

Artificial Daylight Photodynamic Therapy with Methyl Aminolevulinate Using an Abbreviated Illumination Protocol with the MultiLite Lamp System in Patients with Actinic Keratoses

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Actinic keratoses (AK) are keratinocyte neoplasms primarily caused by chronic photodamage. They can potentially evolve into invasive and metastatic cutaneous squamous cell carcinoma (SCC), if left untreated (1, 2). To avoid transition to an invasive SCC, consistent treatment of AK is therefore crucial (3). Photodynamic therapy (PDT) is approved for the treatment of actinic keratoses (AK) and field cancerization. Aminolevulinic acid (ALA) and its methyl ester methyl aminolevulinate (MAL) are approved topical agents that act as precursors to the endogenous photosensitizer protoporphyrin IX in PDT (4). The method of PDT has been improved continuously since its introduction in 2002. In response to the limitations of conventional and daylight PDT, the use of artificial daylight (ADL) with a variety of certified light sources mimicking the spectrum of daylight without ultraviolet radiation has been established in clinical practice. Treatment results were comparable with those achieved with natural daylight PDT and conventional PDT (5–7). The aim of this observational study was to evaluate the effectiveness of MAL in ADL-PDT using the MultiLite illumination lamp in daily routine. In line with the summary of product characteristics (SmPC), ADL-PDT with MAL involves a maximum of 30-min incubation followed by 2 h of illumination. However, the 2-h duration of light exposure has been identified as a limiting factor particularly for elderly patients. In addition to evaluating the effect of MAL, the present study aimed to investigate the effectiveness and tolerability of MAL-ADL-PDT using an abbreviated illumination period (1 h) following an extended incubation period (1 h).

MATERIALS AND METHODS

The study enrolled 30 adult patients with a confirmed diagnosis of AK on the face or scalp, for which MAL-ADL-PDT was indicated. Outcome parameters assessed at month 3 were the Actinic Keratosis Area and Severity Index (AKASI) score (8), lesion count and treatment satisfaction. During illumination, pain was assessed on a visual analogue scale (VAS) from 0 (no pain) to 10 (worst pain).

Procedure

MAL-ADL-PDT using 160 mg/g MAL cream was performed at the baseline visit using an abbreviated protocol. Prior to treatment, any hyperkeratoses in the intended treatment area were carefully removed with a curette and the stratum corneum was roughened. A thin layer of MAL was applied onto the skin in the treatment area. After 1-h incubation, ADL exposure was started for 1 h using the CE-certified and approved ADL lamp system MultiLite. Afterwards, the residues of MAL were washed off to avoid subsequent phototoxic reactions. The patient was advised to remain indoors for the remainder of the day, if possible and to use UV protection.

Statistical analysis

All documented data were analysed primarily descriptively, supplemented by inferential statistical tests. Exploratory analyses were carried out to investigate the changes in the AKASI score and in the number of lesions from baseline to month 3, respectively. The analyses were performed using *t*-test for dependent samples and Wilcoxon signed-rank test for independent samples. All tests were two-sided, and significance was declared at the 0.05 level. All *p*-values are considered nominal. Statistical analyses were carried out using Microsoft excel.

RESULTS

A total of 30 patients (28 males, 2 females) were included in the study. Median age was 67 years. Nineteen patients (63.3%) had received prior therapy for AK: imiquimod, diclofenac, tribanibulin and ADL-PDT. None had received immunosuppressive drugs. Treatment locations were scalp in 12 patients (40.0%), forehead in 7 (23.3%) and 11 patients (36.7%) were treated in both locations.

Effectiveness

Median AKASI improved significantly from 5.6 at baseline to 1.9 at month 3 (nominal $p < 0.0001$) (Fig. 1). Five patients (16.7%) achieved a 100% reduction in AKASI, 3 (10.0%) a reduction of >80% to <100%

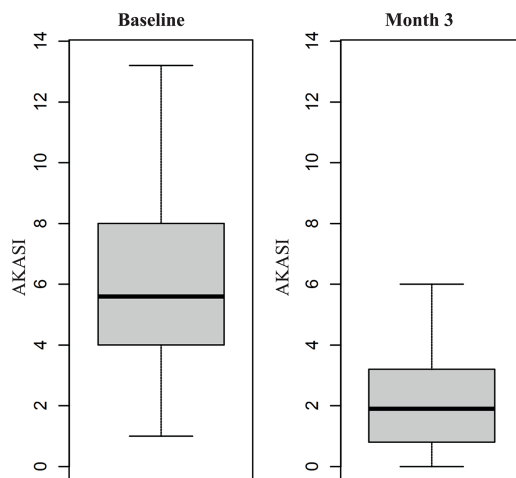


Fig. 1. Change in AKASI from baseline to post-treatment assessment.

and the remaining 22 patients (73.3%) achieved an AKASI reduction of less than 80%. Significant AKASI improvement was also gained across all treated locations. Median lesion count decreased significantly from 6.5 (mean [SD] 9.97 [8.4]) at baseline to 0 (mean [SD] 0.53 [0.9]) at month 3 (mean reduction ~95 %; $p < 0.0001$) (Fig. 2). A 100% reduction was achieved by 21 patients (70.0%) and a reduction of >80% to <100% by 9 patients (30.0%). After 3 months, both patients and investigators rated treatment satisfaction for all patients as very good. Fig. 3 shows the photo documentation of two patients.

Safety

Mean rating of pain on the VAS was 0.3 ± 0.7 at illumination start, 0.4 ± 0.6 after 30 min and 0.3 ± 0.6 after 50 min. Mean heart rate remained unchanged at treatment start, as well as after 30 and 50 min. All patients reported experiencing moderate-to-very severe cutaneous reactions.

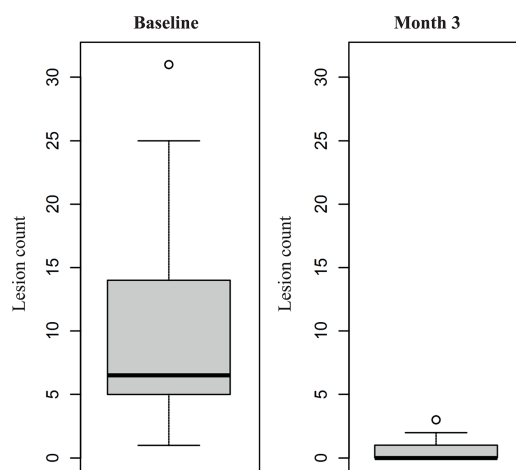


Fig. 2. Change in lesion count from baseline to post-treatment assessment.

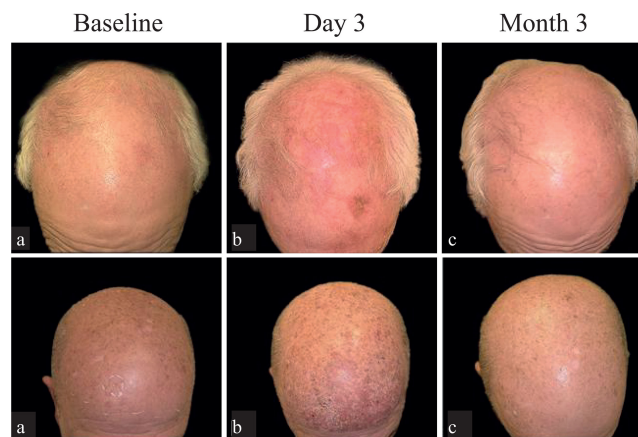


Fig. 3. Clinical images of two patients taken at baseline (A), day 3 (B), and month 3 (C).

DISCUSSION

The adaptation of the PDT protocol with extended incubation and shortened illumination is another step towards improving the procedure in terms of patient convenience without weakening the outcome. The proportion of patients achieving complete lesion clearance (70%) exceeded percentages observed in a clinical trial (17%) (5) and the noninterventional study ArtLight (14.6%) (7), which both applied MAL-ADL-PDT in accordance with the SmPC, i.e. 30-min incubation with MAL, followed by 2-h illumination. Similarly, the median decrease in AKASI from baseline to month 3 (5.6 to 1.9) was more pronounced in the present study than in ArtLight (6.2 to 3.4) (7). Comparisons between studies must be interpreted with caution, however, due to different confounders. For instance, patients in ArtLight had a higher lesion count at baseline (median 16) compared to the present study (median 6.5). By contrast, an inpatient comparative study examining 1 h vs 2 h illumination after 30-min incubation with MAL in 55 patients did not find any differences in effectiveness (overall lesion clearance 72.9 % vs 71.1%) between the 2 protocols (9).

The reason for the 30-min time limit provided in the SmPC for MAL is to avoid excessive porphyrin IX accumulation, which can lead to increased pain upon exposure to light (10, 11). The present data demonstrate that doubling the incubation time to increase the loading dose of PPIX did not lead to increased levels of pain. Throughout the illumination period, mean pain levels remained below 1 on the VAS. Similar nonexistent pain was observed in a clinical trial (median 0, range 0–1) (5), while a small proportion (6.3%) of patients from the ArtLight study reported moderate-to-severe pain (4–9 on the VAS) during treatment (7). No unexpected adverse events were discovered.

This study is limited by its noncontrolled real-world setting, which may be obscured by unknown confounders in patient cohorts. The participation of

a single centre may enhance selection bias. On the other hand, performing all PDTs by the same physician ensures reliability and reproducibility. The sample size of 30 patients provides a preliminary outlook into the feasibility of the altered protocol, but further studies in larger populations are warranted to confirm results. The strength of the study is the use of an objective score to assess parameters of photodamage, with a distinctive description assigned to each score point in order to minimize error (8).

In conclusion, the use of the MultiLite lamp system in combination with an abbreviated illumination protocol was associated with effective lesion reduction and high patient satisfaction. MAL-ADL-PDT with MultiLite and the altered protocol is a convenient procedure to treat AKs and prevent progression to SCC that can be applied all year round.

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Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: The study protocol was reviewed by the ethics committee of the University Witten-Herdecke, Alfred-Herrhausen-Str. 50, 58448 Witten (ref no. 254/2023) prior to the study's commencement.

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