



Daylight photodynamic therapy in 25 patients with actinic keratosis and evaluation of efficacy by confocal microscopy

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ABSTRACT

Background: Daylight photodynamic therapy (PDT) has been reported as having similar efficacy to conventional photodynamic therapy in actinic keratosis treatment.

Methods: 25 patients with actinic keratosis of the scalp and/or face were submitted to a daylight photodynamic therapy session. Adverse reactions were evaluated after one week and efficacy after 3 months. Confocal Microscopy was performed in 6 patients, before and one week after the treatment.

Our aim was to compare our results with others studies and analyse the changes occurring in the epidermis and upper dermis with confocal microscopy.

Results: 76% of the patients were male. The mean age was 74.2 years. In 51.7% of patients the treatment site was the scalp. Mean cure rate at 3 months was 74%. Aesthetic results were excellent in all patients and only one patient reported mild pain during the 2 h exposure. Confocal Microscopy showed a normalization of the honeycomb pattern in all of the patients.

Conclusions: This therapy has similar results to conventional photodynamic therapy and stands out for less discomfort, fewer adverse effects and better cost-effectiveness. Using confocal microscopy it's possible to *in vivo* demonstrate the efficacy of this method, with normalization of the honeycomb pattern in the epidermis following successful PDT.

1. Background

Actinic keratosis (AK) is the most common photoinduced and precancerous skin lesion, resulting from keratinocyte dysplasia in the epidermis [1–3].

The risk of a single AK turning into a squamous cell carcinoma (SCC) remains unknown, but different studies demonstrate an annual transformation rate between 0.03% and 20%, depending on the population and the lesion itself [4,5]. Several studies proved the existence of a field cancerization that is defined as an area of subclinical changes in the periphery of visible AKs that displays the same genetic changes found in the lesion itself [6–9]. New imaging technology, such as reflectance confocal microscopy (RCM), ...with a sensitivity of 80% and a specificity of 98.6% when performed by skilled readers for AK. Also with this technique, the changes in the epidermis near the AK can be visualized [10,11].

Management can be divided on lesion-directed or field-directed therapy. Field-directed therapy not only treats the obvious AKs but also areas with subclinical disease [12].

Conventional photodynamic therapy (c-PDT), a field-directed established therapy, has efficacy rates up to 90% in some studies, but with moderate-intense pain as major side effect [13]. Similar equivalent efficacy to conventional photodynamic therapy has been reported with daylight photodynamic therapy (dl-PDT) for the treatment of actinic keratosis on the face, with less pain and greater patient convenience [14,15].

2. Objective

To compare our results with other studies made on the same topic and evaluate the efficacy of the dl-PDT with confocal microscopy.

3. Materials and methods

All patients provided written informed consent of their participation.

Inclusion criteria were age over 18 and actinic damaged skin with multiple AK in the face or scalp.

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Exclusion criteria included allergy to MAL or his cream ingredients, history of photosensitivity-related disorders, pregnancy and lactation.

Participants qualified for statistical analysis if they fulfilled the criteria and didn't miss the treatment and follow-up consultations.

The study was conducted between April and July 2016, in the Department of Dermatology, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal.

Demographic data of the patients was obtained at the baseline consult. AK were counted and mapped, using an anatomic diagram. An image recording was made. Six patients were randomly selected for confocal microscopy before and after the dl-PDT session. The AKs were imaged with the Vivascope® 1500 and three blocks were taken: intraepidermal, dermoepidermal junction and upper dermis. The honeycomb pattern regularity, presence of parakeratosis, and the presence of high nucleated keratinocytes and inflammation were evaluated.

A daylight photodynamic therapy session was performed. A chemical sunscreen was placed 15 min prior to skin preparation (removal with a curette of the scales and crusts), followed by a thin application, in all the treated area, of a 16% methylaminolevulinate cream (Metvix®). After that, the patients stayed 30 min indoors and subsequently went outside for two hours. After this period they returned indoors and the cream remnant was removed. Finally, our patients were advised to spend the rest of the day indoors. When the temperature was less than 10 °C or an overcast day, the treatment was rescheduled.

Adverse reactions were evaluated after 24 h and one week later. Efficacy was evaluated after 3 months, comparing the number of AK and an iconographic record was made again. Confocal Microscopy was performed in the six selected patients, before and one week and 3 months after treatment.

A questionnaire about the degree of satisfaction with the procedure and presence of pain during it was obtained from all patients. If they had already undergone a c-PDT procedure a comparison was asked.

For statistical analysis we use Statistical Package for the Social Sciences (SPSS inc.), version 23.

4. Results

A total of 25 of 27 patients completed the study and were eligible for statistical analysis. Nineteen (76%) of the patients were male. The mean age was 74.2 (SD 7,2) years. In 13 (52%) patients the treatment site was the scalp, while in 12 (48%) was the face. A total of 114 AKs were treated, 72 AKs grade I, 35 grade II and 7 grade III. Twenty-four hours after the treatment, 23% of the patients had no erythema, 23% had a mild erythema, 42% had a moderate erythema and 12% a severe erythema, with crust formation in 90% of the patients. Mean cure rate at 3 months was 74% and lower in patients with type II and III actinic keratosis. Fifteen patients had a 90% efficacy rate, 4 patients had efficacy rates between 70–89% and 6 patients had efficacy rates between 50–69%. Aesthetic results were excellent in all patients. The pain score was 1.1 in a scale of 0-10. All patients that previously had done c-PDT, preferred dl-PDT instead.

The results from the evaluation with RCM are shown in the Table 1 and Fig. 1. The results seen at one week post-treatment with confocal

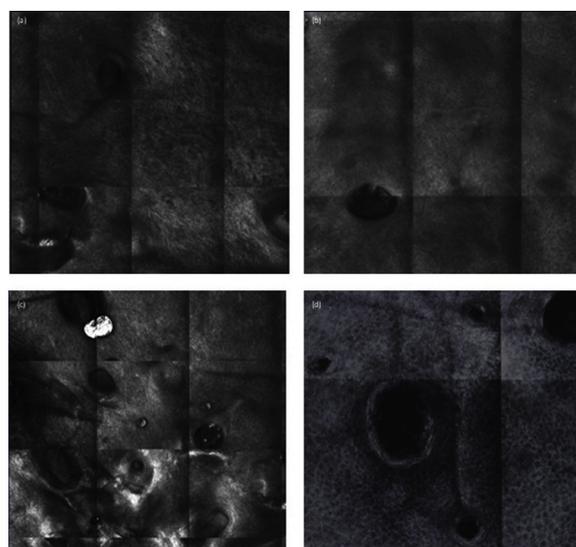


Fig. 1. (a) Mosaic image from the epidermidis before treatment with atypical honeycomb pattern. (c) Mosaic image at level of stratum corneum showing abnormal honeycomb pattern, with some bright areas in the lower part of the image suggesting hiperkeratinization. (b) and (d) Mosaic image after one week of treatment with normalization of the honeycomb pattern.

microscopy remains the same at 3 months evaluation.

5. Discussion

The first studies proving the efficacy and safety of dl-PDT with MAL were conducted in Copenhagen [14–21]. Subsequently other studies where made, namely in Brazil, Europe and Australia [22,23].

Response rates have been similar in various countries [14–23]. In the phase III multicentric study, made in Europe, the mean clearance rate of AK was 75–83% after one treatment for patients with Grade I/II AK [14–21]. In the phase III study made in Australia, the response rate was higher, 89% [23]. As to efficacy both studies didn't demonstrate any statistical difference between c-PDT and dl-PDT [14–21,23].

Pain scores already published with dl-PDT were generally low and some of them report no pain at all, which is a major advantage for dl-PDT versus c-PDT [14–23].

Comparing the evidence already published with our study we found similar efficacy rates (74%) and pain scores (1.1, in a scale of 0–10). All the patients had a good cosmetic result. The main limitation of our study is the small sample size and the lack of a control group.

In regards to confocal microscopy, this technique was used to prove the efficacy of multiple treatments (cryotherapy, imiquimod), but for dl-PDT there is only one study published with 20 patients, demonstrating that *in vivo* confocal microscopy can be a good tool to fill the gap between clinical evaluation and histological evaluation, using the atypical scoring system [24–26].

Our results support the use of this technique to evaluate the results

Table 1
Results from the evaluation of the efficacy of dl-PDT with confocal microscopy.

RCM criteria of AK	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	Before	After										
Scale	+	–	+	–	–	–	+	–	+	–	+	–
Nucleated cells in stratum corneum	+	–	–	–	–	–	–	–	+	–	–	–
Intraepithelial nucleated cells	+	+	+	+	+	+	+	–	+	+	+	+
Atypical honeycomb pattern	+	–	+	–	+	–	+	–	+	–	+	–
Dermal inflammatory cells	+	–	–	–	–	–	–	–	+	+	–	–
Actinic elastosis	+	–	+	–	+	+	+	–	+	–	+	–

with dl-PDT and for follow-up with better accuracy.

6. Conclusion

This study corroborates others already made in this context. This therapy besides having similar results to conventional photodynamic therapy stands out for mild discomfort, fewer adverse effects and a higher rate of cost-effectiveness. Confocal microscopy revealed and incredible utility in the follow-up of these patients, causing no tissue damage and demonstrated a normalization of honeycomb and resolution of AKs faster than the clinical evaluation.

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Declarations of interest

None.

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