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Single versus two-treatment schedule of methyl aminolevulinate daylight photodynamic therapy for actinic keratosis of the face and scalp: An intra-patient randomized trial

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ABSTRACT

Background: Efficacy of daylight-photodynamic therapy (DL-PDT) with methyl aminolaevulinate (MAL) has been reported to gradually decrease as the severity of actinic keratosis (AK) lesions increases. Repeated treatments have been suggested to increase the efficacy of DL-PDT. Aim of our pilot study was to evaluate the efficacy and tolerability of a single versus two-treatment schedule of MAL DL-PDT for the treatment of multiple AKs of the face/scalp in a prospective, intra-patient, comparison study.

Methods: Patients with multiple AKs of the face/scalp received a single treatment of MAL DL-PDT or 2 treatments, 1 week apart, on either half-side. Weather conditions and outdoor temperature were recorded during daylight exposure. Visual analog scale for pain was assessed immediately after each session, and severity of local skin reactions after 2 days. Treatment efficacy was evaluated at 3 months.

Results: Thirty-one patients with multiple AKs of the face/scalp were enrolled and completed the study. No significant difference was observed between single and two-treatment schedule in the lesion complete response rate for total AKs (80.7% vs 85.6%, $p = 0.28$) and for AKs divided by grade (grade I: 88.5% vs 89.2%, $p = 0.79$; grade II: 67.3% vs 71.0%, $p = 0.71$; grade III: 50.0% vs 55.6%, $p \approx 1.00$). Pain was significantly higher during the second session ($p = 0.04$). Local skin reactions were generally mild, but more severe after the first treatment ($p < 0.01$).

Conclusions: The two-treatment schedule did not improve significantly the efficacy of MAL DL-PDT for AKs of the face and scalp as compared to the single-treatment. Alternative strategies might be recommended to optimize the efficacy of DL-PDT.

1. Introduction

Actinic keratoses (AKs) are increasingly becoming a focus for health care systems due to global ageing because of their high prevalence, chronicity and risk of progression to invasive squamous cell carcinoma (SCC), which has been estimated to be 0.60% at 1 year and 2.57% at 4 years [1–3].

AKs often develop as multiple lesions on chronically sun-damaged, field-cancerized skin. The therapeutic approach of AKs has been recently changed by two innovative concepts demonstrating that clinical appearance does not match to the histological grading of AKs [4,5] and that direct transformation from AK I to invasive SCC (differentiated pathway) is more prevalent than sequential progression (classic pathway) as mechanism of transformation of AKs to invasive SCC [6]. Therefore, all AKs present in the cancerization field should be treated, while preserving an appropriate tolerability.

Accumulating evidences from clinical trials and real-world practice indicate that photodynamic therapy (PDT) has become an important treatment strategy for AK and has the potential to reduce/delay the development of new lesions [7,8]. Daylight photodynamic therapy (DL-PDT) is a simple and practical treatment option for AK I and II and for actinic damage of the face and scalp that allows treatment of multiple lesions and large areas with high tolerability [9]. Patient satisfaction and motivation for retreatment with DL-PDT, if needed, are very high [10].

Several randomized comparative studies showed that the overall

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therapeutic efficacy of DL-PDT and conventional PDT (c-PDT) using MAL is comparable for patients with AK I and II [11–16]. Efficacy of DL-PDT has been reported to gradually decrease as the severity of AK lesions increases (grade I to III) with lower complete response rates in moderate to thick AKs than in thin AKs [17]. A recent meta-analysis of randomized controlled trials indeed indicated that the grade of AK lesions affects complete response to DL-PDT [16].

Tarstedt et al. reported that a two-treatment schedule of MAL c-PDT improves lesion complete response rate of thicker AK lesions while it shows similar efficacy to a single treatment for thin lesions [18]. Thus, repeated treatments have been suggested as a procedure that might increase the efficacy also of DL-PDT.

We performed an intra-patient, left-right, prospective, single-center, comparison pilot study to evaluate the efficacy and tolerability of single versus two-treatment schedule of MAL DL-PDT in patients with multiple AKs of the face and scalp.

2. Materials and methods

2.1. Study population

This pilot study was conducted from June to September 2016 at the Department of Dermatology, University of L'Aquila, in Center Italy, and prospectively enrolled patients with a clinical and dermoscopic diagnosis of multiple AKs of the face and scalp. Eligible patients were aged 18 years or older and were required to have two symmetrical target areas with at least 2 grade II (moderately thick) or grade III (thick) AK lesions on each half-side. Basic demographic information, phenotypic characteristics, medical history and sun exposure habits [19] of patients were collected through a standardized questionnaire. Exclusion criteria included all known conditions contraindicated for PDT and patients who underwent AK treatment in the same area or therapy with oral immunosuppressive drugs within the previous 3 months. The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Local Ethics Committee. All subjects provided their written informed consent prior to study entry.

2.2. DL-PDT procedure

At baseline, AK lesions were photographed, counted and mapped using a clear plastic template and graded according to severity [4]. Each patient received both treatment regimens either on the face or scalp: all patients were treated with a single treatment of DL-PDT on one side and 2 treatments, 1 week apart, on the other side according to a randomization procedure. For DL-PDT treatment, an organic sunscreen (Actinica Lotion®, Galderma Laboratories, Paris, France) was applied on all sun-exposed areas and, after 15 min, scales and crusts were gently removed [9]. MAL cream (Metvix®; Galderma) was applied in a 1-mm thick layer to the entire treatment area and left uncovered for 30 min in the dark. Patients then underwent continuous daylight treatment for 2 h in the hospital garden close to the Clinic. The daylight illumination was performed between 11 a.m. and 3 p.m. At the end of daylight exposure, residual MAL cream was wiped off, followed by application of a lenitive cream. Patients were instructed to avoid daylight for the following 24 h. One week later, the same procedure was carried out on the side randomized to 2 DL-PDT treatments while the single-treatment half-side was covered without application of any cream besides sunscreen during daylight exposure. Grading of AK lesions was performed by the same investigator (A.P.) at baseline and at the 3-month follow-up visit while another investigator (C.G.) performed the treatment procedure. On the day of treatment, weather conditions (sunny, partly sunny or cloudy) and outdoor temperature during daylight exposure were recorded by the investigator for each patient. Rainy and very overcast days were avoided.

2.3. Efficacy, safety and satisfaction assessment

Treatment efficacy was evaluated 3 months after last treatment. Our primary endpoint was the proportion of AK lesions with complete response for each treated half-side. AK lesions were identified by using the baseline plastic template and clinical photographs. Lesion complete response was defined as complete disappearance of the lesion, visually and by palpation, although mild erythema might persist. Patients were not evaluated for new lesions in the treatment area.

The subject's assessment of maximal pain immediately after each session of DL-PDT, was recorded using a Visual Analog Scale (VAS). Ratings occurred on a 0–10 scale (0 = no pain, 10 = very severe pain). Local skin reactions (LSR) (erythema, edema, pustular eruption and crusting) were evaluated 2 days after treatment and classified according to severity (none, mild, moderate, and severe).

2.4. Statistical analysis

We computed mean and standard deviations, absolute and relative frequencies to summarize sample characteristics. Treatment efficacy was assessed by computing rates of complete response per 100 lesions-patients, defined by the number of completely responding lesions divided by the number of baseline lesions treated for each individual patient. We compared the efficacy of a single treatment versus 2 treatments of DL-PDT by performing a Poisson random intercept linear mixed model, adjusting for the baseline number of lesions, sex, phototype, and site. Wald statistics assessed the overall model fitting ($\chi 2_{Wald} = 50.15$, $p < 0.01$). The model included an interaction term between treatment and baseline number of lesions before each treatment. The proportion of the total residual variance due to the residual variability between subjects was estimated by means of the intraclass correlation coefficient (ICC = 0.49 ± 0.14). Univariate Wilcoxon as well as Cochrane and McNemar tests were performed to support indications of efficacy and to compare VAS and LSR score differences across treatment groups. Hence, the association between treatment efficacy and the outcome measure (either VAS or LSR) was estimated by Spearman correlation. In general, p values less than 0.05 were considered statistically significant. All statistical analysis was performed using the statistical package STATA (version 14).

3. Results

3.1. Study sample

A total of 31 patients with multiple AKs of the scalp (21 patients, 67.7%) or of the face (10 patients, 32.3%) were enrolled in the study (Table 1). The majority of subjects were men (6 women, 19.4%) and the mean age was 76.8 ± 8.8 years (range 54–94 years). We treated 626 AKs and the majority of the lesions was grade I-II. The total number of AKs per side was similar (single treatment: 10.2 ± 0.6; 2 treatments: 10 ± 0.4, p = 0.90), as well as the proportion of AKs classified by grade. Sample characteristics are detailed in Table 1. Weather was rated as sunny during 27 (87.1%) treatments and cloudy during 4 (12.9%) at the first session of DL-PDT; similarly, it was sunny during 30 (96.8%) treatments and cloudy during 1 (3.2%) at the second session. The mean outdoor temperature was 24.3 °C ± 3.2 (range: 20–29 °C) during the first DL-PDT session and 25.1 °C ± 3.5 (range: 20–29 °C) during the second one. No significant differences in outdoor temperature occurred between the first and the second session (p = 0.22) of DL-PDT.

3.2. Treatment efficacy at 3 months

All patients completed the 3-month follow-up visit. Lesion complete response rate is shown in Table 2. No significant difference was observed in the complete response rate of all grades AK between 1 treatment and 2 treatments of MAL DL-PDT (80.7% vs 85.6%, p = 0.28)

Table 1
Patients' characteristics and distribution of treated lesions per patient by treatment arm.

	Variable	Patients n = 31 (%)
Gender	Men	25 (80.6)
	Women	6 (19.4)
Age (years)	Mean (SD)	76.8 (8.8)
	Min/Max	54-94
BMI	Mean (SD)	25.9 (3.2)
Phototype	II	20 (64.5)
	III	11 (35.5)
Site	Scalp	21 (67.7)
	Face	10 (32.3)
	1 treatment DL-PDT	2 treatments DL-PDT
	Mean (SD)	Mean (SD)
Overall AK	10.2 (0.6)	10 (0.4)
AK I	7.6 (0.6)	7 (0.5)
AK II	2.3 (0.2)	2.6 (0.2)
AK III	0.2 (0.1)	0.4 (0.1)

DL-PDT, Daylight photodynamic therapy; AK, actinic keratosis.

Table 2
Clinical lesion complete response rate per patient by treatment arm 3 months after MAL DL-PDT.

	Baseline AK (n)	Total Complete Response n (%)	Lesion complete response rate		
			1 treatment (%)	2 treatments (%)	*p*
Overall AK	626	518 (82.7)	80.7	85.6	0.28
Grade I AK	454	404 (89.0)	88.5	89.2	0.79
Grade II AK	154	106 (68.8)	67.3	71	0.71
Grade III AK	18	9 (50)	50	55.6	1.00

AK, actinic keratosis.

(Fig. 1) with only an increased trend for the second treatment. A similar result was found for AKs divided by grade (grade I: v. 88.5% vs 89.2%, p = 0.79; grade II: 67.3% vs 71.0%, p = 0.71; grade III: 50.0% vs 55.6%, p ≈ 1.00). Multivariate Poisson regression did not detect statistically significant values for the other predictors included in the model, i.e. sex, phototype, and anatomical site (scalp or head). In addition, pain VAS and severity of LSR did not demonstrate association with efficacy.

Table 3
Local skin reaction prevalence by treatment arm.

Adverse Events		1st treatment n = 31 (%)	2nd treatment n = 31 (%)	p value
Erythema	Mean Score (SE)	1.29 (0.12)	1.06 (0.08)	0.09[a]
	None	3 (9.7)	2 (6.5)	0.08[b]
	Mild	17 (54.8)	25 (80.6)	
	Moderate	11 (35.5)	4 (12.9)	
Edema	Mean Score (SE)	0.45 (0.10)	0.29 (0.08)	0.27[a]
	None	18 (58.1)	22 (71.0)	0.40[b]
	Mild	12 (38.7)	9 (29.0)	
	Moderate	1 (3.2)	0	
Pustular eruption	Mean Score (SE)	0.06 (0.04)	0.0	na
	None	29 (93.5)	31 (100)	na
	Mild	2 (6.5)	0	
	Moderate	0	0	
Crusting	Mean Score (SE)	1.29 (0.11)	0.90 (0.11)	< 0.01[a]
	None	3 (9.7)	8 (25.8)	0.07[b]
	Mild	16 (51.6)	18 (58.1)	
	Moderate	12 (38.7)	5 (16.1)	

p-values from [a]Wilcoxon signed rank test and [b]Chi-square test.

The Poisson counting model detected statistically significant interaction between 1 treatment and 2 treatments and corresponding baseline values, showing a slight advantage, according with the baseline, of 2 treatments compared to 1 treatment, with an estimated advantage of 3% increase in lesion reduction ($RR_{treatment1}$ = 1.10, 95% CI = [1.06, 1.14]; $RR_{treatment2}$ = 1.13, 95% CI = [1.07, 1.18]).

3.3. Safety

The 2nd treatment of MAL DL-PDT was associated with higher pain as compared to the 1st treatment. (ΔVAS = -0.26, p = 0.04). The average subject's reported pain VAS score was 2.58 (SD = 0.99) for the 1st treatment and 2.84 (SD = 0.82) for the 2nd treatment. No adverse event was serious or led to study discontinuation. LSR prevalence is shown in Table 3. LSRs were generally mild but the 1st treatment was associated with increased severity of LSRs than the 2nd treatment (ΔLSR = 0.83, p < 0.01) (Fig. 2). This association was mainly driven by crusting (p < 0.01). This pattern was robust to adjustment for age, sex, phototype, outdoor temperature, and lesion site. Fair skin (p = 0.01) and face location of AKs (p = 0.02) but not age, sex, or weather conditions were associated with the severity of LSRs.

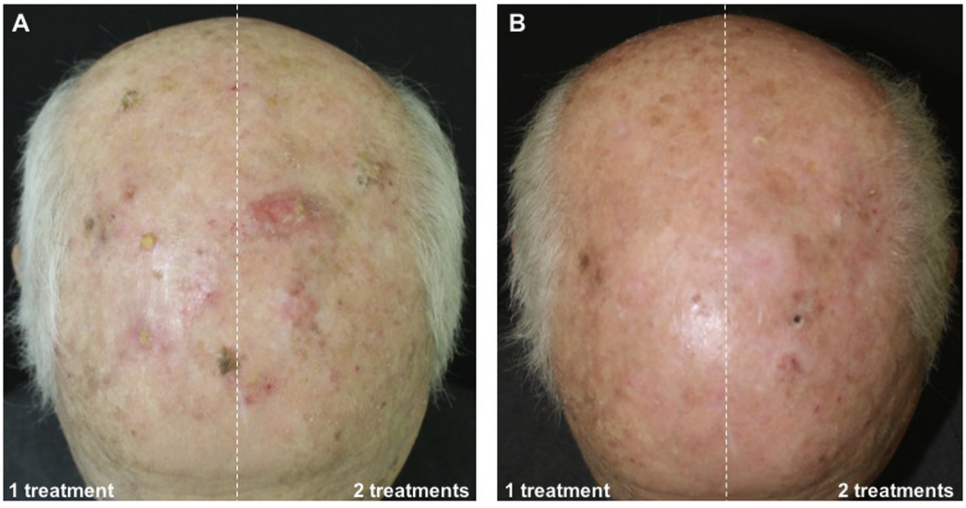

Fig. 1. Multiple AKs of the scalp.
Half-side comparison of single treatment versus two treatments of MAL DL-PDT. Baseline (A) and 3 months (B) after MAL DL-PDT treatment.

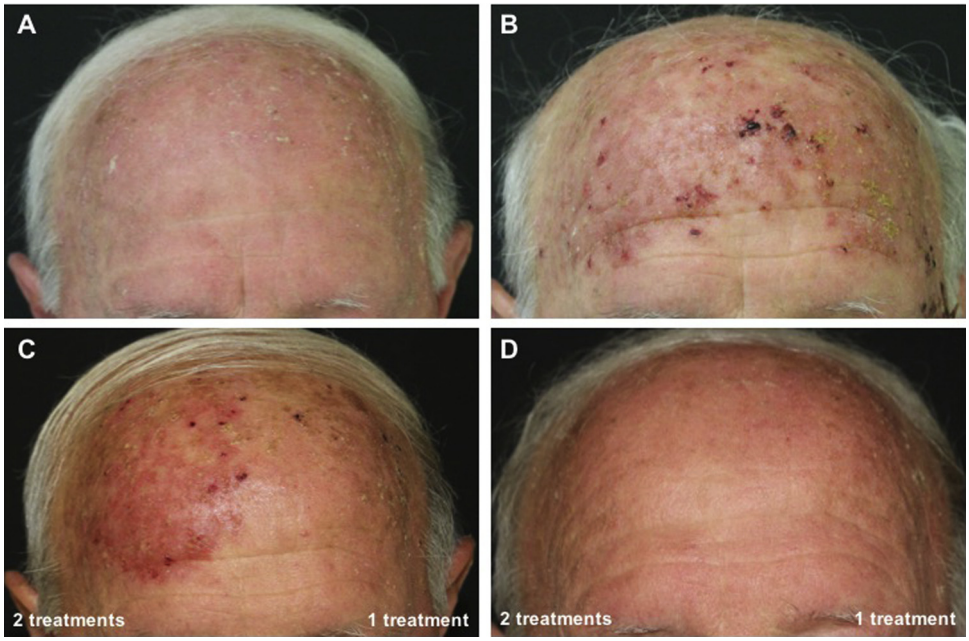

Fig. 2. Local skin reactions after MAL DL-PDT treatment.
A) Baseline; B) 2 days after 1st treatment; C) 2 days after 2nd treatment; D) 3 months after treatment.

4. Discussion

In the present study, we investigated the efficacy and tolerability of a single treatment versus two-treatment schedule of MAL DL-PDT in patients with multiple AKs of the face and scalp. We observed that complete response rate of all grade AKs was similar between 1 and 2 treatments of MAL DL-PDT. An estimated slight advantage of 3% increase in lesion reduction of overall AKs was found for the two-treatment schedule as compared to the single treatment. The 2nd treatment was associated with higher pain and reduced severity of LSR as compared to the 1st treatment.

Randomized controlled trials and real-life evidence suggest that grade of AK lesions may affect complete response to MAL DL-PDT after a single treatment. Efficacy of MAL DL-PDT differed according to the grade of treated AKs in the two pivotal registration trials with 89.2% of the lesions showing complete response in the COMET 1 trial including only mild AKs as compared to 70% in the COMET 2 including both mild and moderate AKs [11,12]. MAL DL-PDT was shown to be less effective for thicker AKs in a monocentric Scandinavian study: the mean lesion response rate was significantly higher in grade I lesions (75.9%) than in grade II (61.2%) and grade III lesions (49.1%) [18]. Our previous study supports that complete response rate of grade II and III AKs is lower than that of grade I lesions after 1 session of MAL DL-PDT (I: 87%; II: 36% and III: 25%) [13]. In a recent meta-analysis including 6 randomized controlled trials for a total of 369 patients with 5556 AK lesions, DL-PDT was non-inferior to c-PDT for complete response in the studies that only included grade I-II AKs but less effective than c-PDT for complete response in studies that also included grade III lesions [16].

Different strategies have been used to potentiate DL-PDT efficacy. Chemical (urea, salicylic acid) or physical (curettage, microdermabrasion, ablative fractional laser, microneedling) pretreatments of AK lesions before DL-PDT have been demonstrated to enhance PpIX production [20–23]. Combination treatment with calcipotriol or 5-fluorouracil prior to DL-PDT have resulted in improved complete response rate when compared to DL-PDT alone [21,24]. Increasing the number of sessions has been suggested to potentially improve the therapeutic efficacy of DL-PDT as previously demonstrated for c-PDT [18]. Tarstedt et al. indeed reported that the single- and two-treatment schedules of MAL c-PDT appeared to be similarly effective for thin lesions (93% vs 89%), while the lesion complete response rate of thicker lesions (70%) improved after a repeated treatment separated by one week (84%) [18]. In our current study, no significant difference was observed in the complete response rate of total AKs and of AKs divided by grade between the two treatment schedules of MAL DL-PDT. An estimated small advantage of 3% increase in lesion reduction was found for the repeated schedule versus the single treatment.

DL-PDT is considered a more convenient option than c-PDT since it is associated with greater tolerability with a significantly reduced maximal pain score and lower occurrence of local adverse events [16]. In our patients, the 2nd treatment of MAL DL-PDT was associated with higher pain than the 1st treatment, thus minimizing the advantages of DL-PDT which is almost painless and its excellent safety profile.

It is a limitation of the present study the low number of AK grade III lesions that did not provide us with an adequate statistical power to compare the two different treatment schedules in this subgroup of lesions. However, the overall number of thick lesions, including both grades II and III, was almost 30% of the total AKs, thus being representative of patients diagnosed in a real-world setting. Finally, we reported the efficacy data at 3 months, since it is considered the optimal time point to evaluate efficacy of DL-PDT.

In conclusion, the two-treatment schedule of DL-PDT with MAL showed similar efficacy to the single-treatment for AKs of the face and scalp. The second treatment was associated with higher pain. Alternative strategies, such as chemical/physical pretreatment or combination therapy, might be recommended to optimize the efficacy of DL-PDT.

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Conflict of interest

MCF and AP received speaker honoraria from Galderma. All the other authors have no conflict of interests to disclose.

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