

Methyl-aminolevulinate photodynamic therapy for the treatment of actinic cheilitis: a retrospective evaluation of 29 patients

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Aim. Multiple treatment modalities have been proposed for actinic cheilitis (AC), and topical photodynamic therapy (PDT) has recently been included among these modalities. We report our experience with PDT using methyl-aminolevulinate (MAL) in AC.

Methods. We performed a retrospective analysis of 29 patients who had undergone MAL-PDT for treatment of AC: 4 patients received one single session and 25 patients two consecutive weekly sessions.

Results. At 3 months, 21 patients (72%) obtained a complete clinical response, which was sustained over a follow-up period of 6-36 months (mean, 20 months) in 20 patients. Cosmetic outcome was generally rated as good or very good. Transient local adverse events related to the procedure were common and mild to moderate in the majority of cases.

Conclusion. Our preliminary experience suggests that MAL-PDT may be considered a valid modality for the treatment of AC, although long-term follow-up studies in large patient series are required to obtain precise data about clinical and histological recurrences.

KEY WORDS: Photochemotherapy - Methyl 5-aminolevulinate - Actinic cheilitis.

Topical photodynamic therapy (PDT) is a therapeutic procedure based on the application to the skin of a photosensitizer which is subsequently activated by light energy, thus producing a photodynamic reaction that is cytotoxic and vasculotoxic.^{1, 2} PDT has become an established treatment modality

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for actinic keratosis and nonmelanoma skin cancers, thanks to the minimal invasiveness of the procedure, and the ability to achieve high response rate and favourable cosmetic outcome.^{3, 4} Preliminary reports have proposed PDT as a new therapeutic approach to actinic cheilitis (AC).⁵⁻¹⁰

We describe the cumulative results obtained in a series of patients with AC treated with PDT using methyl-aminolevulinate (MAL), the methyl ester of the porphyrin precursor 5-aminolevulinic acid.

Materials and methods

We performed a retrospective chart review involving patients with AC who had undergone treatment with MAL-PDT in a hospital outpatient setting. The patient series consisted of 29 subjects, 20 males and 9 females, with a mean age of 71.5 years (range, 53-88 years). AC was diagnosed clinically in all cases, with histological confirmation required in 6 cases. None of the patients presented any known contraindication to the use of PDT. Ten patients had never used any treatment for their AC in the past, whereas 19 patients had previously been treated with other therapeutic modalities (cryosurgery, topical 5-fluorouracil and/or imiquimod cream) without any sub-

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stantial benefit, and such treatments were interrupted at least two months before the baseline evaluation. An informed consent was obtained prior to PDT treatment. Scales and crusts, when present, were gently removed. Subsequently, a thick layer (approximately 1 mm) of MAL 160 mg/g cream (Metvix®, Galderma Italy) was applied for 2-3 hours. Thereafter, the skin was exposed to red light (Aktilite CL 128, PhotoCure ASA, Oslo, Norway) at a fluence of 37 J/cm². As concerns the application time of the cream, it lasted 3 hours in the first 3 patients but was then reduced to 2 hours in order to improve the tolerability. All subjects were instructed to apply local antiseptics and topical preparations containing antibiotics and corticosteroids for 5-7 days after the therapeutic procedure.

Patients were evaluated one week after the first MAL-PDT session, when a second session was performed as needed. In the post-treatment phase, patients were assessed monthly during the initial 3 months and every 3 months thereafter.

Information on safety and tolerability of MAL-PDT treatment was also collected.

Results

Of the 29 patients examined, 25 patients underwent two consecutive weekly MAL-PDT sessions, whereas only one session was performed in 4 patients. At 3 months, complete remission of AC was achieved in 21 patients (72%), a partial response (with a moderate to good improvement) was observed in 4 subjects, whereas 3 patients did not have any noticeable clinical change and a patient presented even an evident enlargement of AC lesions as compared to baseline. Most patients who were partial responders or non-responders received alternative treatment modalities. Among patients with an initial complete response, 20 of them remained disease-free over a follow-up period of 6 to 36 months (mean, 20 months), while a patient showed signs of clinical recurrence of AC 30 months after treatment.

Regardless of clinical outcome, cosmetic results were rated as good to excellent in 28 patients (97%). Only a patient developed scarring within the treated area.

The most frequent adverse events were transient and related to the procedure. Erythema was observed in 24 patients, edema in 19 patients, and erosions or

ulcerative lesions in 16 patients. In patients in whom the time of MAL cream application lasted 3 hours, oedema and blistering were particularly intense. Twenty-six patients complained of pain or burning sensation during the procedure. Such symptoms were graded as mild and tolerable in 11 cases, moderate (requiring irradiation period to be split) in 9 cases, and severe (requiring temporary discontinuation of illumination, application of cold dressings and air cooling) in 6 patients.

Discussion

AC is a common premalignant condition which can progress into invasive squamous cell carcinoma. Effective treatment is mandatory in order to minimise the risk of malignant transformation.¹¹ Multiple treatment methods have been reported for AC, including cryosurgery, electrosurgery, carbon dioxide laser ablation, 5-fluorouracil, imiquimod or scalpel vermilionectomy, which are aimed at inducing destruction/removal of the damaged epithelium.

PDT has been proposed as a therapeutic intervention for AC, as suggested by case reports and open-label studies,⁵⁻¹⁰ which have however considered different treatment protocols and photosensitizers, including 5-aminolevulinic acid (ALA), MAL and methylaminooxopentanoate. The largest study population evaluated until recently is that described by Sotiriou *et al* in 2010,¹⁰ consisting of 38 patients with AC who received two ALA-PDT sessions at 2-week interval. These authors noted a complete clinical response at 3 months in 68% of cases, being this rate almost similar to our results, whereas at 18 months the clinical recurrence and histological recurrence rates reported by the Greek colleagues were 15.4% and 34.6%, respectively.¹⁰

In our preliminary experience, the cosmetic outcome was very favourable and the recurrence rate appeared to be particularly low, with only a patient presenting with signs of recurrence among complete responders examined over an average follow-up period of 20 months.

Local transient reactions due to the procedure occurred in the majority of our patients. These reactions were mild to moderate in many cases. The development of severe pain, oedema and blistering in the initial 3 patients in whom MAL cream was applied for

3 hours prior to the illumination led us to modify our treatment protocol, changing the application time of the cream to 2 hours, with an overall improvement of the tolerability profile of the procedure.

Conclusions

Our study have several limitations, including the retrospective design, the small patient sample, the short follow-up period, and the absence of histological assessment of response. Nevertheless, awaiting more precise information from long-term follow-up experiences in large patient populations and taking into account that treatment procedure and protocols require optimization, our preliminary results suggest that MAL-PDT may be considered a new valid therapeutic approach to AC, showing an excellent cosmetic outcome and a sustained clinical response in most patients.

Riassunto

Terapia fotodinamica con acido metil-aminolevulinico per il trattamento della cheilite attinica: valutazione retrospettiva di 29 pazienti

Obiettivo. Numerosi approcci terapeutici sono stati proposti per il trattamento della cheilite attinica (CA) e, tra questi, è stata inclusa recentemente la terapia fotodinamica (PDT). Riportiamo la nostra esperienza relativa al trattamento della CA con PDT ed acido metil-aminolevulinico topico (MAL).

Metodi. È stata eseguita un'analisi retrospettiva di 29 pazienti con CA che erano stati sottoposti a trattamento con MAL-PDT: 4 erano stati trattati con una singola seduta e 25 con due sedute settimanali consecutive.

Risultati. A 3 mesi, 21 pazienti (72%) hanno ottenuto una risposta clinica completa, che si è mantenuta in 20 pazienti nell'arco di un periodo di follow-up della durata media di 20 mesi (range: 6-36 mesi). Il risultato cosmetico è stato giudicato buono o molto buono nella maggioranza

dei pazienti. Eventi avversi locali transitori, correlati alla procedura, sono stati piuttosto frequenti e di entità lieve-moderata in gran parte dei casi.

Conclusione. La nostra esperienza preliminare suggerisce che il trattamento con MAL-PDT può essere considerato un valido approccio alla CA, sebbene siano necessarie valutazioni a lungo termine in un numero consistente di pazienti per delineare dati precisi sul tasso di recidiva clinica ed istologica.

PAROLE CHIAVE: Terapia fotodinamica - 5-metil-aminolevulinato - Cheilite attinica.

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