrin IX in the target tissue, and therefore significantly increases the effectiveness of PDT [61, 62]. While in a clinical trial by Togsverd-Bo et al. after a single PDT 67% of the lesions were completely healed, the response rate of the combined procedure increased to 90% [61]. In addition, there are reports of an improved efficacy by a combination treatment of PDT with imiquimod 5% [63] or a combination of 5-fluorouracil and imiquimod cream [64]. Also the combination of a field-directed treatment followed by a lesion-directed treatment of isolated, refractory AK represents a possible option, for example the application of diclofenac sodium gel followed by a treatment of an 5-FU-containing lacquer for remaining hyperkeratotic AK. Even if it would be a matter of a few clinical trials with small numbers, it makes sense to apply combination procedures in profound and refractory cases. Since AK is a chronic disease, treatment is conducted with the objective of a long remission phase. Here the combination procedures also seem to be superior to monotherapies [61—64].

The choice of the therapeutic regime should be according to the clinical findings and the needs of the patient in the first instance. Depending on the occurrence of the AK-lesions, it is advisable to start with a lesion- or field-directed monotherapy. A final assessment should be performed three months after the end of therapy. In case of a complete clinical response regular checks are recommended. If an insufficient healing of the lesions is shown after a treatment-period of three months despite adequate therapy, the treatment should be repeated or replaced by another therapy or be added by a combination procedure. In case of patients with significantly higher risk of transition of AK into SCC, control consultation should be more frequent..

Conclusion

The main cause of actinic keratoses is chronic UV exposure. The application of a consistent UV-protection (textile, sun protection products) is therefore essential. Due to the risk of transition to SCC in about 6—10% of cases, a treatment of AK is recommended. There are numerous lesion- and field-directed therapeutic options for the treatment of AK, the recently approved methods have a high therapeutic effectiveness following evidence-based criteria. The selection of the suitable therapy should be discussed with the patient. Because of the chronicity of the disease, sometimes a change in the course of the regimen can be useful. In refractory cases, or very early recurrences, a combination therapy could be of help. The patient should be informed about the need for a long-term therapy and prophylaxis (light protection). In case of clinically indifferent lesions a biopsy is necessary in order to exclude an already existing SCC.

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Conflict of interest

T. Strunk participated as investigator in clinical studies in the indication area of the companies Almirall, Biofrontera, Galderma and Leo and received fees for consultancy and lectures from Biofrontera and Galderma
L.R. Braathen participated as investigator in clinical trials with Photocure and has received lecture and consultant fees from Galderma.
R.-M. Szeimies participated as investigator in clinical trials in the indication area of the companies Almirall, Biofrontera, Galderma and Leo and received from the above-mentioned companies as well as from MEDA and photonamic lecture and consultants' fees. He is a member of the advisory boards of Almirall, Biofrontera, Galderma, Leo and photonamic. RMS is also involved in the development of an ALA-containing TTS and a LED lamp for the PDT