COMPARISON OF TOPICAL METHYL AMINOLEVULINATE PHOTODYNAMIC THERAPY VERSUS PLACEBO PHOTODYNAMIC THERAPY IN NODULAR BCC

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INTRODUCTION

Basal cell carcinoma (BCC) is a frequent skin malignancy, and accounts for approximately 75% of all non-melanoma skin cancers, affecting mostly the head and neck in fair-skinned individuals.

Simple surgical excision is currently regarded as the treatment of choice; however, cosmetic outcome is often less than optimal. Photodynamic therapy (PDT) is a treatment modality, involving the activation of a photosensitizing agent by light, leading to the formation of reactive oxygen species. This process results in local tissue destruction and may, therefore, offer an attractive alternative to surgery. Application of methyl aminolevulinate (MAL) leads to the selective formation of photoactive porphyrins in tumor cells. Previous clinical experience has been promising and patients with nodular BCC (nBCC) were recruited for participation in this multicenter, randomized trial to assess the efficacy, safety and cosmetic outcome of MAL-PDT.[1-5]

OBJECTIVE

To investigate the efficacy, safety and cosmetic outcome of MAL-PDT.

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled comparison.

Patient selection

- Females and males above 18 years with primary nBCC, histologically verified by punch biopsy. Patients with lesions in mid-face, large, recurrent or morphemic lesions were excluded from the study.

Treatment

- Patients were randomized to PDT with either MAL or placebo cream (Figure 1). Surface debridement (up to 4 times) was performed prior to cream application (Figure 2). All eligible lesions within a patient were given the same treatment (MAL or placebo). PDT (red light (570-670 nm) and total light dose of 75 J/cm^2) was performed after 3 hours of application of MAL or placebo cream.
- After three months, lesions with no clinical response or progression were surgically excised and lesions with partial response were re-treated.
- nBCC manifesting complete clinical response (CCR) at 6 months after last treatment were excised to determine the complete histologic response (CHR).
- The specimen so obtained was sliced into sections not more than 3 mm thick. The center of each specimen was sequentially sectioned in 1 mm increments for the first 3 mm in either direction from the center. The remainder of the specimen was sectioned every 3 mm.

Efficacy assessment

- The histological lesion CR rate;
- The clinical lesion CR rate;
- The cosmetic outcome 3 and 6 months after last PDT.

Safety

- Tolerability up to 6 months after the last treatment.

RESULTS

Patient disposition

- A total of 65 patients were included in the study: 33 patients (51%) with MAL-PDT and 32 patients (49%) with placebo PDT (Figure 3);
- No statistically significant difference at inclusion between the treatment groups was found with respect to gender, age or skin type (Table 1);
- One patient in the placebo group was lost to follow-up and discontinued the study prematurely;
- The 65 patients included in the study had a total of 86 lesions (45 lesions for the 33 MAL-PDT patients and the 32 patients treated with placebo-PDT had 41 lesions). Six of these lesions (7%) were not treated, as they were not nBCC as revealed by histological diagnosis (4 in the MAL-PDT group and 2 in the placebo group). These lesions were excluded from all analyses;
- 41 BCC lesions received 2 treatments (1 week apart) of MAL-PDT and 39 BCC 2 treatments of placebo cream PDT.

Efficacy

At the end of the study:

- The overall lesion CHR was 78% (32/41) for MAL-PDT vs 33% (13/39) for placebo-PDT (Figure 3);
- The overall lesion CCR was 80% (33/41) for MAL-PDT vs 51% (20/39) for placebo-PDT (Figure 4);
- In the MAL-PDT group, among the 32 lesions assessed as clinically cured, 28 (87.5%) had no signs of malignancy at histological evaluation, suggesting that approximately 12.5% could potentially show up as clinical recurrences later, if they had not been excised;
- Among sites showing CCR, investigator-assessed cosmetic outcome was excellent or good in 93% of MAL-PDT sites versus 90% for placebo-PDT sites;
- CCR with MAL-PDT was significantly superior ($p<0.001$) compared to placebo-PDT;
- There was no indication that the histological aspect of the non-responder lesions differed from the initial aspect. Lesions did not show a more agressive aspect.

Safety

No systemic adverse reactions occurred in either treatment group. Local AEs were common, with 91% in the MAL-PDT group and 75% in the placebo group. Mild to moderate erythema, burning, stinging, and pain occurred in both groups. Median duration of pain was 2 days after MAL-PDT versus 3-6 days after placebo-PDT. All serious AEs in both groups were unrelated to treatment.

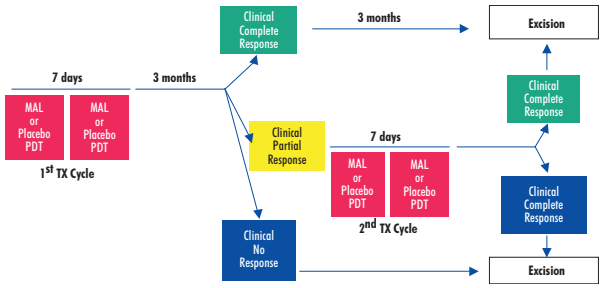
PATIENT DISPOSITION

Table 1

Demographic Parameter	MAL-PDT N=33 n (%)	Placebo-PDT N=32 n (%)	Total (N=65) n (%)
Gender			
Male	25 (76%)	25 (78%)	50 (77%)
Female	8 (24%)	7 (22%)	5 (23%)
Race			
Caucasian	33 (100%)	32 (100%)	65 (100%)
Age (years)			
Mean	62.0	67	65.0
SD	14	14	14
Minimum	28	28	28
Median	62	62	65
Maximum	88	88	88
Skin Phototype			
I	11 (33%)	8 (25%)	19 (29%)
II	16 (48%)	16 (50%)	32 (49%)
III	4 (12%)	5(16%)	9 (14%)
IV	2 (6%)	3(9%)	5 (8%)

Figure 1

SEQUENCE AND DURATION OF STUDY PERIODS



LESION PREPARATION AND CREAM APPLICATION

Figure 2

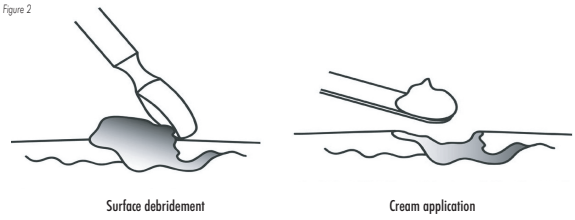
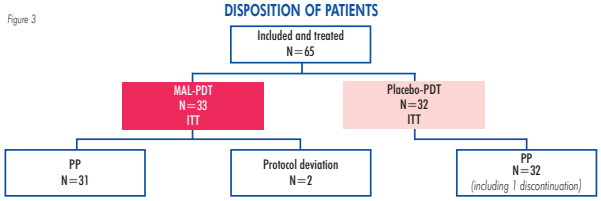


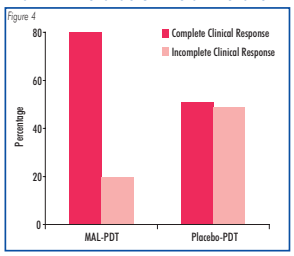
Figure 3

DISPOSITION OF PATIENTS



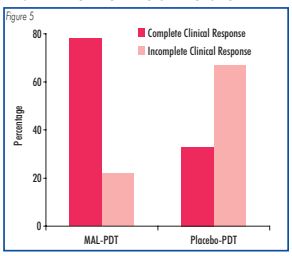
OVERALL HISTOLOGICAL LESION RESPONSE

Figure 4



OVERALL CLINICAL LESION RESPONSE RATE

Figure 5



PATIENT AT BASELINE AND 6 MONTHS AFTER TREATMENT WITH MAL-PDT

Figure 6

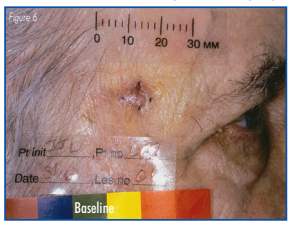
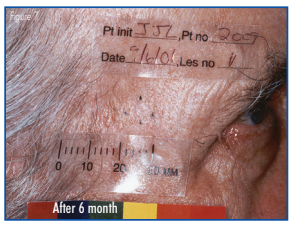


Figure 7



CONCLUSIONS

- MAL-PDT is significantly superior ($p<0.001$) in the treatment of nBCC compared to placebo-PDT.
- Photodynamic therapy with MAL is efficient and safe.
- The cosmetic outcome with MAL-PDT is excellent.

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