Comparison of Topical Methyl Aminolevulinate Photodynamic Therapy With Cryotherapy or Fluorouracil for Treatment of Squamous Cell Carcinoma In Situ

Results of a Multicenter Randomized Trial

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Objective: To compare the efficacy, tolerability, and cosmetic outcome of photodynamic therapy (PDT) using topical methyl aminolevulinate with cryotherapy or topical fluorouracil for treatment of squamous cell carcinoma in situ.

Design: Randomized, placebo-controlled study, with follow-up at 3 and 12 months after last treatment.

Setting: Forty outpatient dermatology centers in 11 European countries.

Patients: Random sample of 225 patients with histologically confirmed squamous cell carcinoma in situ (lesion size, 6-40 mm) and no evidence of progression.

Interventions: Treatment with PDT with methyl aminolevulinate (160 mg/g; n=96) or matching placebo cream (n=17), cryotherapy (n=82), or topical fluorouracil (5% cream; n=30). Methyl aminolevulinate or placebo cream was applied for 3 hours before illumination with broad-band red light (75 J/cm², 570-670 nm). Treatment was repeated 1 week later. Cryotherapy was performed with liquid nitrogen spray. Fluorouracil was applied for 4 weeks. Lesions with a partial response at 3 months were re-treated.

Main Outcome Measures: Clinically verified complete response of lesions; blinded and on-site assessment of cosmetic outcome (4-point rating scale).

Results: At 12 months, the estimated sustained lesion complete response rate with methyl aminolevulinate PDT was superior to that with cryotherapy (80% vs 67%; odds ratio, 1.77; 95% confidence interval, 1.01-3.12; P=.047), and better than that with fluorouracil (80% vs 69%; odds ratio, 1.64; 95% confidence interval, 0.78-3.45; P=.19). Cosmetic outcome at 3 months was good or excellent in 94% of patients treated with methyl aminolevulinate PDT vs 66% with cryotherapy and 76% with fluorouracil, and was maintained at 12 months.

Conclusion: Methyl aminolevulinate PDT is an effective treatment option for squamous cell carcinoma in situ, with excellent cosmesis.

Arch Dermatol. 2006;142:729-735

ONMELANOMA SKIN CANCER, including intraepithelial squamous cell carcinoma (SCC in situ), is the most common cancer in white persons, particularly in northwestern Europe,¹ the United States,² and Australia,³ and the incidence continues to rise.⁴ Squamous cell carcinoma in situ is especially common in elderly patients, typically occurring on the lower part of the legs.³ The condition is associated with a small risk of progression (about 3%).⁵ Current treatment guidelines⁷ suggest that the available treatment options (including cryotherapy, curettage, excision, and topical fluorouracil) are broadly similar in efficacy, with recurrence rates of about 5% to 10% at 12 months. However, cryotherapy can be painful (up to 10-fold higher risk of pain than with curettage⁶), which may limit treatment of multiple lesions, and healing, particularly of large lesions, can be slow (up to 3 months⁸). Topical fluorouracil can require prolonged treatment and typically causes local irritation.⁷ Photodynamic therapy (PDT) is a noninvasive and precisely directed treatment that...
METHODS

PATIENTS

Patients 18 years or older with histologically confirmed diagnosis of SCC in situ from a biopsy specimen taken within 5 months, and with no evidence of any change in appearance suggestive of lesion progression, were enrolled in 40 hospital outpatient dermatology clinics in 11 European countries. Lesions that had been treated within the previous 3 months or that were strongly pigmented, less than 6 mm or more than 40 mm in diameter, or located on the genitalia were excluded. The study was approved by the ethics committee responsible for each center, and all patients gave written informed consent.

PROCEDURES

Eligible patients were randomized to PDT with topical methyl aminolevulinate cream, 160 mg/g (Metvix; PhotoCure ASA, Oslo, Norway/Galderma SA, Paris, France), or matching placebo cream in a double-blinded fashion, or standard therapy chosen by the treating investigator (cryotherapy or fluorouracil).

TREATMENTS

Before application of methyl aminolevulinate or placebo cream, the lesions were prepared by gentle surface debridement with a curette. Methyl aminolevulinate PDT was performed as previously described. Briefly, the cream was applied to the lesions for 4 hours, then washed off with 0.9% saline solution before illumination with noncoherent red light (CureLight lamp, PhotoCure ASA; wavelength, 670-670 nm; light dose, 75 J/cm²). Patients wore protective eyewear when lesions close to the eyes were treated. Treatment was repeated once after 1 week for a complete treatment cycle.

Cryotherapy was performed with a handheld liquid nitrogen spray, using a single freeze/thaw cycle. After an initial ice field formation with a 2-mm rim of clinically healthy tissue, the ice field was maintained for a minimum of 20 seconds. Topical 5% fluorouracil cream (Efudix; Valeant Pharmaceuticals International, Basingstoke, England) was applied for 4 weeks, once daily during the first week and twice daily thereafter. Patients attended the clinic at weeks 0, 1, and 4, and completed a diary noting the date and time of each application of cream. In each group, lesions with a partial response (described in the next section) at 12 weeks were retreated.

STATISTICAL ANALYSIS

Assuming that the patient complete response rate with methyl aminolevulinate PDT and standard therapy (cryotherapy or fluorouracil) was 85%, at least 90 patients were required in each active treatment group (methyl aminolevulinate PDT and standard therapy) to be able to show with an $\alpha$ of 5% and a power of 90% that methyl aminolevulinate PDT was no more than 15% inferior to standard therapy. In addition, assuming that the patient complete response rate with placebo PDT was 35%, at least 15 patients were required in this group ($\alpha$, 5%; power, 90%).

Efficacy analyses were based on the per-protocol population, excluding patients in whom the diagnosis of SCC in situ was not confirmed or who received less than 50% of fluorouracil medication and only 1 treatment in the first PDT cycle.

**Figure 1.** Disposition of patients in the study. MAL indicates methyl aminolevulinate; PDT, photodynamic therapy; and PP, per protocol.
and patients or lesions with missing response assessment at 3 months. The complete lesion response rate was analyzed by a time-to-failure approach. For lesions that did not respond completely at 3 months, failure time was recorded as 3 months, and for lesions recurrent at the 12-month assessment, the failure time was 12 months. Factors of influence were analyzed by means of a complementary log-log model and logistic regression model with maximum lesion diameter as the covariate. The odds ratio for complete response (methyl aminolevulinate PDT vs standard therapy) and the corresponding 95% confidence interval (CI) were calculated by the method proposed by Guo and Lin. Cosmetic outcome was summarized with 95% CI, with the use of Clopper-Pearson CI for the rates.

**RESULTS**

Of 229 patients enrolled in the study, 225 had at least 1 lesion treated; 96 (43%) with 124 lesions were treated with methyl aminolevulinate PDT, 17 (8%) with 24 lesions were treated with placebo PDT, 82 (36%) with 91 lesions were treated with cryotherapy, and 30 (13%) with 36 lesions were treated with topical fluorouracil. Four randomized patients were not treated: 3 patients allocated to methyl aminolevulinate PDT (2 withdrew consent and 1 had a spontaneous remission) and 1 patient allocated to fluorouracil who was unavailable for follow-up.

Patient disposition is summarized in Figure 1. Sixteen patients were excluded from the per-protocol population: 5 treated with methyl aminolevulinate PDT, 2 with placebo PDT, 5 with cryotherapy, and 4 with fluorouracil. In total, 31 lesions were excluded from the per-protocol population: 13 treated with methyl aminolevulinate PDT, 5 with placebo PDT, 6 with cryotherapy, and 7 with fluorouracil. Patient and lesion characteristics of the 4 treatment groups were similar (Table 1).

Treatment was administered as per protocol, with a mean illumination time of 10 minutes 37 seconds and mean light dose of 75 J/cm² (methyl aminolevulinate PDT), mean total freezing time of 25 seconds (cryotherapy), and mean number of fluorouracil applications of 42 and 45 in the first and second treatment periods, respectively. Most lesions were treated with 1 methyl aminolevulinate PDT treatment cycle (84%), 1 cryotherapy session (71%), and 1 fluorouracil treatment period (72%) (Table 2).

**LESION COMPLETE RESPONSE RATES**

The clinically verified complete response rate of lesions 3 months after last treatment was 93% (103/111) in the methyl aminolevulinate PDT group, 21% (4/19) in the placebo PDT group, 86% (73/85) in the cryotherapy group, and 83% (24/29) in the fluorouracil group (Table 3). The estimated sustained complete response rate of lesions at 12 months was 80% in the methyl aminolevulinate PDT group, 67% in the cryotherapy group, and 69% in the fluorouracil group (Figure 2), with a statistically significant difference between methyl aminolevulinate PDT and the combined standard therapy group (odds ratio, 1.73; 95% CI, 1.03-2.93; P = .04). The odds for a lesion to be in complete response after 12 months were 73% higher in the methyl aminolevulinate PDT group than in the standard therapy group. On further analysis, methyl aminolevulinate PDT was significantly different from cryotherapy (odds ratio, 1.77; 95% CI, 1.01-3.12; P = .047), although methyl aminolevulinate PDT and fluorouracil did not differ signifi-

### Table 1. Patient and Lesion Characteristics at Baseline, All Patients Treated

<table>
<thead>
<tr>
<th></th>
<th>MAL PDT (n = 96)</th>
<th>Placebo PDT (n = 17)</th>
<th>Cryotherapy (n = 82)</th>
<th>Topical Fluorouracil (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>71.9 (43-89)</td>
<td>73.4 (53-88)</td>
<td>74.0 (45-99)</td>
<td>72.5 (39-86)</td>
</tr>
<tr>
<td>Race, No. (%) white</td>
<td>68 (71)</td>
<td>14 (82)</td>
<td>56 (88)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Skin type (Fitzpatrick score), No. (%)</td>
<td>10 (10)</td>
<td>4 (24)</td>
<td>3 (4)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>I</td>
<td>45 (47)</td>
<td>9 (53)</td>
<td>40 (49)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>II</td>
<td>36 (38)</td>
<td>3 (18)</td>
<td>32 (39)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>IV/ V</td>
<td>5 (6)</td>
<td>1 (6)</td>
<td>7 (9)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Total No. of lesions</td>
<td>124</td>
<td>24</td>
<td>91</td>
<td>36</td>
</tr>
<tr>
<td>No. of lesions per patient, No. (%)</td>
<td>1 (84)</td>
<td>13 (76)</td>
<td>77 (94)</td>
<td>26 (87)</td>
</tr>
<tr>
<td>2</td>
<td>8 (8)</td>
<td>2 (12)</td>
<td>2 (2)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>3</td>
<td>7 (7)</td>
<td>2 (12)</td>
<td>3 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Largest lesion diameter, mean (range), mm</td>
<td>18.9 (5-40)</td>
<td>19.3 (8-40)</td>
<td>19.4 (6-45)</td>
<td>20.9 (9-37)</td>
</tr>
<tr>
<td>Lesion size, No. (%), mm</td>
<td>5-14</td>
<td>48 (39)</td>
<td>8 (33)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>15-29</td>
<td>54 (44)</td>
<td>12 (50)</td>
<td>52 (57)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>≥30</td>
<td>22 (18)</td>
<td>4 (17)</td>
<td>11 (12)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Lesion location, No. (%)</td>
<td>Face, scalp</td>
<td>29 (23)</td>
<td>6 (25)</td>
<td>26 (29)</td>
</tr>
<tr>
<td>Neck, trunk</td>
<td>15 (12)</td>
<td>2 (8)</td>
<td>13 (14)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Extremities</td>
<td>80 (65)</td>
<td>16 (67)</td>
<td>52 (57)</td>
<td>25 (69)</td>
</tr>
</tbody>
</table>

Abbreviations: MAL, methyl aminolevulinate; PDT, photodynamic therapy. *Because of rounding, percentages may not all total 100.
sificantly (odds ratio, 1.64; 95% CI, 0.78-3.45; P = .19).

Maximum lesion diameter at baseline had a statistically significant influence on the lesion complete response rate in all treatment groups (P/H11021.001). Overall, the estimated sustained lesion complete response rates 12 months after last active treatment by diameter were 82% in lesions up to 14 mm, 77% in lesions 15 to 19 mm, 71% in lesions 20 to 29 mm, and 55% in lesions 30 mm or larger. Lesion response seemed to be independent of lesion location.

Lesion recurrence rates 12 months after the last treatment were 15% (15/103) in the methyl aminolevulinate PDT group, 50% (2/4) in the placebo PDT group, 21% (15/73) in the cryotherapy group, and 17% (4/24) in the fluorouracil group (Table 3).

**COSMETIC OUTCOME**

Cosmetic outcome (on-site evaluation) at 3 months was clearly superior with methyl aminolevulinate PDT com-
pared with either cryotherapy or fluorouracil, with a good or excellent outcome in 94% (77/82) (95% CI, 86%-98%) of patients treated with methyl aminolevulinate PDT vs 66% (43/65) (95% CI, 53%-77%) treated with cryotherapy and 76% (16/21) (95% CI, 53%-92%) treated with fluorouracil; and this was maintained for 12 months (Figure 3). Blinded reading of cosmetic outcome showed a high degree of concordance between the evaluation made by the investigator and the independent reviewer (Figure 4).

SAFETY

Local adverse events were commonly reported in each treatment group (Table 4). Most treatment-related local events reported with methyl aminolevulinate PDT were mild (60%) or moderate (34%), and only 6% were regarded as severe. By comparison, 12% of related local events with cryotherapy were severe.

Serious adverse events (including 4 deaths) were reported for 9 patients: 4 treated with methyl aminolevulinate PDT, 2 with placebo, and 3 with cryotherapy. With the exception of lymphangitis and skin necrosis reported for 1 patient in the cryotherapy group, these events were considered by the investigator as related to preexisting conditions and not related to treatment. Three patients, 2 in the methyl aminolevulinate PDT group (bleeding skin with aggravated cough; skin pain and malaise) and 1 in the fluorouracil group (skin ulceration), discontinued treatment because of suspected treatment-related adverse events.

COMMENT

Until now, there have been few well-designed, controlled randomized studies of SCC in situ, with current treatment guidelines predominantly based on limited data from open uncontrolled studies. The results of this pan-European study, the largest randomized controlled study reported to date, clearly demonstrate that topical methyl aminolevulinate PDT is an effective treatment option for SCC in situ, with sustained lesion response rates at 12 months significantly higher than those for cryotherapy and higher (although not statistically so) than those for fluorouracil (80% vs 67% and 69%). Methyl aminolevulinate PDT was at least as effective as standard therapy for larger lesions. Topical methyl aminolevulinate PDT also gave a superior cosmetic outcome compared with both cryotherapy and topical fluorouracil, an important clinical advantage given that, as most patients with SCC in situ are elderly, with lesions typically on the lower extremities, healing and hence optimal cosmesis can be compromised. The profile of local adverse events with methyl aminolevulinate PDT observed in the current study was consistent with that previously reported.

Methyl aminolevulinate PDT is a relatively simple noninvasive procedure that permits treatment of multiple lesions during 1 session (with the option to safely repeat treatment if required), which has practical advantages, particularly in elderly patients unwilling to

![Figure 2](https://archderm.jamanetwork.com/)

**Figure 2.** Estimated sustained lesion complete response (CR) rate over time, per-protocol population. MAL indicates methyl aminolevulinate; PDT, photodynamic therapy.

![Figure 3](https://archderm.jamanetwork.com/)

**Figure 3.** Comparison of overall cosmetic outcome at 3 and 12 months, as assessed by the on-site investigator, per-protocol population. MAL indicates methyl aminolevulinate; PDT, photodynamic therapy.

![Figure 4](https://archderm.jamanetwork.com/)

**Figure 4.** Overall cosmetic outcome at 3 months, as assessed by the on-site investigator and by the blinded independent reviewer, per-protocol population. MAL indicates methyl aminolevulinate; PDT, photodynamic therapy.
undergo invasive procedures. Although follow-up to 24 months is still continuing, the high clearance rate with methyl aminolevulinate PDT at 3 months, which was sustained at 12 months, together with favorable cosmetic outcome and safety profile, indicates that methyl aminolevulinate PDT is a promising treatment alternative that warrants consideration in the clinical management of SCC in situ.

Accepted for Publication: January 17, 2006.

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Financial Disclosure: Dr Morton has received financial support from Galderma, PhotoCure ASA, Phototherapeutics UK, and Schering AG for performing clinical trials.

Funding/Support: This study was supported by PhotoCure ASA, which paid the recruiting centers to cover study costs and helped obtain funding.

Role of the Sponsors: PhotoCure ASA and Parexel Medstat Research AS, participated in study concept and design; Parexel GmbH participated in statistical analysis; and Smerud Medical Research ASA participated in study supervision.

Previous Presentation: Interim results of this study (not final data as reported herein) were presented at the annual general meeting of the British Association of Dermatology Meeting; July 7, 2004; Belfast, Northern Ireland.

Acknowledgment: Other investigators who enrolled subjects in the study were as follows: Finland: A. Laukanen, MD, Kuopio University Hospital, Kuopio; A. Oikarinen, MD, Oulu University Hospital, Oulu; T. Reunala, MD, Tampere University Hospital, Tampere; and O. Saksela, MD, University Central Hospital, Helsinki. France: N. Basset-Séguin, MD, St Louis Hospital, Paris; J. C. Beani, MD, CHU Michallon, Grenoble; A. Clady, MD, CHU Edouard Hérriot, Lyon; M. Delaunay, MD, Hôpital Saint-André, Bordeaux; B. Dreno, MD, CHU Hotel-Dieu, Nantes; L. Thomas, MD, Hôpital Hotel-Dieu, Lyon; and P. Thomas, MD, CHU Claude Huriez, Lille. Germany: C. Beier, MD, Goethe Universität, Frankfurt; H. Fesq, MD, Dermatologische Klinik der TU München, München; K. Gardlo, MD, Heinrich-Heine Universität, Düsseldorf; and P. Lehmann, MD, Klinik für Dermatologie, Allergologie und Umweltsmedizin, Wuppertal. Norway: J. Ø. Holm, MD, Ullevål Sykehus, Oslo; T. Morken, MD, Haukeland Sykehus, Bergen; and J. Ronnevig, MD, Rikshospitalet, Oslo. Switzerland: L. Braathen, MD, Inselspital, Bern; and R. Dummer, MD, Universitätsspital, Zürich. Sweden: M. Maroti, MD, Lansjukhuset Ryhov, Jonköping. United Kingdom: R. Azurdia, MD, Royal Liverpool and Broadgreen University Hospitals, Liverpool, England; N. Cox, MD, Cumberland Infirmary, Carlisle, England; A. Y. Finlay, MD, University of Wales College of Medicine, Cardiff, Wales; and R. Groves, MD, Chelsea and Westminster Hospital, London, England. We thank Eckart Haneke, MD, for performing blinded assessment of cosmetic outcome.

Table 4. Adverse Events, All Treated Patients

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>MAL PDT (n = 96)</th>
<th>Placebo PDT (n = 17)</th>
<th>Placebo + MAL PDT* (n = 8)</th>
<th>Cryotherapy (n = 82)</th>
<th>Topical Fluorouracil (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>19 (20)</td>
<td>4 (24)</td>
<td>2 (25)</td>
<td>20 (24)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Erythema</td>
<td>8 (8)</td>
<td>2 (12)</td>
<td>1 (13)</td>
<td>8 (10)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>16 (17)</td>
<td>3 (18)</td>
<td>0</td>
<td>6 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Crusting</td>
<td>8 (8)</td>
<td>1 (6)</td>
<td>2 (25)</td>
<td>3 (4)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Stinging</td>
<td>9 (9)</td>
<td>1 (6)</td>
<td>1 (13)</td>
<td>1 (1)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
<td>6 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Irritation</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Itching</td>
<td>1 (1)</td>
<td>2 (12)</td>
<td>0</td>
<td>0</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Edema</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>5 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Blistering</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Warmth</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

*Patients in this group all received placebo PDT in the first PDT cycle.

†Adverse skin reactions reported by more than 2 patients, and considered by the investigators as of uncertain or related causality.
REFERENCES


Announcement

Free color publication if color illustrations enhance the didactic value of the article.