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Treatment of Bowen's disease with photodynamic therapy. Observational study in 171 patients with 5-aminolaevulinic acid (BF-200 ALA) and methyl aminolaevulinate (MAL)

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ABSTRACT

An observational study was carried out in the photodynamic therapy (PDT) section of Fuenlabrada's hospital (Madrid, Spain). Our goal was to investigate the efficacy and safety of PDT in Bowen's disease (BD). Between June 2011-June 2017 171 patients (191 lesions) with diagnosis of BD were enrolled in the study (95 women and 76 men; average age of 74.31 years). Lesions were treated with one 5-aminolaevulinic acid (BF-200 ALA)-PDT or methyl-5-aminolaevulinate (MAL)-PDT cycle of two sessions in one week. A second treatment cycle was performed in cases of clinical persistence at 12 weeks. Our results showed that 47/55 lesions were resolved (84.75%) after one or two ALA-PDT cycle and 75/136 lesions (55.15%) after one or two MAL-PDT cycles, in the 12-month follow-up. In conclusion PDT is a safe and non-invasive treatment option in BD. In addition, our results suggest a better response with ALA-PDT over MAL-PDT. Limits: observational study with a limited number of patients.

1. Background

Bowen´s disease (BD) is an intraepidermal squamous cell carcinoma (SCC), originally described in 1912 [1]. Photosensitizer precursors used in Europe include methyl-5-aminolaevulinate cream (MAL, Metvix®; Nordic AB,Uppsala, Sweden), 5-aminolaevulinic acid nanoemulsion gel (BF-200 ALA, Ameluz®; Biofrontera AG, Leverkusen, Germany) and a patch containing 5-aminolaevulinic acid (5-ALA, Alacare®; Sprig Pharma AG, Egerkingen, Switzerland).

2. Aims

We designed a prospective observational study in real clinical practice to investigate the efficacy and safety of PDT in BD. The study was carried out according to the ethics principles of the declaration of Helsinki.

3. Methods

3.1. Inclusion criteria

Patients aged 18 years and older, with a clinical, dermoscopic and histological (using a 4 mm punch) diagnosis of BD. All patients received information about the study and gave their informed consent prior to treatment.

3.2. Exclusion criteria

Personal history of porphyria or photosensitivity, presence of a genetic skin cancer disorder, allergic reaction to ingredients of the photosensitizer's precursor, immunosuppression, pregnancy or lactation and history of previous treatment on BD lesions.

3.3. Clinical protocol

Photosensitizer precursors employed were 5-aminolevulinic acid

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(BF-200 ALA, Ameluz®) and methyl-aminolevulinate (MAL, Metvix®). The choice of using ALA- or MAL-PDT was made based on the preferences of the prescribing physician, and not depending on the lesion or patient features. All lesions were treated with one ALA-PDT or MAL-PDT cycle of two sessions in one week. The photosensitizer precursor was applied for 3 h under occlusion. Later, lesions were illuminated with the same LED lamp emitting red light (635 nm wavelength) for 8 min, reaching a final total dose of 37 J/cm^2. A second treatment cycle, with the same photosensitizer's precursor, was performed in cases of clinical persistence at 12 weeks. Follow-up was made at 12, 24 and 52 weeks after last session.

4. Results

Between June 2011 and June 2017, a total of 171 patients (191 lesions) were enrolled in the study. By sex, 95 women and 76 men. Average age 74.31 years. By location 93 head and neck lesions, 58 lower extremity lesions, 19 upper extremity lesions, 15 trunk lesions and 6 genital lesions. A total of 55 lesions were treated with ALA-PDT and 136 with MAL-PDT. 41/55 lesions presented clinical and dermoscopic complete clearance after one ALA-PDT cycle. 48/55 lesions were resolved after two ALA-PDT cycles. In the 12-month follow-up one recurrence was reported, so a final clearance rate of 84.75% (47/55 lesions) was achieved. 78/136 lesions presented clinical and dermoscopic clearance after one MAL-PDT cycle. 104/136 lesions were resolved after two MAL-PDT cycles. However, in the 12-month follow-up we obtained a high recurrence rate (29/104 lesions; 27.88%), so the final clearance rate at 12 months was 55.15% (75/136 lesions). Histological resolution was confirmed in 60% of patients (without differences between one or the other precursor); rest of them rejected the post-treatment biopsy.

To perform the statistical analysis we use the statistical software SPSS 21®. First, we carried out a Kolmogorov-Smirnov test demonstrating that data do not follow the normal distribution. Then we performed a Chi-squared test comparing photosensitizer precursors to resolution of Bowen's disease. This test reject the independence between both variables, obtaining a p-value < 0.001 (99.9% confidence interval). Thus, ALA-PDT is greater associated to complete clinical clearance than MAL-PDT (Fig. 1). This statistical trend is maintained in the analysis by subgroups according to the location of the lesion, age and sex (although the limited number of patients not allowed statistical significance in some of the subgroups analyzed) (Table 1).

Safety: pain rates were assessed following the visual analogue scale (VAS, 0–10). Low scores (VAS, 0–3) were presented in 58% from ALA-PDT group and in 52% from MAL-PDT group. Medium scores (VAS, 4–7) were presented in 35% from ALA-PDT group and 39% from MAL-PDT group. High scores (VAS, 8–10) were presented in 7% from ALA-PDT group and 9% from MAL-PDT group. Treatment was interrupted due to severe pain in 3 patients from the ALA-PDT (5.45%) group and in 3 patients from the MAL-PDT group (2.21%). These results do not show significant differences between one or another drug in terms of pain. Erythema (43.63%), desquamation (32.73%) and superficial wounds (10.91%) were the most frequent side effects from ALA-PDT group. Erythema (41.91%), desquamation (37.5%) and superficial wounds (13.97%) were also the most frequent side effects from MAL-PDT group. Long-term complications were not reported in either of the two treatment groups.

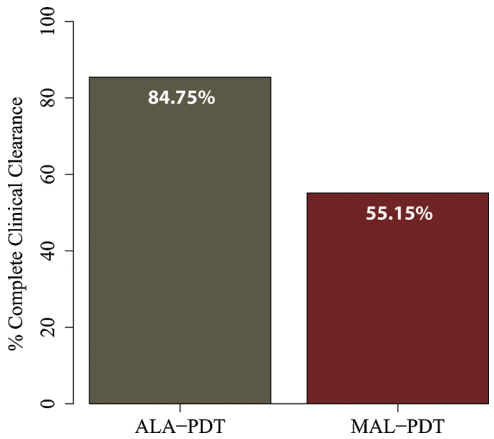

Fig. 1. Percentage of lesion complete clearance rate at 12 months between ALA-PDT and MAL-PDT. MAL: methyl-aminolevulinic acid. ALA: 5-aminolevulinic acid. PDT: photodynamic therapy.

Table 1
Percentages of complete clinical clearance per photosensitizer precursor and subgroup. MAL: methyl-aminolevulinic acid. ALA: 5-aminolevulinic acid. PDT: photodynamic therapy.

	MAL-PDT (nº lesions = 136)	ALA-PDT (nº lesions = 55)
Age, n (%)		
< 61	10/16 (62.50)	4/4 (100)
61-70	20/35 (57.14)	12/14 (85.71)
71-80	22/37 (62.16)	20/22 (90.90)
81-90	20/41 (48.78)	11/15 (73.33)
> 90	3/7 (42.86)	na
Sex, n (%)		
Male	35/58 (60.34)	24/30 (80)
Female	40/78 (51.28)	23/25 (92)
Lesion location, n (%)		
Head and neck	37/61 (60.66)	29/32 (90.63)
Lower extremities	20/47 (42.55)	9/11 (81.82)
Upper extremities	9/13 (69.23)	4/6 (66.67)
Trunk	8/11 (72.73)	3/4 (75)
Genital	2/4 (50)	1/2 (50)

5. Conclusion

There are several alternatives for treatment of BD [2,3], although guidelines for the management of BD of the British Association of Dermatologists [4] consider PDT with the highest strength of recommendation (A) over the rest of therapeutic options.

To our knowledge, only one comparative study, by Tarstedt et al [5], between MAL-PDT and ALA-PDT for BD treatment has been published. In this study 9 patients were treated with ALA-PDT and 18 patients with MAL-PDT. Results showed clinical clearance of 89% with ALA-PDT and 78% with MAL-PDT without statistically significant differences. However, these results cannot be compared with those of our work, since in the Tarstedt study, 5-aminolevulinic acid was prepared by the hospital pharmacy (ALA cream as 20% aminolevulinic acid hydrochloride in a standard ointment), while we use the commercial formulation BF-200 ALA.

In addition, a review of cases series has recently been published [6]. In this paper authors analyse the efficacy of ALA-PDT or MAL-PDT in 12 groups of patients. The clinical clearance rates are between 66% and 97% according to the different series, with a recurrence rate ranging from 0% to 31%. However, as in the study of Tarstedt, the 5-aminolevulinic acid formulations employed are not the same as the one used in our study.

We can conclude that PDT is a safe and non-invasive treatment option in BD. Our results suggest a higher rate of complete clinical clearance with BF-200 ALA-PDT over MAL-PDT, at 12 months of follow-up. In most patients, tolerance to the therapy was good or regular, with no significant differences between the two groups. No long-term adverse effects were reported. However, it is a not randomized observational study and these data should be confirmed with experimental studies with a larger number of patients.

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Declaration of Competing Interest

None of the authors has any conflict of interest to be disclosed.

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