Using Photodynamic Therapy to Estimate Effectiveness of Innovative Combined Diclofenac and Tazaroten Therapy of Disseminated Actinic Keratosis

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ABSTRACT Early diagnosis and therapy of precancerous lesions and malignant tumors belong to the most challenging tasks in modern medicine. Photodynamic diagnosis can help diagnose both precancerous lesions and early carcinoma. Actinic keratosis (AK) is the most common precancerous lesion of the skin. The available data show a high effectiveness of diclofenac in treating multifocal AK. We report a case of a 52-year-old woman who complained of multiple disseminated AK lesions predominantly on the lower limbs and trunk with a significant exacerbation within the last 6 months. Due to the spreading of disease and a high number of AK foci, as well as technical problems with visiting the hospital (PDT Laboratory), photodynamic therapy was not applied. The patient was treated for 2 months with a combination of local administration of 3% diclofenac and 0.1% tazaroten and 3% diclofenac only as a half side (left-right) comparison. The effects of therapy were later clinically evaluated and verified by means of photodynamic diagnosis (PDD) directly after therapy and at a follow-up examination 3 months later. The evaluation of treatment was blinded.

Treatment with diclofenac only on the right side of the body resulted in clearing of 55% of all treated lesions, which increased to 60% three months after finishing therapy. On the left side of the body, where combined therapy (diclofenac 2 times daily on uneven dates and diclofenac once a day + tazaroten once a day on even dates) was used, 77.5% pathologic lesions disappeared, but this did not increase at follow up.

The treatment of multifocal, disseminated AK is a difficult task and also burdensome for the patient due to side effects like scarring or burning and itching which occur during most therapies. Combined therapy with diclofenac and tazaroten supported by PDD may improve the effects of routine treatment of AK.

KEY WORDS: actinic keratosis, diclofenac, tazaroten, photodynamic diagnosis

INTRODUCTION

Early diagnosis and therapy of precancerous disorders and malignant tumors belongs to the most challenging tasks in the modern medicine. Treatment methods are often comprised of a combination of

biological, chemical, physical, and pharmacological approaches. Photodynamic diagnosis (PDD) can help diagnose both precancerous lesions and early cancer and enables the evaluation of the effectiveness of other previously applied therapeutic methods, e.g. surgery or photodynamic therapy (PDT). The foundation of PDD is the fluorescence of photosensitizing drug which is administered systemically or locally and sensitized with light at 405 nm (1-3). PDT has been used successfully for many years in dermatology and for malignant and non-malignant diseases (4,5). This method received much attention because of its therapeutic and cosmetic effects that made this therapy a treatment of choice in a number of maladies.

Actinic keratosis (AK) is the most common precancerous lesion of the skin and 0.1-15% of develop into a skin squamous cell carcinoma (SCC) (6). AK usually develops in open skin areas: the face, neck, and limbs, and it presents as hyperchromatic (overcolored), yellow-brownish, hyperkeratotic lesions (7). When its keratotic layer is removed, AKs show a bleeding surface. These lesions grow slowly and last for years before malignant transformation can occur.

Long sun exposure related to work, sun-baths, and a bright skin phototype predispose to AK (6).

Cryotherapy, laser therapy, and photodynamic therapy (PDT) as well as local application of cytotoxic preparations (podofilotoxin, fluorouracil) and imiquimod, a local immunomodulator, are common methods of treatment of AK (8-9).

More invasive methods can lead to scarring, so therapy for multifocal AK can also cause cosmetic problems (10,11). Locally acting preparations, e.g. imiquimod, often cause pain and thus the patients discontinue treatment (12,13).

During recent years 3% diclofenac gel (Solaraze®) was introduced to AK therapy in the USA, Canada, and some European countries, with promising results (14). This preparation is a non-steroidal anti-inflammatory drug (NSAID) and inhibits cyclooxygenase-2 (COX-2) thus reducing prostaglandin synthesis which is commonly elevated in AK patients (15,16).

The available data show a high effectiveness of diclofenac in treating multifocal AKs with positive responses at 40 to 85% and with relatively small side effects (17-19).

Retinoids are a group of drugs which was introduced to dermatology in the 1980s and is comprised of retinol (vitamin A derivative) and its analogs. Retinoids are used in medicine because they influence epithelial cell growth and differentiation, and regulate apoptosis through the activation of genes via nuclear receptors, RAR and RXR (20,21). Tazaroten belongs to the new generation of retinoids. It has a specific affinity to RAR receptors, and thus regulates proliferation and differentiation of the cells. Tazaroten inhibits arachidonic acid pathway and reduces inflammatory reactions, and also regulates the keratinization process (22,23). Unlike other retinoids, tazaroten is well tolerated by the skin. In dermatology, it is mainly used in treating psoriasis and acne vulgaris (24,25).

By analyzing the characteristics and effects of diclofenac and tazaroten, authors decided to investigate whether their use will increase the overall effectiveness of the treatment of numerous, disseminated, and eruptive AK in a patient with chronic exposure to sunlight. We report a case of a 52-year-old woman with multiple disseminated AK lesions.

PATIENTS AND METHODS

A 52-year-old woman was admitted to the Photodynamic Therapy Laboratory because of multifocal actinic keratosis (AK) which had occurred predominantly on the lower limbs and trunk during the last 3 years with a significant exacerbation within the last 6 months (Figure 1).

Due to the spreading of disease and high number of AK foci and technical problems with visiting the hospital (PDT Laboratory), PDT was not applied.

The lesions were coarse, grey-yellowish, and oozed when rubbed. For the last 10 years the patient had spent a lot of time working in the sunlight during the summer in southern Europe. She had a bright skin phototype and presented with skin photoaging, i.e. telangiectatic lesions, deep wrinkles, and over coloring of the skin. The patient had not used any protection against UV radiation. She often got severe sunburns; her economic status did not allow her to avoid this type of field work. The patient felt generally

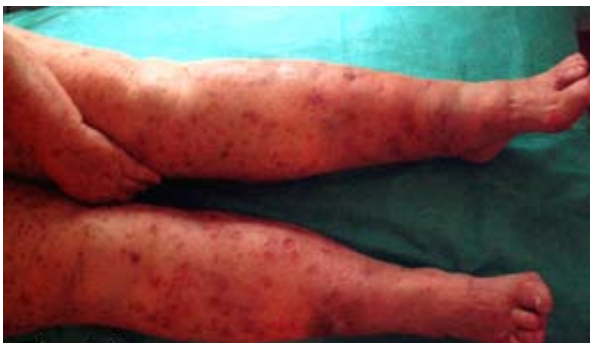

Figure 1. Disseminated actinic keratosis lesions on the lower limbs before therapy.

Table 1. Treatment procedure and effect, PDD examination

		Effect of AK therapy (total response) in % (number of disappeared lesions)		Control PDD	
Number of areas/number of AK per area	**Preparation**	**Complete responses directly after therapy**	**Three months after therapy**	**Directly after therapy**	**After three months**
Right side 10/ 2-4 (altogether 33 lesions)	**Diclofenac only** 2 times daily	55 (18)	60 (20)	Single red fluorescence in 3 areas	Small foci of red fluorescence in 3 areas
Left side 10/ 2-4 (altogether 27 lesions)	Diclofenac and tazaroten (**combined therapy**): diclofenac only 2 times per day on uneven dates and diclofenac with *Tazaroten* on even dates, diclofenac once a day, in the morning) and tazaroten (once a day, in the evening)	77.5 (21)	77.5 (21)	Lack of red fluorescence	Lack of red fluorescence

healthy, however, and had been drinking tea with St. John's wort every day, which reportedly helped her digestion.

The therapy was performed as a half side (left-right) treatment. Ten areas of the skin, each 5 cm^2 large with 2-4 AK lesions, were arbitrarily chosen on each side of the body. The areas contained altogether 27 lesions on the left and 33 lesions on the right. The lesions on the right side were treated using 3% diclofenac gel at 0.5 g per area, two times daily. On the left side, in addition to diclofenac once per day, 0.1% tazaroten cream was applied in the evening every other day (Table 1). The schedule of therapy was as follows: diclofenac two times daily on uneven dates, and on even dates diclofenac in the morning and tazaroten in the evening, for 60 days. Due to a difficult personal economic situation the patient had to stop treatment after 2 months since she was doing seasonal work outside the country.

A clinical control examination was carried out directly after the start of the treatment, and then 3 months later. The professional who evaluated the effect of treatment was not informed how the drugs were administered. The effectiveness of the treatment was evaluated in two ways:

A) Clinically, with relation to the total responses (complete disappearing of AK foci in treated skin areas) directly after treatment and three months after.

B) Using photodynamic detection (PDD), which verifies clinical evaluation. A control PDD examination was also carried out directly after finishing treatment and three months after.

Levulan® Kerastick® (DUSA Pharmaceuticals) was used in this study. The AK lesions were treated with the cream under occlusion, and irradiated 1.5 hours later with a blue light (405 nm) from a halogen light source (Penta Lamps, Teclas). Red fluorescence was observed in pathological lesions.

RESULTS

In the course of treatment with 3% diclofenac the main reported symptoms were itching, dry skin, and erythema. Symptoms in areas subjected to treatment with 0.1% tazaroten were dryness, burning, and erythema which increased during the first two weeks and then disappeared. The results of monotherapy and combined therapy are shown in Table 1. We observed no increase in hyperpigmentation after treatment.

Figure 2 shows lesions on the right side of the body before treatment, during a photodynamic diagnosis session. The effectiveness of the treatment using only diclofenac on the right side of the body amounted to 55% (i.e. 55% of complete responses to the therapy). After 30 days from the end of treatment, the number of cured lesions increased to 60%. Control examination using PDD three months after treatment revealed a single red fluorescing foci in 3 areas which were treated with diclofenac only (Figure 3).

On the left side of the body where combined

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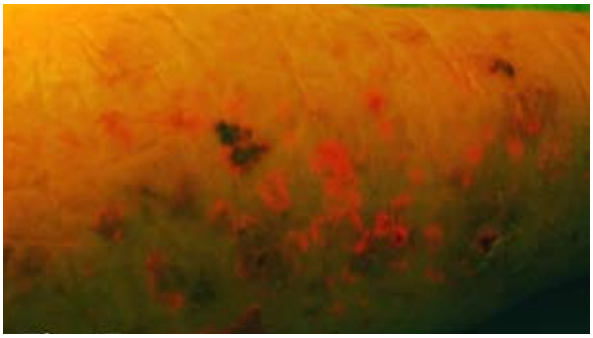

Figure 2. Photodynamic diagnostics of actinic keratosis lesions before therapy (intense red fluorescence).

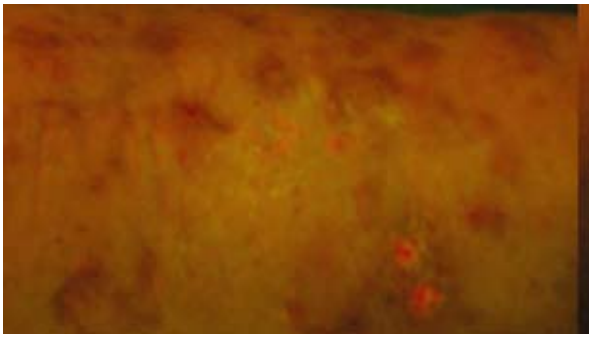

Figure 3. Photodynamic diagnostics three months after therapy with diclofenac only revealed a single red fluorescing foci in 3 areas.

therapy (diclofenac 2 times daily on uneven dates and diclofenac once a day + tazaroten once a day on even dates) was used, 77.5% of pathological lesions disappeared (i.e. 77.5% complete responses to the therapy). Some lesions disappeared rapidly within 6 weeks, though the application of diclofenac and tazaroten continued until the end of scheduled treatment protocol, i.e. for 60 days. Results of PDD after 3 months are shown in Figure 4 no red fluorescence was observed. There was no further reduction in the pathological AK foci during the next 3 months after therapy, and thus the rate of complete responses was still 77.5%. PDD did not reveal new pathological lesions in areas treated with combined therapy.

DISCUSSION

Actinic keratosis is one of the most frequent precancerous lesions in humans, and is attributed to prolonged exposure to UV radiation. It mainly affects older people, and the lesions occur progressively over many years. Actinic keratosis occurs predominantly in areas of the skin that are exposed to the sunlight.

In our case the AK foci also occurred in areas protected by clothes, i.e. on the trunk and lower limbs. A dynamic dissemination of lesions was observed over a very short period of time, i.e. in 6 months. The AK localized in areas such as the trunk and limbs is predisposed to squamous cell carcinoma. The reason why these lesions grow so fast is not known. There are reports in which the eruptive type (form) of AK was described, e.g. after heart transplantation or in patients with Kindler syndrome, a genodermatosis with hypersensitivity to the light (26-28). In multifocal AK the application of immunomodulator, imiquimod (Aldara®) is highly recommended (29-31). The contraindication to imiquimod is an impairment of immunological mechanisms (32,33). For the same reason (rapid eruption of lesions suggests immunodeficiency) the authors rejected the application of the cytostatic 5-fluorouracil.

In this study we used monotherapy with 3% diclofenac and a combined therapy using the above preparation and tazaroten. Diclofenac gel, which was approved for treating multifocal AK is a safe and well tolerated preparation. The patient bore this therapy well and the local undesired symptoms, such as burning and redness of the skin that usually occur during the therapy using diclofenac, were transient. The reported effectiveness of the treatment of AK with Diclofenac uneven – it varies from reducing the size to complete disappearance of lesions. Rivers et al. reported a very high efficacy of AK treatment with 5% Imiquimod cream. Fifty percent of patients experienced complete clearance of AK lesions, and 75% of patients experienced partial clearance of AK lesions after imiquimod treatment (34). Fariba et al. reported a complete eradication of lesions in only 9.3% and reduction in 65% of cases after using 3% diclofenac in

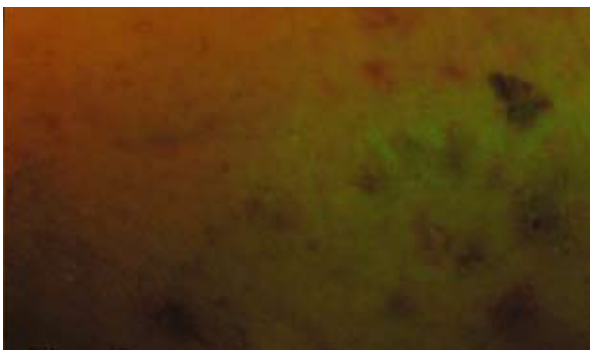

Figure 4. Photodynamic diagnostics three months after therapy with diclofenac and tazaroten showed no red fluorescence.

2.5% hyaluronan gel (35). Nelson et al. reported high effectiveness of treatment for AK in 78% of patients (36). Berlin and Rigel combined application of diclofenac with cryotherapy and found that this modification increased the effects from 21% to 46% (37).

The combination of diclofenac with tazaroten in our study increased successful treatment of the lesions to 77.5% in comparison with the 60% from monotherapy. The control PDD examination 3 months after therapy confirmed stable therapeutic effects for the combined method (see Table 1). Monotherapy using diclofenac gel did not prevent recurrent lesions that fluoresced in 3 treated areas 3 months after therapy.

The treatment of multifocal, disseminated AK is a difficult task and also burdensome for patients because of side effects that include burning and itching. Frequently, the patients discontinue pharmacological treatment because of the above symptoms. The eradication of more intense lesions using more aggressive methods can cause scarring and over coloring of the skin, which is often unacceptable to patients. Therefore, it is necessary to search for new effective therapeutic methods. The combination of two preparations – an anti-inflammatory drug, diclofenac, and tazaroten that regulates growth and differentiation of cells – resulted in promising therapeutic effects. Increasing side effects which were caused by tazaroten, i.e. burning pain and skin dryness, disappeared within 2 weeks. Due to the above complications tazaroten was applied once a day in the evening every second day. The promising effects of the therapy in this patient encourage application of this combined treatment for multifocal AK especially when imiquimod and 5-fluorouracil are used, because the impairment of the immune system must be excluded. Photodynamic therapy was planned as a continuation of the treatment, which did not take place due to the patient's trip abroad. After half a year, we received information from the family that the patient was operated for a tumor of the gastrointestinal tract, and contact with the patient was lost.

With this report we would like to emphasize the effectiveness of PDD in dermatooncologic diagnostics. Sieroń et al stressed the significance of PDD and PDT in treating tumors (38). Other reports supported those findings, especially in relation to evaluation of tumor margins, effects of therapy and follow-ups (39-41). PDD, in contrast with histological examination, is an optical method and thus this does not require tissue biopsies. Clinical applications of PDD in diagnosis are still uncommon. Our intention was to draw the attention of practitioners to the usefulness of PDD in evaluating the effects of treatment and long-term observations in patients with skin disorders treated with different methods.

CONCLUSION

This case suggests that further clinical studies on the effectiveness of local combined therapy in treating multifocal AK are needed.

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