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Daylight photodynamic therapy for severe facial and scalp actinic keratosis: a prospective non-sponsored single-centre study employing the actinic keratosis area and severity index (AKASI)

Background: Daylight photodynamic therapy (DL-PDT) is an effective and convenient treatment for multiple actinic keratosis (AKs). There are limited tools to evaluate the outcome of AK treatment. Recently, the actinic keratosis area and severity index (AKASI) has been proposed as a quantitative tool for assessing AK severity. *Objectives:* To investigate patient satisfaction and efficacy of DL-PDT for severe AKs and to validate AKASI scoring as a quantitative tool for assessing the outcome of DL-PDT treatment. *Materials & methods:* In this prospective single-centre study, we analysed the results of patients treated with one or two cycles of DL-PDT for severe AKs in the facial or scalp area. *Results:* Forty patients (37 male and three female) with a mean age of 74 years (range: 56-87 years) were included and received either one ($n = 20$) or two ($n = 20$) cycles of DL-PDT. At baseline, most patients (95%) had 20 or more lesions. Patients treated with one cycle of DL-PDT showed a mean AKASI reduction of 45.5% ($p < 0.001$). Patients eligible for two cycles of DL-PDT demonstrated a mean AKASI reduction of 23.7% ($p < 0.05$) after one and 48.2% ($p < 0.001$) after two cycles. Patients participating in this study were either very satisfied (67.5%) or satisfied (32.5%). Almost all patients (97.5%) would recommend DL-PDT to other patients. *Conclusions:* DL-PDT is a well-tolerated, safe and efficient treatment option for field cancerisation in the facial and scalp area with high patient satisfaction. AKASI scoring has proven useful as a quantitative tool for assessing the outcome of DL-PDT treatment.

Key words: actinic keratosis, actinic keratosis area and severity index (AKASI), daylight photodynamic therapy (DL-PDT), methyl aminolevulinate (MAL), photodynamic therapy, protoporphyrin IX (PpIX)

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Actinic keratosis (AK) represents one of the most frequently diagnosed skin diseases in dermatological practice with prevalence in Europe of about 49% in men and 28% in women [1, 2]. AKs are regarded as precursors of invasive squamous cell carcinoma (SCC) and the rates of malignant transformation are considerable. Progression of AK to SCC has been reported in up to 10% of immunocompetent patients [3].

Importantly, the risk of transformation to SCC rises with the presence of an increasing number of AK lesions. In the absence of tools that can predict when and which AK lesions progress into invasive SCC, current guidelines suggest treating all AK lesions [4]. Treatment options for AKs include destructive therapies such as cryo-, electro- or excisional surgery, topical treatments (*e.g.* diclofenac, imiquimod, 5-fluorouracil, ingenol mebutate) or photodynamic therapy (PDT) with a topical photosensitizing agent (*e.g.* methyl aminolevulinate [MAL] cream) [5]. Both the well-established conventional PDT (C-PDT) with red or blue light and the recently described modified therapeutic option of PDT with daylight (DL-PDT) result in activation of the photosensitizer, which is metabolized into protoporphyrin IX (PpIX). Absorption of PpIX by dysplastic cells leads to cell necrosis and apoptosis. DL-PDT has been reported to be as efficient as C-PDT but easier to handle and less painful [6-9]. However, comprehensive data on the therapy regimen and conditions of DL-PDT in daily practice is limited.

The objective of the present non-sponsored prospective study was to obtain further insight into the practical use of DL-PDT for severe facial and scalp AKs in a German cohort. In particular, we focused on the comparison between one and two cycles of DL-PDT, weather conditions, and patient satisfaction. Treatment outcome was measured by different scoring systems, including the recently published actinic keratosis area and severity index (AKASI) in order to validate this new quantitative tool for assessing AK severity after DL-PDT [10-12].

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Materials and methods

Study population

We prospectively analysed patients receiving DL-PDT for multiple AKs in the facial or scalp area at the Department of Dermatology, University Medical Centre Tübingen, Germany, between June 2017 and October 2017. Eligible patients were aged 18 years or older. Further inclusion criteria were the presence of at least 10 AKs, Grade I and/or II, each with a diameter of more than 5 mm in the facial and/or scalp area with an AKASI score of >6. Hyperkeratotic thicker AK lesions (Grade III) present in the field-cancerized treatment area were also treated together with the thinner lesions. Exclusion criteria comprised concomitant topical or physical treatment for AKs. Any prior treatments had to be discontinued for at least four weeks prior to baseline. The study was approved by the local ethics committee (Study number: 286/2017BO1) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study initiation.

Data assessment

At baseline, the extent and severity of AKs were assessed by the recently described AKASI score [10]. Additionally, all AKs >5 mm in diameter were documented and graded clinically according to Olsen scoring (I: mild, slightly palpable AK, more easily felt than seen; II: moderate, moderately thick AK, easily felt; and III: thick, very thick AK) [13]. In addition, treatment outcome was assessed by physician global assessment (PGA) and patient global assessment (PtGA) using a scale from 0 to 4 (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe). In order to avoid interobserver variability, the same physician performed all scorings for all patients. Patients received and filled out a questionnaire using rating scales to examine sensations and patient satisfaction with the therapy. Illuminance during daylight exposure was measured and recorded for each patient by a lux meter (Peak Tech® 5165 Digital Lux Meter, Ahrensburg, Germany). Global radiation was recorded by a nearby weather station (Agrarmeteorologie Baden-Wuerttemberg, Germany). Additionally, lesions were photodocumented before and after treatment (*figure 1*).

Study protocol

Organic sunscreen without any mineral filters (Actinica® lotion, SPF 50+, Galderma Laboratorium, Düsseldorf, Germany) was applied to the entire area prior to daylight exposure. After an absorption time of the applied sunscreen of at least 15 minutes, curettage of individual lesions was performed in order to remove scales and crusts and to roughen the surface of the lesions. Subsequently, a thin layer of methyl aminolevulinate (MAL) cream (Luxerm® 160 mg/g creme, Galderma Laboratorium, Düsseldorf, Germany) was applied. After two hours of exposure to daylight, remnant MAL cream was removed. At an interval of six to 10 weeks after the first cycle of DL-PDT, a follow-up visit was scheduled for each patient to reassess the treated areas. Patients with an AKASI score >6 and a Δ AKASI <33% improvement (first follow-up visit compared to baseline) were eligible for a second cycle of DL-PDT. Patients receiving a second treatment presented for a second follow-up visit and clinical reassessment after six to 10 weeks.

Table 1. Demographic and clinical characteristics of the study group at baseline.

	Patients, *n* (%) **n = 40**
Age (years), mean ± SD (range)	74 ± 7.93 (56-87)
Gender	
Male	37 (92.5)
Female	3 (7.5)
Skin phototype	
Type II	36 (90)
Type III	4 (10)
Immunosuppression	4 (10)
History of skin cancer	
No	6 (15)
Yes	34 (85)
Non-melanoma skin cancer (NMSC)	26
Malignant melanoma (MM)	2
NMSC and MM	6
Previous AK treatment	
Topical therapies	
Diclofenac	31 (77.5)
Imiquimod	8 (20)
Fluorouracil	7 (17.5)
Ingenol mebutate	6 (15)
Destructive therapies	
Ablative laser	4 (10)
Chemical peeling	5 (12.5)
Cryotherapy	24 (60)
Surgery	40 (100)
Photodynamic therapies (PDT)	
Conventional PDT (C-PDT)	12 (30)
Daylight PDT (DL-PDT)	3 (7.5)
Past medical history of PDT treatment (years), mean ± SD (range)	***n* = 15**
C-PDT	6.1 ± 3.3 (2-10)
DL-PDT	0.6 ± 0.4 (0.2-1)

Statistical analysis

Statistical analysis was performed using Graph Pad PRISM 6 software. Differences between multiple groups were tested for significance using the Kruskal-Wallis test, followed by Dunn's post-hoc test for multiple comparisons.

Results

Study cohort and DL-PDT conditions

A total of 40 patients with a mean age of 74 years (range: 56-87 years) were enrolled in the study (*table 1*).

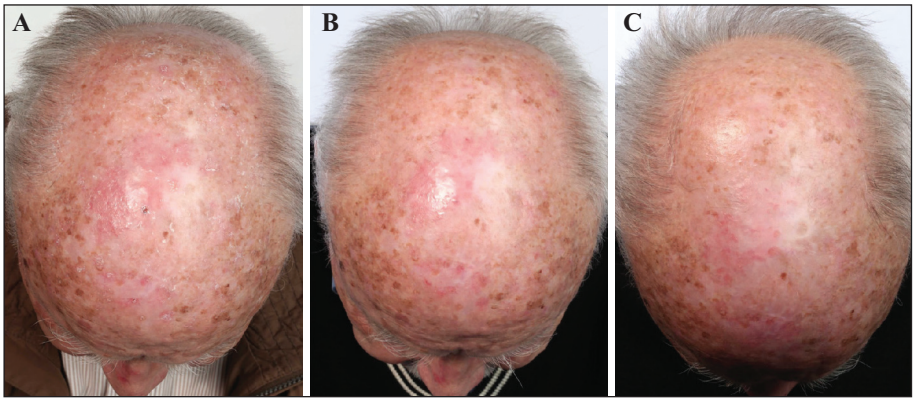

Figure 1. Severe actinic keratosis (AKs) in a patient treated with two cycles of daylight photodynamic therapy (DL-PDT). **A**) Clinical picture with baseline AKASI score of 13.0. **B**) One cycle of DL-PDT resulted in moderate improvement with an AKASI score of 9.0 at the first follow-up visit. **C**) More than 50% improvement (AKASI 5.8) was visible after the second cycle of DL-PDT, as presented at follow-up visit 2.

Table 2. Description of treated AK lesions at baseline.

Baseline characteristics	**Patients, n (%)** $n = 40$
Number of lesions	
≥ 10	2 (5)
≥ 20	15 (37.5)
≥ 30	14 (35)
≥ 40	9 (22.5)
Severity of lesions	
Predominance of Grade I	14 (35)
Predominance of Grade II	25 (62.5)
Equal number of Grade I and II	1 (2.5)
Presence of Grade III	35 (87.5)
Location of lesions ($n = 1317$)	
Face ($n = 612$)	40 (100)
Scalp ($n = 705$)	36 (90)

All patients completed the study. Mean patient follow-up was 58 days after treatment (range: 40-87 days). The vast majority of study patients were male (37/40; 92.5%) with a predominant skin phototype II (36/40; 90%). Among all study patients, our study cohort comprised four immunosuppressed patients (10%) due to immunosuppressive medication for lymphoma, hepatitis, mixed connective tissue disease or after organ transplantation. Of note, 34 patients (85%) had a history of skin cancer, namely non-melanoma skin cancer (NMSC; $n = 26$), malignant melanoma (MM; $n = 2$) or both ($n = 6$) (*table 1*).

All patients enrolled in this study reported the use of one or more previous treatments for AKs, including destructive therapies (*e.g.* surgery), topical therapies (*e.g.* diclofenac), and PDT (*table 1*). Of the latter group, three patients previously received DL-PDT and 12 patients had been treated with C-PDT. Before study treatment, most patients (95%) had 20 or more lesions (*table 2*). All patients presented with lesions on the face ($n = 612$) and in addition 36/40 patients presented with lesions on the scalp ($n = 705$). In most patients, Grade II AKs were predominant (*table 2*). Weather conditions, illuminance, and global radiation during DL-PDT were recorded for all patients and are summarised in *table 3*.

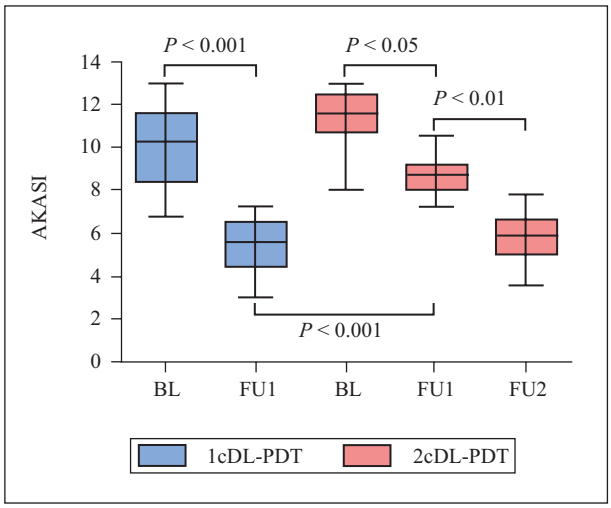

Figure 2. Treatment outcome of DL-PDT based on AKASI scores of patients with severe AKs receiving one cycle (1cDL-PDT group; blue bars; $n = 20$) or two cycles (2cDL-PDT group; red bars; $n = 20$) of DL-PDT, as determined at baseline (BL), follow-up visit 1 (6 to 8 weeks after first treatment; FU1), and follow-up visit 2 (6 to 8 weeks after second treatment; FU2). The box-and-whisker plots represent the minimum, interquartile range (25-75th percentile), and maximum of the AKASI score, and the line within the box is the median value. Statistical significance was calculated using one-way ANOVA and Dunn's multiple comparison test.

Efficacy of DL-PDT

The mean AKASI score for all patients at baseline was 10.8 ±0.3 (mean ± SEM). Patients who presented with an AKASI >6 and a Δ AKASI improvement of <33% at the first follow-up visit (FU1) were eligible for a second cycle of DL-PDT (2cDL-PDT; $n = 20$). All other patients discontinued the study after the first cycle (1cDL-PDT; $n = 20$). In the following, these two groups (1cDL-PDT and 2cDL-PDT) are analysed separately. The mean baseline AKASI for the 2cDL-PDT group was slightly higher than that for the 1cDL-PDT group (11.4 ± 0.3 vs 10.1 ± 0.4) (*figure 2, table 4*). At FU1, the mean AKASI score for the 1cDL-PDT

Table 3. Weather conditions during daylight photodynamic therapy.

First cycle	Patients ($n = 40$), n (%)
Weather	
Sunny	21 (52.5)
Mixed sunny/cloudy	16 (40)
Cloudy	3 (7.5)
Rainy	0 (0)
Illuminance (lux), mean ± SD (range)	
Start of DL exposure	54490 ± 37641 (6400-116300)
Middle of DL exposure	54987 ± 35910 (10900-117900)
End of DL exposure	52135 ± 33952 (9290-106700)
Global radiation (Wh/m^2), mean ± SD (range)	
1st hour of DL exposure	674.2 ± 136.6 (265.3-907.5)
2nd hour of DL exposure	680.1 ± 135.2 (263.4-886.7)
Second cycle	**Patients ($n = 20$), n (%)**
Weather	
Sunny	6 (30)
Mixed sunny/cloudy	9 (45)
Cloudy	5 (25)
Rainy	0 (0)
Illuminance (lux), mean ± SD (range)	
Start of DL exposure	43020 ± 31543 (8500-114800)
Mid of DL exposure	29620 ± 26945 (5700-99000)
End of DL exposure	31940 ± 29303 (4900-107900)
Global radiation (Wh/m^2), mean ± SD (range)	
1st hour of DL exposure	447.2 ± 98.7 (284.6-609.9)
2nd hour of DL exposure	457.6 ± 175.4 (89.4-677.3)

DL: daylight

group was 5.5 ± 0.3 ($p < 0.001$; 45.5% AKASI reduction compared to baseline) (*table 4*). The mean AKASI after the first treatment for the 2cDL-PDT group was 8.7 ± 0.2 ($p < 0.05$; 23.7% AKASI reduction compared to baseline) (*table 4*) and further improved to 5.9 ± 0.2 ($p < 0.001$ compared to baseline and $p < 0.01$ compared to FU1; 48.2% AKASI reduction compared to baseline) (*table 4*) after the second treatment at the second follow-up visit (FU2). The mean AKASI scores between the 1cDL-PDT and 2cDL-PDT groups at FU1 were significantly different ($p < 0.001$). No statistical difference was present when comparing the AKASI scores after the first cycle of 1cDL-PDT at FU1 with the results of the second cycle of the 2cDL-PDT group at FU2 (*figure 2*).

When focusing on the total number of all lesions in all 40 patients, we observed a reduction from 1,317 lesions at baseline to 438 lesions at FU1. Additionally, in all patients, 51 lesions newly developed at FU1. The mean lesion number at baseline was higher in the 2cDL-PDT group (35.1) compared to the 1cDL-PDT group (30.8) (*table 4*). However, this difference was not statistically significant. In the 1cDL-PDT group, the total number of lesions decreased from 615 at baseline to 137 with a lesion response rate of 77.7% (*table 4*). A total of 14 new lesions were detected at FU1 in the 1cDL-PDT group. The 2cDL-PDT group demonstrated a reduction in the total number of lesions from 702 at baseline to 301 at FU1 (57.1% lesion response rate) and 150 lesions were present at FU2 after the second DL-PDT cycle. From baseline to FU2, a 78.6% lesion response rate was noted (*table 4*). Overall, in the 2cDL-PDT group, 37 new lesions were identified at FU1 and five lesions at FU2, respectively.

Next, we analysed the response of the lesions to DL-PDT with respect to lesion grade (*figure 3*). The 1cDL-PDT group revealed a statistically significant reduction in Grade I, Grade II, and Grade III lesions from 12.4 ± 1.3 to 4.4 ± 0.6 lesions (mean ± SEM; $p < 0.001$), 13.7 ± 1.6 to 2.1 ± 0.6 lesions (mean ± SEM; $p < 0.001$), and 4.7 ± 1.2 to 0.4 ± 0.3 (mean ± SEM; $p < 0.001$), respectively. In the 2cDL-PDT group, the treatment revealed a statistically significant reduction in Grade I lesions from 11.5 ± 1.2 to 5.4 ± 0.9 lesions (mean ± SEM; $p < 0.01$) at FU1 and to 3.4 ± 0.5 lesions at FU2 ($p < 0.001$). Treatment of Grade II lesions revealed a statistically significant reduction in lesions from 14.9 ± 1.8 to 5.7 ± 0.7 (mean ± SEM; $p < 0.01$) after one treatment with DL-PDT and to 2.4 ± 0.3 after two treatments with DL-PDT ($p < 0.001$). Grade III lesions diminished from 8.8 ± 1.7 to 4.0 ± 1.3 lesions (mean ± SEM; ns) at FU1 and to 1.7 ± 0.7 lesions ($p < 0.001$) at FU2 (*figure 3*). Of note, patients in the 1cDL-PDT group showed a significantly better treatment response than patients in the 2cDL-PDT group for Grade III lesions after single treatment at FU1 ($p < 0.05$) (*figure 3*).

We further assessed treatment outcome based on PGA and PtGA (*figure 4*). At baseline, 50% of the patients in the 1cDL-PDT group and 80% of the patients in the 2cDL-PDT group were rated as PGA3 or PGA4 (moderate to severe disease). At FU1, 100% of patients in the 1cDL-PDT

Table 4. Lesion response rate and AKASI reduction.

Treatment group	Number of patients (n)	Mean number of lesions at baseline	Mean AKASI at baseline	Mean lesion response rate at FU1 (and FU2) compared to baseline (%)	Mean AKASI reduction at FU1 (and FU2) compared to baseline (%)
1cDL-PDT	20	30.8	10.1	77.7	45.5
2cDL-PDT	20	35.1	11.4	57.1 (78.6)	23.7 (48.2)

DL-PDT: daylight photodynamic therapy

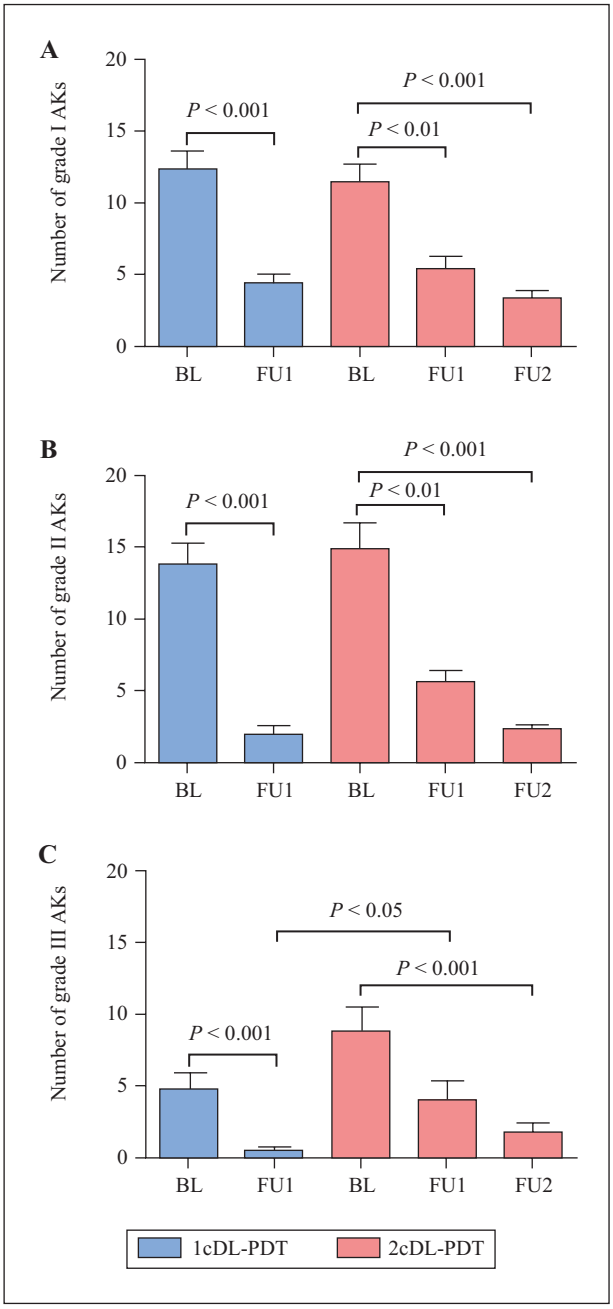

Figure 3. Reduction of Grade I to III AKs by DL-PDT in patients with severe AKs. The total number of AKs with Olsen Grade I (**A**), II (**B**) and III (**C**) is presented in patients receiving one cycle of DL-PDT (1cDL-PDT; blue bars; $n = 20$) and patients receiving two cycles of DL-PDT (2cDL-PDT; red bars; $n = 20$) at baseline (BL) and follow-up visit 1 (FU1) and 2 (FU2). Bars represent mean ± SEM. Statistical significance was calculated using one-way ANOVA and Dunn's multiple comparison test.

group were rated as almost clear (PGA1) while only 20% of patients in the 2cDL-PDT group achieved this rating. After the second treatment, the proportion of patients with PGA1 in the 2cDL-PDT group increased to 85% (*figure 4*). The majority of patients (80%) in each treatment group rated the severity of their disease as mild or moderate. At FU1, 100%

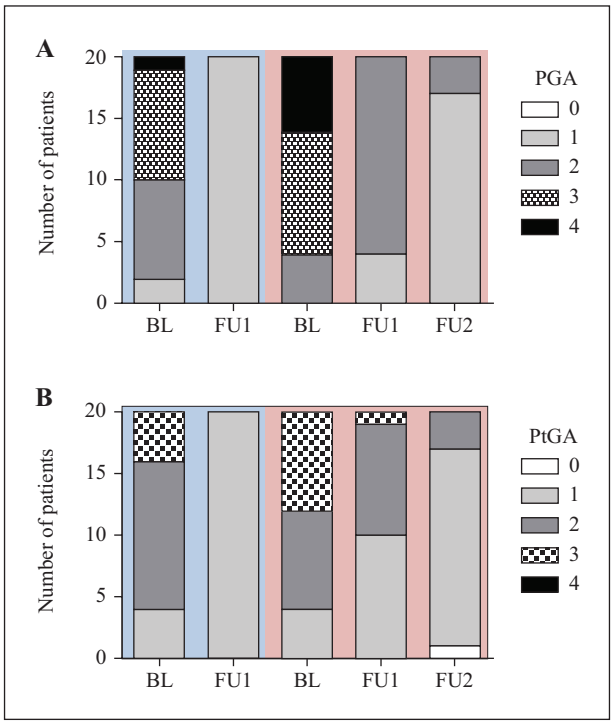

Figure 4. Outcome of severe AKs treated with DL-PDT as determined by physician and patient global assessment scores. The physician global assessment (PGA) **(A)** and patient global assessment (PtGA) **(B)** were evaluated (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) for each patient receiving one (1cDL-PDT; blue background; $n = 20$) or two (2cDL-PDT; red background; $n = 20$) cycles of DL-PDT. Scores were documented at baseline (BL), follow-up visit 1 (FU1) and 2 (FU2).

of patients in the 1cDL-PDT group and 50% of the patients in the 2cDL-PDT group rated their disease as almost clear (PtGA1). At FU2, 80% of patients indicated PtGA1 and 5% of patients evaluated their disease to be cleared (*figure 4*).

Safety

During DL-PDT and within the first 48 hours after therapy, pain, burning and itching were evaluated by patients on a scale ranging from 0 to 10 (0 = no sensation; 10 = maximum sensation) (*figure 5*). While most patients reported the sensation of burning during and after the DL-PDT procedure, the sensation of itching was more dominant after the procedure (*figure 5*). Notably, the sensation of pain did not seem to play a major role, neither during nor after the procedure (*figure 5*).

Patients were also asked to report adverse events within four weeks after the DL-PDT procedure. Therapy-related symptoms occurring within four weeks after the first cycle of DL-PDT occurred in 25/40 patients and comprised erythema ($n = 21$), marked crusting ($n = 9$), pain ($n = 3$), hair loss ($n = 1$), burning ($n = 1$), and tenderness on palpation ($n = 1$). Symptoms occurring within four weeks after the second cycle of DL-PDT occurred in 9/20 patients and comprised erythema ($n = 7$), marked crusting ($n = 3$), pain ($n = 1$), hair loss ($n = 1$), and tenderness on palpation ($n = 1$).

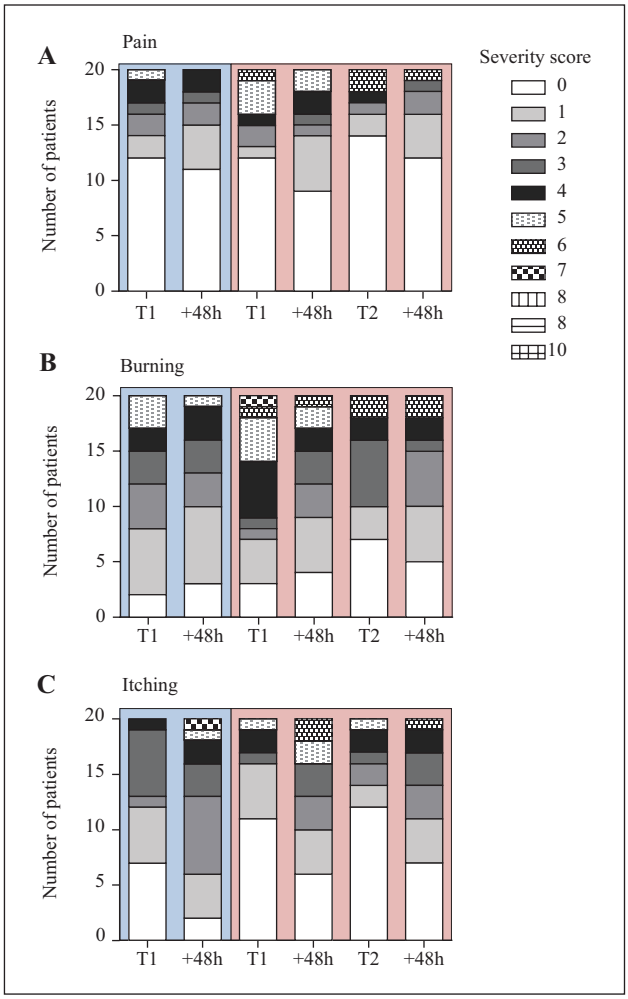

Figure 5. DL-PDT-related adverse events in patients with severe AKs. Sensations of pain (**A**), burning (**B**), and itching (**C**) based on scores from 0 (no sensation) to 10 (maximum sensation) were recorded during or within 48 hours after the first DL exposure (T1; 1cDL-PDT group with blue background; $n = 20$, and 2cDL-PDT group with red background; $n = 20$) or the second DL exposure (T2; 2cDL-PDT group). While most patients reported the sensation of burning during and within 48 hours after the DL-PDT procedure, the sensation of itching was more dominant after the procedure. Sensations of pain were either absent or of limited severity.

Patient satisfaction with DL-PDT

Patient satisfaction was evaluated based on the questionnaire. All patients included in this study ($n = 40$) answered the questionnaire. The majority of patients (29/40; 72,5%) were not bothered by the presence of their AKs and only six patients (15%) felt strongly restricted in daily life due to their skin changes. After receiving DL-PDT, most of the patients (first cycle: 33/40; 82.5%; second cycle: 17/20; 85%) reported that they were not restricted at all in their daily life due to the procedure. A minority of patients (first cycle: 6/40; second cycle: 2/20) was restricted in daily life for one week and one patient (first and second cycle) was restricted in daily life for two weeks after DL-PDT. None of the patients were restricted in daily life for three weeks or more.

Table 5. Patient satisfaction with daylight photodynamic therapy (DL-PDT).

	Patients ($n = 40$), n (%)
General satisfaction with DL-PDT	
Very satisfied	27 (67.5)
Satisfied	13 (32.5)
No impact	0 (0)
Unsatisfied	0 (0)
Very unsatisfied	0 (0)
Result of DL-PDT	
Very good	17 (42.5)
Good	22 (55)
Satisfying	1 (2.5)
Sufficient	0 (0)
Bad	0 (0)
Impact of DL-PDT results on quality of life	
Clear improvement	12 (30)
Improvement	17 (42.5)
No impact	11 (27.5)
Deterioration	0 (0)
Clear deterioration	0 (0)
Would you recommend DL-PDT to other patients suffering from AKs?	
Yes	39 (97.5)
No	0 (0)
Don't know	1 (2.5)

Patients were very satisfied (67.5%) or satisfied (32.5%) with the procedure of DL-PDT (*table 5*). Most patients rated the result of DL-PDT as very good (42.5%) or good (55%). One patient (2.5%) was satisfied with the result. Whereas 27.5% of patients indicated no impact on their quality of life after DL-PDT, 72.5% of patients stated a clear improvement or improvement in their quality of life (*table 5*). Finally, almost all patients (97.5%) reported that they would recommend DL-PDT to other patients suffering from AKs (*table 5*).

Discussion

Recently, a new scoring system for assessing the severity of multiple AKs has been introduced [10]. This scoring system, namely AKASI, has proven useful in one retrospective pilot study as a quantitative tool for the evaluation of treatment success after C-PDT [12]. Our present study is the first prospective trial to investigate treatment outcome in patients with severe AKs receiving one or two cycles of DL-PDT employing AKASI. Schmitz *et al.* [12] reported a median absolute difference of AKASI of 2.6 (range: 1.6 to 5.4) and an improvement of at least 50% of the AKASI score (AKASI50) in 72.7% of patients with AKs treated with C-PDT. By using DL-PDT, we reveal a median absolute difference of AKASI of 4.6 (range: 1.4 to 7.0) for patients in the 1cDL-PDT group at FU1 and a median absolute difference of AKASI of 3.0 (range: 0.8 to 4.0) and 5.8 (range: 3.0 to 8.0) for patients in the 2c-DL-PDT group at FU1 and FU2, respectively. In the 1cDL-PDT group,

45.0% of our patients achieved an AKASI50 at FU1. When patients were treated with two cycles of DL-PDT (2cDL-PDT group), no patient achieved an AKASI50 at FU1. At FU2, 45.0% of patients achieved an AKASI50. Compared to the study of Schmitz *et al.* [12], our study shows higher absolute improvement in AKASI, but a lower number of patients with an AKASI50 response. This is best explained by the disease severity and inclusion criteria in our cohort. First, the patient population treated by Schmitz *et al.* [12] had a high proportion of therapy-naïve patients (39.4%), whereas in our study, all patients (100%) were refractory to previous treatments with a history of one or more prior treatments. Second, AK disease severity of the patients at baseline was very different. The median AKASI at baseline in our cohort with Grade I, II and III lesions was almost three times higher (11.2; range: 6.8-13.0) as compared to the cohort of Schmitz *et al.* [12] (median AKASI: 3.8; range: 1.0 to 7.8). Furthermore, we performed a prospective study and assessed different scoring tools. Thus, the heterogeneity of the study populations, study design, and the different treatment modalities used (C-PDT versus DL-PDT) limit the comparison of the AKASI response in these two studies.

In previous studies, different measurements such as lesion response rate and complete clearance rate have been proposed for the evaluation of efficacy endpoints in AK treatment [14, 15]. In patients with numerous and severe AKs distributed in large areas, the lesion response rate is more meaningful than the complete clearance rate. Our study on DL-PDT for severe AKs revealed an overall lesion response rate of 77.7% for patients receiving one single session of DL-PDT (1cDL-PDT group). This result is consistent with the lesion response rates reported in the literature for one session of DL-PDT in patients with AKs ranging from 68.0% to 89.2% [7, 9, 16-20].

To date, limited data exists on the comparison between AKASI scoring and lesion response rates [10, 21]. Of note, high AKASI scores do not seem to correlate with total lesion counts as well as low AKASI scores [21]. In our cohort of patients with severe and treatment-refractory AKs, the lesion response rates were high (77.7% to 78.6%), whereas the AKASI reduction was between 45.1% and 48.2% (*table 4*). This indicates that besides lesion response rate as an efficacy measure, AKASI50 could be a reasonable endpoint for measuring treatment success in patients with baseline AKASI of >10.

To the best of our knowledge, this is the first study evaluating treatment success by lesion response rates, AKASI, PGA, and PtGA separately after one and two treatment cycles of DL-PDT.

DL-PDT using two treatment sessions has previously been reported [22-25]. However, the two sessions of DL-PDT were performed one week apart from each other without separate analysis of treatment success after each cycle. Obviously, such an analysis only makes sense if the treatment sessions are not too close to each other. For this reason, we chose a period of six to eight weeks between the two DL-PDT cycles allowing clinical evaluation and the possibility of a second treatment for patients in a region with restricted sunlight during certain months. Based on the evaluation of treatment success at two time points in our study, we could identify patients with severe AKs that benefit from a second treatment cycle of DL-PDT, particularly for Grade II and Grade III AKs (*figure 3*).

Besides analysis of the lesion response rate and analysis of AKASI, we also assessed PGA and PtGA (*figure 4*). In our study, patients of the 1cDL-PDT group all showed a PGA1 and PtGA1 at FU1. In contrast, a PGA1 and PtGA1 were only achieved in 15% (3/20) of patients of the 2cDL-PDT group at FU1. Compared to AKASI and lesion response rate, PGA and PtGA are more simple tools for analysing treatment success and for identifying patients that may benefit from a second treatment with DL-PDT. Our analysis shows that single patients who would still benefit from a second treatment would be missed based on PGA and PtGA scoring.

In contrast to C-PDT, DL-PDT has been reported in several studies as a less painful and more convenient therapy with high patient tolerability and high patient satisfaction [17, 26, 27]. In line with these studies, our analysis confirms high patient satisfaction with well tolerable pain levels, independent of the number of DL-PDT sessions performed. Importantly, the majority of our study patients (97.5%) would recommend DL-PDT to other patients suffering from AKs, further underlining the convenience of the procedure. The present prospective single-centre study confirms the high efficacy and patient satisfaction with DL-PDT for the treatment of severe AKs of the face and scalp. For countries, in particular, like Germany with weather conditions that restrict the period of time when DL-PDT can be used, we propose a modified treatment protocol with a shortened follow-up period and a second DL-PDT during the same season. Since we could identify patients with severe AKs that benefit from a second DL-PDT treatment in the same season, future investigations may help to find associated parameters that explain the different responses. In our study with 40 patients, we did not find significant differences in patient age, prior treatments, or AK severity at baseline that could predict the need for two DL-PDT cycles from the beginning. As confirmed by the additional scores (lesion response rates, PGA, and PtGA), the AKASI thresholds set at FU1 appeared to be helpful when performing a second cycle of DL-PDT in patients with severe AKs. The present trial is the first to investigate treatment outcome with DL-PDT by means of AKASI thresholds in patients with severe AKs, and confirms the reliability of this new assessment tool for AK evaluation. ■

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