Photodiagnosis and Photodynamic Therapy 27 (2019) 198–202

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

PDT with PPIX absorption peaks adjusted wavelengths: Safety and efficacy of a new irradiation procedure for actinic keratoses on the head

C. von Dobbeler[a,b,1,*], L. Schmitz[c,1], K. Dicke[a,b], R.M. Szeimies[d], T. Dirschka[a,b]

[a] CentroDerm Clinic, Heinz-Fangman-Straße 57, Wuppertal, Germany
[b] Faculty of Health, University Witten-Herdecke, Alfred-Herrhausen-Straße 50, Witten, Germany
[c] Ruhr University Bochum, Faculty of Medicine, Department of Dermatology, Germany
[d] Clinic for Dermatology and Allergology, Klinikum Vest, Recklinghausen, Germany

ARTICLE INFO

Keywords:
Actinic keratosis
AKASI
ALA
NMSC
Photodynamic therapy
PPIX adjusted PDT
Daylight photodynamic therapy

ABSTRACT

Background: Daylight photodynamic therapy (dl-PDT) is an effective and almost painless treatment for patients with actinic keratoses (AKs) but carries important limitations due to seasonal conditions. PDT with Protoporphyrin IX (PPIX) peaks adjusted wavelengths might overcome these shortcomings. The aim of this study was to determine safety and efficacy of ALA-PDT with a new irradiation procedure.

Methods: Patients with AKs on the head received ALA-PDT with a new irradiation device. Emitted wavelengths are adjusted to PPIX absorption peaks (457 nm, 523 nm, 593 nm, 631 nm; 20.000 lx). PDT protocol was adapted for both 1 h of incubation and irradiation time. Outcome was assessed by AK area and severity index (AKASI) and lesion count (LC) prior to and 3 months after treatment. Safety was monitored by blood pressure and pulse measurements throughout treatment. Pain was determined by use of a visual analog scale (VAS).

Results: Overall, 39 patients were included and showed a significant AKASI reduction ($P < 0.0001$) 3 months after PDT (mean AKASI of 2 ± 1.6) compared to baseline (5.2 ± 1.9). Mean reduction rate was 63.7% ± 24.2%, accordingly. Eight patients (20.5%) achieved AKASI 100, eleven (28.2%) AKASI 75 and thirty (76.9%) AKASI 50, respectively. There were no significant changes in blood pressure and pulse throughout treatment. Median VAS for pain during irradiation was 0 (0–1), 1 (0–1) and 0 (0–1) at the beginning, in the meantime and at the end, respectively.

Conclusions: ALA-PDT with a new irradiation procedure is a safe, effective and almost painless treatment option for patients with AKs on the head.

1. Introduction

Actinic keratoses (AKs) are early *in situ* squamous cell carcinoma (SCC) of the skin and are frequently encountered in dermatological practice. [1–4] Every AK lesion bears the potential to progress into an invasive tumor with subsequent risk of metastasis [5]. Therefore, a consequent treatment of cancerized fields is currently the most promising approach to prevent progression [6].

Photodynamic therapy (PDT) is a well-established and effective treatment option for AKs. [7–14] PDT shows high treatment efficacy with AK lesion clearance rates up to 90% [9,8–14]. Mainly, there are two established approaches to perform PDT. Conventional PDT (c-PDT) utilizes artificial light sources to activate protoporphyrin IX (PPIX) after 3 h of incubation. Red light is most commonly used and covers the 630 nm activation peak of PPIX. [15] The main limitations of c-PDT are intense pain and burning sensation in the treatment area during and after illumination. This is most probably based on the long incubation time of 3 h within c-PDT protocol which allows PPIX to diffuse into the surrounding tissue. When being activated, it causes irritation of cutaneous nerves leading to these intense pain sensations [16].

In contrast, daylight PDT (dl-PDT) uses natural daylight as light source and follows a different protocol. The incubation takes maximum 30 min and patients are then exposed to natural daylight for 2 h. This procedure leads to a continuous synthesis and activation of PPIX, which then does not spread to peripheral structures. [15–18] Hence, dl-PDT proved to be significantly less painful while showing a treatment outcome non-inferior to c-PDT [19–21]. Moreover, all PPIX peaks are addressed by natural daylight compared to an activation of the 630 nm absorption peak only by red light when performing c-PDT. However, main limitations of dl-PDT are UV-radiation exposure during

* Corresponding author at: CentroDerm Clinic, Heinz-Fangman-Straße 57, D-42287, Wuppertal, Germany.
E-mail address: c.vondobbeler@centroderm.de (C. von Dobbeler).
[1] Both authors contributed equally.

https://doi.org/10.1016/j.pdpdt.2019.05.015
Received 24 February 2019; Received in revised form 7 May 2019; Accepted 13 May 2019
Available online 07 June 2019
1572-1000/ © 2019 Elsevier B.V. All rights reserved.

irradiation, hence requirement for application of a chemical sunscreen and dependency on outside weather conditions. Besides, the light dose has to be at least 8 J/cm^2 and mean outside temperatures must be above 10 °C to guarantee treatment efficacy. [22–25] Another limitation of this approach is that patient´s adherence is hard to control. To overcome the aforementioned limitations, the use of a greenhouse has already been described as an alternative to enhance performance of dl-PDT. However, the light intensity during wintertime remains a major set-back of this approach [26].

In order to combine the advantages of c-PDT and dl-PDT an adapted protocol and an artificial light source emitting wavelengths adapted to PPIX absorption peaks could be useful. Different studies have already shown comparable results and painless application of artificial light sources using the established dl-PDT protocol. [27,28]

Apart from high treatment efficacy and painless application, the 2 h irradiation time within the dl-DPT protocol still poses a discomfort for the patients. Therefore, a shorter irradiation time would be useful especially because the patient population undergoing PDT is of advanced age. In order to combine as much advantages of both dl-PDT and c-PDT a modified irradiation procedure (m-PDT) was designed. The aim of this study is to evaluate the safety and treatment efficacy of the new m-PDT procedure in patients with AKs on the head.

2. Material & methods

2.1. Study population

This prospective, single-armed, non-randomized, monocentric study was conducted at the Centroderm clinic in Wuppertal, Germany. The study was designed according to the Declaration of Helsinki and was approved by the ethics committee of the University of Witten/Herdecke (No. 160/2017). Only patients with a diagnosis of AK on the scalp or/and the face were included in the study. Immunocompromised patients and patients with inflammatory skin diseases in the treatment area were excluded from the study. Informed consent was obtained from all patients.

2.2. Data assessment

Baseline characteristics and demographic data of the patients were documented. Severity of AK was assessed by lesion count (LC) and calculation of Actinic Keratosis Area and Severity Index (AKASI). AKASI is an established tool for a field-directed assessment of AK severity on the head [30,31]. LC and AKASI were evaluated prior to treatment (V0) and three months (V1) after PDT. Pain was assessed by a 11-point visual analog scale (VAS, 0 = no pain, 10 = worst imaginable pain) and vital parameters (blood pressure and pulse) were documented at the beginning, meanwhile and at the end of treatment. Local skin reactions (LSR) were documented 2–5 days after treatment according to common terminology criteria for adverse events (CTCAE V4.03). Patients were asked to report any adverse event during treatment or follow-up visits.

2.3. Photodynamic therapy - procedure

Pretreatment of AK lesions was done by degreasing of the skin with Octenidin dihydrochloride (Octenisept®, Schülke & Mayr GmbH, Norderstedt, Germany) and gentle curettage to remove hyperkeratotic scales or crusts. A nanoemulsion of 5-ALA (Ameluz® 78 mg/g, Biofrontera, Leverkusen, Germany) was used as photosensitizer. The nanoemulsion was applied to the treatment area and incubated for 1 h under light-tight occlusive dressing (plastic dressing foil [Tegaderm™, 3 M Medica, Neuss, Germany] and aluminium foil) to avoid photobleaching. After incubation, the coverage was removed and residuals of the nanoemulsion were wiped off. Patients were then seated in the irradiation booth and a fluorescence diagnostic with an integrated wood light source (400 nm) was carried out to visualize PPIX accumulation prior to illumination. Afterwards, patients were irradiated for 1 h with 20 J/cm^2.

Fig. 1. The medisun® daylight 9000 booth (Schulze & Böhm GmbH, Brühl, Germany; CE0197). The LED spotlights emit wavelengths adjusted to the PPIX absorption peaks (457 nm, 523 nm, 593 nm and 631 nm). The average irradiance is 5.6 mW/cm^2 and illuminance 20.000 lx for every part of the skin surface on the head during irradiation.

2.4. Photodynamic therapy – light source

The medisun® daylight 9000 booth (Schulze & Böhm GmbH, Brühl, Germany; CE0197; Fig.1) was used as light source. The device meets the German provisions of a class 2a medical device and contains a three-dimensional exposure field around the head consisting of 8 high-performance LED spotlights with 120 W each. The three-dimensional exposure field enables even distribution of light radiation on the complete head throughout the treatment. The LED spotlights emit wavelengths of the daylight spectrum. In this study, wavelengths between 410–700 nm were used with peaks at 457 nm, 523 nm, 593 nm and 631 nm. Thus, almost all PPIX absorption peaks were addressed without UV-radiation exposure (Fig.2). During irradiation, the average irradiance was 5.6 mW/cm^2 and the illuminance 20.000 lx for every part of the skin surface on the head.

2.5. Statistical analysis

Statistical analysis was performed using the statistical package MedCalc software version 18.11 (Ostend, Belgium). Data distribution was assessed using the Kolmogorov-Smirnov test. In case of normal distribution data was expressed as mean and standard deviation (SD); if there was no normal distribution, data was expressed as median and

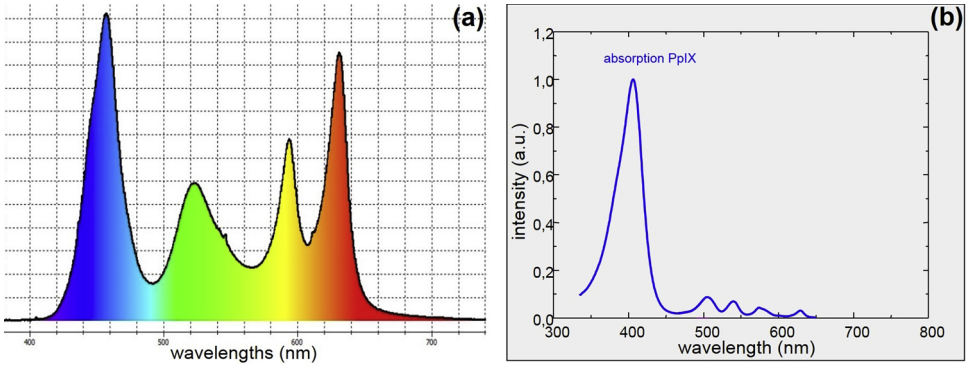

Fig. 2. Wavelength spectrum emitted during m-PDT (a) and absorption spectrum of photosensitizer PPIX (b, reproduced with permission from RM Szeimies). [29] The wavelength spectrum covers 410–700 nm and is adjusted at PPIX absorption peaks without UV radiation exposure. Wavelengths are presented in nm.

interquartile range. For statistical analysis of data Wilcoxon test and *t*-test were used for paired samples and the *t*-test and Mann-Whitney U test for unpaired samples. P-values < 0.05 were considered to be statistically significant.

3. Results

In total, 39 patients completed the study. Most patients were male (92.3%), the mean age was 73 (± 7.7) years. The majority of patients presented a Fitzpatrick skin type II (89.7%). Twenty-nine patients (74.4%) received at least one AK treatment prior to this study. Mean follow-up period was 93 (± 9.3) days. Further patient´s characteristics are shown in Table 1.

Mean LC showed a significant reduction rate of 80.4% (± 16.4%) based on 15.8 (± 8.2) AKs at V0 and 3.4 (± 3.7) AKs at V1 (P < 0.0001). Mean AKASI at V0 was 5.2 (± 1.9) compared to a mean AKASI of 2 (± 1.6) at V1, showing a significant reduction rate of 63.7% (± 24.2%, P < 0.0001, Fig. 3).

In total, all patients showed a significant reduction of AKASI and LC at V1 compared to V0. Eight patients (20.5%) showed an AKASI 100 (complete clearance), 11 (28.2%) an AKASI 75 and 30 (76.9%) an AKASI 50, respectively. Subgroup analysis comparing treatment naïve patients and patients with at least one past treatment for AK revealed no significant differences in AKASI reduction rate (60% vs. 61.1%, P = 0.48).

Median VAS for pain during irradiation was 0 (0–1) after 5 min, 1 (0–1) after 30 min and 0 (0–1) after 1 h, respectively. There were no significant changes in blood pressure and pulse throughout the treatment. LSR (erythema, scaling, crusts, sterile pustules) after m-PDT were within the range of well-known skin reactions following c-PDT or dl-PDT (Fig. 4). Treatment related adverse events (up to 5 days after PDT) were seen in 20.5% of patients, in which headache and burning sensation in the treatment area were the most common. All adverse events were classified as CTCAE Grade 1.

Investigator´s and patient´s satisfaction with treatment outcome did not differ significantly and were 2 (1.5–2) and 2 (1–2.75) respectively (P = 0.11) when applying a scale from 1 to 6 (1 = very good, 6 = very bad). On the other hand, Investigator´s and patient´s satisfaction with cosmetic outcome differed significantly (2 [1,2] and 2 [1,2], P = 0.0078).

Table 1
Demographic and clinical characteristics (n = 39).

Characteristic	n	(%)
Sex		
Male	36	(92.3)
Female	3	(7.7)
Age, years	73	(7.7)*
Skin Type Fitzpatrick		
I	4	(10.3)
II	35	(89.7)
III-VI	0	(0)
UV exposure (increased)	34	(87.2)
leisure activities	32	(82.1)#
occupational	2	(7.7)#
History		
mean time since first diagnosis of AK, years	6.3	(6.1)*
treatment naïve patients	10	(25.6)
history of at least > 1 AK treatment	29	(74.4)
ablative intervention (e.g. laser, curettage)	20	(51.3)#
photodynamic therapy	25	(64.1)
topical agents (e.g. DFS, 5-FU/SA)	8	(20.5)
skin cancer (invasive)	15	(38.5)
Follow-up, days	93	(9.3)*

AK: actinic keratosis;
DFS: 3% diclofenac sodium in 2.5% hyaluronic gel;
5-FU/SA: 0.5% 5-Fluorouracil in 10% salicylic acid;
* Data are expressed as mean (standard deviation).
# % referring to overall study population.

4. Discussion

This is the first study evaluating the safety and efficacy of PDT conducted with an adapted protocol using a new irradiation device. Modification of the conventional dl-PDT protocol aimed to combine the advantages of c-PDT and dl-PDT, e.g. high treatment efficacy, painless application, short irradiation time and independence from outside seasonal conditions, and avoid disadvantages of each procedure.

While showing high treatment efficacy, c-PDT leads to intense pain and burning sensation due to long incubation time of 3 h. [9–14,16] When performing dl-PDT, patients are incubated for up to 30 min and then exposed to natural daylight for 2 h. This leads to a continuous accumulation and activation of PPIX with almost painless application of PDT [16,17]. In this protocol incubation time was 1 h to achieve a higher loading dose of PPIX compared to conventional dl-PDT protocol. Since topical application of 5-ALA leads to rapid accumulation of PPIX in skin tumors, it was assumed that 1 h of incubation provides a sufficient loading dose of PPIX to effectively perform PDT [32,33]. Afterwards, patients were irradiated for 1 h with 20 J/cm^2. Thus, m-PDT protocol combines features of c-PDT and dl-PDT.

dl-PDT is an effective, well tolerated and almost painless treatment option for patients with AKs on the face and scalp. [19] However, performance of dl-PDT is limited by weather conditions, geographical location, time of year as well as patient´s adherence to the protocol (e.g. interruptions, deficient light exposure) [22–25]. Also, repetitive use of dl-PDT is sometimes required and the next treatment must possibly be postponed 3–6 months due to seasonal conditions leaving the patient at risk to develop an invasive SCC in the meantime. Artificial light sources imitating daylight might overcome the shortcomings of dl-PDT. Different studies have already shown comparable results with artificial

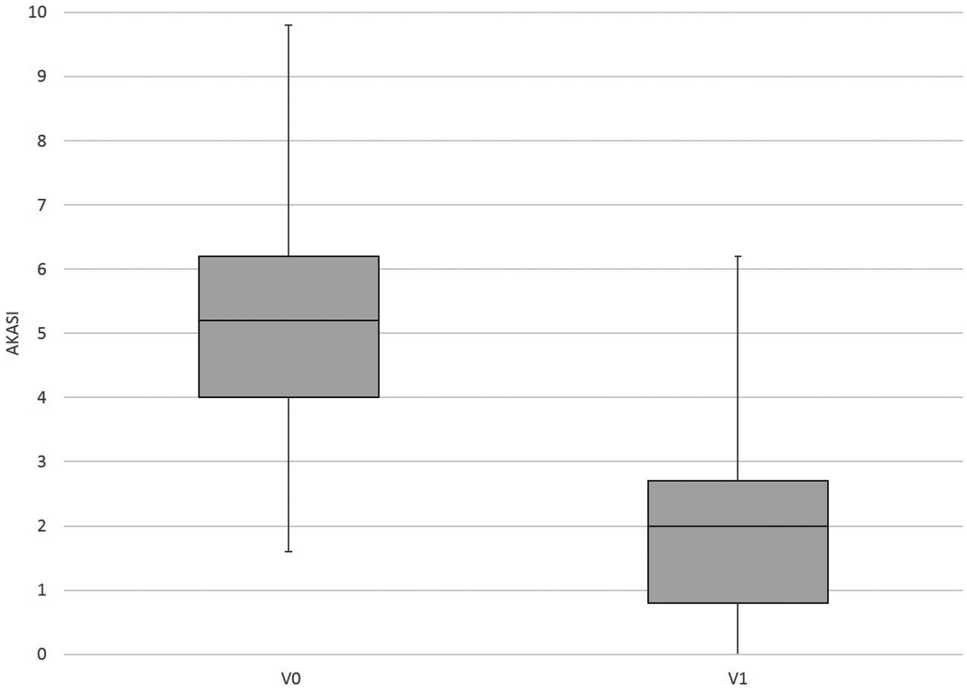

Fig. 3. Box-and-Whisker Plot showing differences in AKASI prior to and 3 months after treatment. *t*-test showed significant differences ($P < 0.0001$) between AKASI at baseline and at the follow-up visit. Mean AKASI at baseline was 5.2 (± 1.9) and 2 (± 1.6) 3 months after treatment, showing a significant reduction rate of 63.7% (± 24.2%).

light sources when applying the established dl-PDT protocol [27,28].

Kellner et al. reported their experience with a simulated daylight system. The IndoorLux® system (Swiss Red AG, Murten, Switzerland) consists of paired illumination sources that are installed at the treatment room´s ceiling. Irradiation covers the spectral areas of the green and red daylight spectrum (570–590 nm and 620–640 nm) over a time period of 2 h. Thirty-two patients with mild-to-moderate AK received 2 sessions of ALA-PDT within 1 week and efficacy was evaluated 3 months after treatment. Mean lesion count at baseline was very low compared to our study (5.9 [± 1.8] vs. 15.8 [± 8.2]). Patient complete clearance rate (PCCR) was 75% and can be compared to 20.5% of our patients achieving AKASI100. However, PCCR only evaluates AK lesions in a predefined treatment area and not on the whole head [30]. Hence achieving AKASI 100 is more difficult than clearing all AK lesions in a circumscribed treatment field. Lower AK complete clearance rates in our study may also be explained by the markedly higher mean lesion count at baseline as well as the fact that PDT was performed twice when using the simulated daylight system. Also, even Olsen grade III lesions were included in our study. Pain during irradiation was assessed by 11-point VAS in both studies and showed comparable results proving both irradiation devices to be almost painless [27].

Compared to the simulated daylight system irradiating patients with light sources installed at the ceiling, the medisun® daylight 9000 booth builds up a three-dimensional exposure field around the head that enables more homogenous irradiation of the whole head. Besides, the wavelength spectrum is adjusted to the PPIX peaks, which might offer better activation of PPIX and therefore more effective PDT. Moreover, the irradiation time of only 1 h could prove useful especially for the elderly population undergoing PDT.

AKASI provides an easy-to-use tool to assess AK severity on the head and face [30,31]. Thus far, literature concerning AKASI is scarce making it hard to compare our results to published literature. Schmitz et al. investigated 33 patients who underwent c-PDT on the head and scalp. Median AKASI at baseline was 3.8, corresponding to a mild-to-moderate AK severity. AKASI showed a reduction rate of 73.7% 3 months after treatment. In contrast, mean AKASI at baseline was higher in our patients (5.2 [± 1.9]), while AKASI reduction rate after 3 months was comparable in both populations (63.7% vs. 73.7%). More patients achieved AKASI 100 (42.4% vs 20.5%) and AKASI 75 (48.5% vs 28.2%) in the analysis by Schmitz et al., while AKASI 50 was slightly

Fig. 4. Shown are photographs of a patient ahead of treatment (a), 3 days after m-PDT (b) and 3 months after m-PDT (c). In this case, the forehead, cheeks and nose were treated. The patient presented with an AKASI of 4.2 at baseline and achieved AKASI 100 three months later.

higher in our study (72.7% vs 76.9%) [31]. Lower AKASI reduction rates as well as less patients achieving AKASI 100 and AKASI 75 may be explained by higher mean AKASI at baseline in our study making it harder to achieve complete clearance of AK.

A main limitation of this study is the relatively small sample size. Moreover, patients were recruited from one center only. Besides, this is the first study evaluating treatment efficacy of an adapted PDT protocol making it hard to compare our results to published literature. Further studies with more patients included need to be conducted to further evaluate this new irradiation procedure. Also, more effective treatment outcome might be enhanced by application of fractional CO_2-Laser ahead of treatment.

In conclusion, PDT with this new irradiation procedure is a safe, effective and almost painless treatment option for patients with AKs on the head. The irradiation device offers an office-based and controlled set-up to perform PDT all year round.

Founding source

Schulze & Böhm GmbH, Biofrontera AG.

Acknowledgments

This work was supported by Schulze & Böhm GmbH (D-50321, Brühl, Germany) and Biofrontera AG (D-51377, Leverkusen, Germany). Schulze & Böhm GmbH provided the medisun® daylight 9000 booth, Biofrontera AG provided 40 samples of Ameluz® gel. Both sponsors did not participate in conducting this study and analyzing the data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2019.05.015.

References

[1] A.B. Ackerman, J.M. Mones, Solar (actinic) keratosis is squamous cell carcinoma, Br. J. Dermatol. 155 (2006) 9–22.
[2] M.R. Heaphy Jr., A.B. Ackerman, The nature of solar keratosis: a critical review in historical perspective, J. Am. Acad. Dermatol. 43 (2000) 138–150.
[3] P. Chetty, F. Choi, T. Mitchell, Primary care review of actinic keratosis and its therapeutic options: a global perspective, Dermatol. Ther. (Heidelb) 5 (2015) 19–35.
[4] T. Rosen, M.G. Lebwohl, Prevalence and awareness of actinic keratosis: barriers and opportunities, J. Am. Acad. Dermatol. 68 (2013) S2–S9.
[5] R.G. Glogau, The risk of progression to invasive disease, J. Am. Acad. Dermatol. 42 (2000) 23–24.
[6] R.N. Werner, E. Stockfleth, S.M. Connolly, et al., Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis – international league of dermatological societies in cooperation with the European dermatology forum – short version, J. Eur. Acad. Dermatol. Venerol. 29 (2015) 2069–2079.
[7] A.K. Gupta, M. Paquet, Network meta-analysis of the outcome' participant complete clearance' in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review, Br. J. Dermatol. 169 (2013) 250–259.
[8] S. Vegter, K. Tolley, A network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe, PLoS One 9 (2014) e96829.
[9] M. Freeman, C. Vinciullo, D. Francis, et al., A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study, J. Dermatolog. Treat. 14 (2003) 99–106.
[10] A. Hauschild, E. Stockfleth, G. Popp, et al., Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies, Br. J. Dermatol. 160 (2009) 1066–1074.
[11] D. Pariser, R. Loss, M. Jarratt, et al., Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study, J. Am. Acad. Dermatol. 59 (2008) 569–576.
[12] D.M. Pariser, N.J. Lowe, D.M. Stewart, et al., Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial, J. Am. Acad. Dermatol. 48 (2003) 227–232.
[13] R.M. Szeimies, L. Torezan, A. Niwa, et al., Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy, Br. J. Dermatol. 167 (2012) 150–159.
[14] M. Tarstedt, I. Rosdahl, B. Berne, et al., A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp, Acta Derm. Venereol. 85 (2005) 424–428.
[15] C.A. Morton, R.M. Szeimies, A. Sidoroff, L.R. Braathen, European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma, J. Eur. Acad. Dermatol. Venereol. 27 (2013) 536–544.
[16] R.M. Szeimies, Pain perception during photodynamic therapy: why is daylight PDT with methyl aminolevulinate almost pain-free? A review on the underlying mechanisms, clinical reflections and resulting opportunities, G. Ital. Dermatol. Venerol. 153 (2018) 793–799.
[17] W.G. Philipp-Dormston, S. Karrer, H. Petering, et al., Daylight PDT with MAL – current data and practical recommendations of an expert panel, J. Dermatol. Ges. 13 (2015) 1240–1249.
[18] T. Dirschka, P. Radny, R. Dominicus, et al., Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolaevulinate for the treatment of actinic keratosis, Br. J. Dermatol. 168 (2013) 825–836.
[19] J.P. Lacour, C. Ulrich, Y. Gilaberte, et al., Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe, J. Eur. Acad. Dermatol. Venereol. 29 (2015) 2342–2348.
[20] D.M. Rubel, L. Spelman, D.F. Murrell, et al., Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial, Br. J. Dermatol. 171 (2014) 1164–1171.
[21] S.R. Wiegell, S. Fabricius, M. Gniadecka, et al., Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study, Br. J. Dermatol. 166 (2012) 1327–1332.
[22] S.R. Wiegell, S. Fabricius, J. Heydenreich, et al., Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographical locations, Br. J. Dermatol. 168 (2013) 186–191.
[23] S.R. Wiegell, M. Haedersdal, P. Eriksen, et al., Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial, Br. J. Dermatol. 160 (2009) 1308–1314.
[24] S.R. Wiegell, M. Haedersdal, P.A. Philipsen, et al., Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study, Br. J. Dermatol. 158 (2008) 740–746.
[25] C.A. Morton, H.C. Wulf, R.M. Szeimies, et al., Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus, J. Eur. Acad. Dermatol. Venereol. 29 (2015) 1718–1723.
[26] C.M. Lerche, I.M. Heerfordt, M. Heydenreich, H.C. Wulf, Alternatives to outdoor daylight illumination for photodynamic therapy—use of greenhouses and artificial light sources, Int. J. Mol. Sci. 17 (2016) 309.
[27] C. Kellner, S. Bauriedl, S. Hollstein, U. Reinhold, Simulated-daylight photodynamic therapy with BF-200 aminolaevulinic acid for actinic keratosis: assessment of the efficacy and tolerability in a retrospective study, Br. J. Dermatol. 172 (2015) 1146–1148.
[28] S.M. O´Gorman, J. Clowry, M. Manley, et al., Artificial white light vs daylight photodynamic therapy for actinic keratoses: a randomized clinical trial, JAMA Dermatol. 152 (2016) 638–644.
[29] R.M. Szeimies, S. Karrer, C. Abels, et al., Photodynamic therapy indermatology, in: J. Krutmann, H. Hönigsmann, C.A. Elmets, P.R. Bergstresser (Eds.), Dermatological Phototherapy and Photodiagnostic Methods, Springer-Verlag, Berlin Heidelberg New York, 2001, p. p212.
[30] T. Dirschka, G. Pellacani, G. Micali, et al., A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index, J. Eur. Acad. Dermatol. Venereol. 31 (2017) 1295–1302.
[31] L. Schmitz, C. von Dobbeler, G. Gupta, et al., Photodynamic therapy leads to significant improvement of actinic keratosis area and severity index (AKASI), Photodiagnosis Photodyn. Ther. 21 (2018) 66–70.
[32] C. Fritsch, P. Lehmann, W. Stahl, et al., Optimum porphyrin accumulation in epithelial skin tumours and psoriatic lesions after topical application of delta-aminolaevulinic acid, Br. J. Cancer 79 (1999) 1603–1608.
[33] C.B. Warren, S. Lohser, L.C. Wene, et al., Noninvasive fluorescence monitoring of protoporphyrin IX production and clinical outcomes in actinic keratoses following short-contact application of 5-aminolevulinate, J. Biomed. Opt. 15 (2010) 051607.