Clinical trial

Photodynamic therapy with methyl aminolevulinate for primary nodular basal cell carcinoma: results of two randomized studies

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Abstract

Background Data suggest that photodynamic therapy using topical methyl aminolevulinate (MAL PDT) may be a noninvasive alternative to excisional surgery for nodular basal cell carcinoma (BCC). In the studies described here, we investigated the histologic response, tolerability, and cosmetic outcome with MAL PDT for primary nodular BCC (≤ 5 mm in depth).

Methods Two multicenter, randomized, double-blind studies with similar design and procedures were conducted. After surface debridement and minor tumor debulking, MAL cream 160 mg/g (66 patients with 75 lesions) or placebo cream (65 patients with 75 lesions) was applied for 3 h, followed by illumination with broad-spectrum red light (75 J/cm^2, 570–670 nm). This was repeated 7 days later. Lesions with a partial response (≥ 50% reduction in greatest diameter) at 3 months were re-treated (21%). Treatment sites were excised at 3 months (clinical nonresponders) or 6 months (clinical responders) after the last treatment.

Results Histologically verified lesion complete response rates were higher with MAL PDT than with placebo [73% (55/75) vs. 27% (20/75)]. Treatment was most effective for facial lesions (89% complete response). Cosmetic outcome was good or excellent in 98% of evaluable, completely responding lesions treated with MAL PDT.

Conclusion Although longer follow-up studies are required, these promising data indicate the potential of topical MAL PDT as a noninvasive treatment alternative for nodular BCC.

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Introduction

Excisional surgery is conventionally regarded as the treatment of choice for basal cell carcinoma (BCC).[1] Although effective, cosmetic outcome following treatment is highly dependent on the anatomic site, lesion size, reconstruction method, and surgeon's expertise.[2,3] Topical photodynamic therapy (PDT) is an alternative approach to the treatment of nonmelanoma skin cancer, including BCC. The procedure involves the activation of a photosensitizing agent by visible light, leading to the creation of reactive oxygen species, which produce highly localized tissue destruction.[4] PDT offers advantages over existing treatment modalities, as it is a simple, noninvasive procedure that selectively targets neoplastic epithelial cells, and potentially may lead to improved cosmetic outcome.

Until recently, aminolevulinic acid (ALA), a precursor in the heme biosynthetic pathway, was the main topical photosensitizing agent used in PDT of BCC. Although effective in the treatment of thin, superficial BCC,[5] response rates in thicker BCC are less satisfactory (ranging from 10% to 53%),[6–9] largely because of the limited depth of tissue penetration of ALA.[10,11] As a result, ALA-based PDT is currently not recommended for the treatment of nodular BCC.[12,13]

Methyl aminolevulinate (MAL), the methyl ester of ALA, offers advantages over ALA,[14–16] particularly with respect to greater selectivity[17] and depth of skin penetration.[14] The efficacy of MAL PDT in the treatment of BCC is supported by clinical evidence from prospective studies.[18–21] Currently, MAL is the only photosensitizer that is accepted for the treatment of BCC in the European Union, Australia, Brazil, Chile, and South Africa. The available clinical experience suggests that MAL PDT may potentially have a role in the treatment of nodular BCC. The two Phase III studies described in this article were conducted in parallel to evaluate the efficacy, tolerability, and cosmetic outcome with PDT using topical MAL for the treatment of primary nodular BCC.

Methods

Study design

These two multicenter, randomized, double-blind, placebo-controlled, prospective studies were performed in Australia (study 308) and the USA (study 307) between October 2000 and September 2002. Each study involved seven outpatient centers. Approval for each study was obtained from the national health authorities and the local independent ethics committees/institutional review boards responsible for each center in each country. The studies were conducted in accordance with the latest revision of the Declaration of Helsinki (Edinburgh, 2000). Written informed consent was obtained from all patients prior to initiation of any study procedures.

Eligible patients, aged at least 18 years, with primary (previously untreated) nodular BCC verified by local histologic examination of a 2–3-mm punch biopsy (subsequently sent to an independent central laboratory for control), and suitable for simple excision surgery, were enrolled. Lesions were excluded if they involved the periorbital area, ears, or nasolabial fold; had a diameter of < 6 mm (any site) or > 15 mm (face or scalp), > 20 mm (extremities or neck) or > 30 mm (trunk); were pigmented; or, on biopsy, showed a morpheaform or infiltrating pattern. Patients with porphyria, Gorlin's syndrome, xeroderma pigmentosum, history of arsenic exposure or allergy to MAL, ALA, or excipients of the cream, who had participated in any other investigational study in the previous 30 days or were likely to be poorly compliant, who were pregnant or breast-feeding were excluded. Concomitant treatment with any immunosuppressive medication was prohibited.

Both studies used the same design (Fig. 1) and procedures. Within 30 days of screening, eligible patients were randomized to PDT using MAL 160 mg/g (PhotoCure ASA, Oslo, Norway) or matching placebo cream, employing a computer-generated randomization scheme prepared by PAREXEL International GmbH, Berlin, Germany. Randomization was stratified by center.

Treatment and follow-up

All clinical staff involved in the study were given adequate training prior to the recruitment of any patients to ensure that the treatment procedure was standardized across centers. In addition, a video describing the preparation procedure was supplied to each center.

The border of each lesion to be treated was initially tattooed for identification using four single 30-gauge needle punctures, one placed at each quadrant, 3 mm outside the clinical tumor edges. Prior to the application of MAL or placebo cream, the surface of the lesion was prepared by gentle tumor surface debridement using a curette, which removed the stratum corneum and surface of the friable tumor tissue, to facilitate access of the cream and light to the tissue. The purpose of this debridement was to debulk rather than remove the tumor. A layer of cream (MAL or placebo), 1 mm thick, was applied to each lesion and 5 mm of surrounding tissue and covered with an adhesive occlusive dressing (e.g. Tegaderm®, 3M, St Paul, MN, USA). After 3 h, the dressings were removed and the cream was washed off with 0.9% saline solution, immediately followed by illumination with noncoherent broad-spectrum red light (CureLight®; wavelength, 570–670 nm; light dose, 75 J/cm^2; light intensity, 50–200 mW/cm^2). To ensure blinding to treatment, a study nurse was responsible for illumination and for monitoring adverse events during treatment sessions and at follow-up.

Patients initially received one treatment cycle, comprising two PDT sessions separated by an interval of 1 week. Response to treatment was assessed at 3 and 6 months. Patients with lesions showing a partial response at 3 months underwent a second treatment cycle, and were then followed up at 6 and 9 months. Lesions that showed no response or progression at 3 months, or noncomplete response at 6 months after a second treatment cycle, were excised. All lesions evaluated as showing a complete

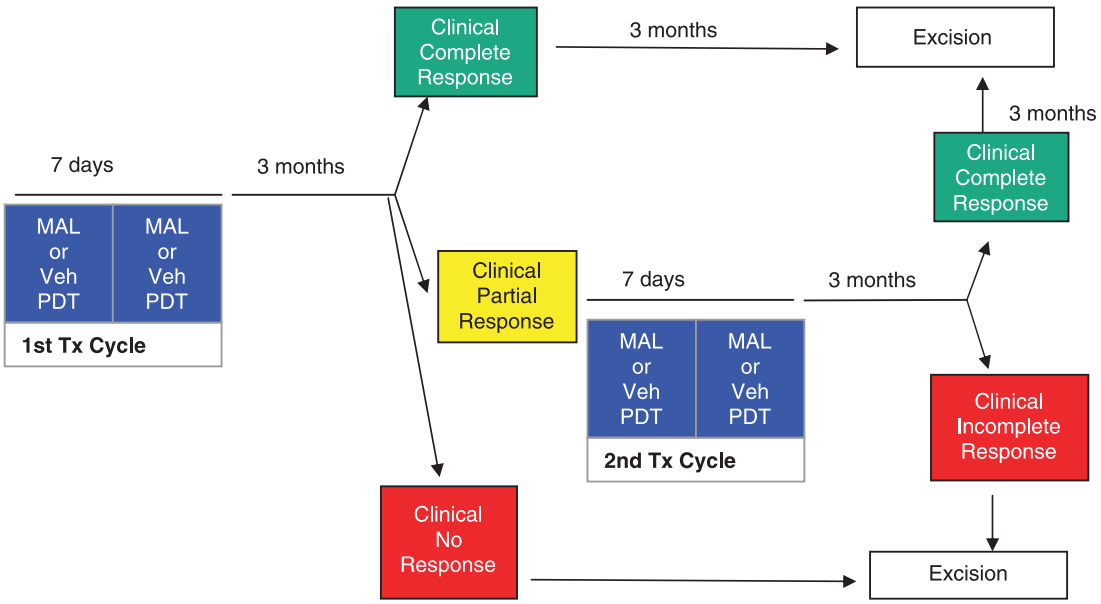

Figure 1 Sequence and duration of study periods. Partial response, ≥ 50% but < 100% reduction in greatest diameter; no response, ≤ 50% reduction in greatest diameter. MAL, methyl aminolevulinate; PDT, photodynamic therapy; Tx, treatment; Veh, vehicle

response at 3 months after treatment were excised for histologic examination 6 months after the last treatment cycle. Safety assessments were performed at 2 and 4 weeks and at 3 months after each treatment cycle.

Evaluations

Lesion response was assessed by the same investigator in each center, who remained blind to treatment, using both clinical (visual appearance and palpation) and histologic evaluation criteria. Lesions were photographed before and at 3 and 6 months post-treatment to assist in the evaluation of clinical response and cosmetic outcome.

The previously marked lesion sites were excised with an additional 3–4-mm margin around the tumor (if clinically apparent) or tattoo. The orientation of the excision specimen was documented macroscopically. There were slight differences between the two independent studies in the handling of excision specimens. In the Australian study, the center of each specimen was sequentially sectioned in 1-mm increments for the first 3 mm in either direction from the center, and thereafter every 3 mm with step sections every 0.5 mm. A mean of 73.6 sections were reviewed per excision specimen (range 9–195; standard deviation, 35.5). There were a mean of 76.5 sections reviewed for negative samples and 70.6 sections reviewed for positive samples. The mean number of sections examined per millimeter of specimen was 3.2 (range, 0.2–16.3; standard deviation, 2.1). In the US study, the specimens were first bisected and then the terminal portions of each bisected portion were separated as "tips." The remaining portions were then further sectioned at least every 3 mm. Each of the resultant dissected specimens was embedded in paraffin from which microscopic sections were taken. A mean of 117.9 sections were reviewed per excision specimen (range, 50–226; standard deviation, 39.7). The mean number of sections examined per millimeter of specimen was 10.7 (range, 1.9–52.1; standard deviation, 10.5). All specimens (negative and positive) in the US trial were treated identically as described above. Although the bread loaf technique has the potential of missing small foci, it was considered to be impractical to cut through in a serial fashion for every block. There was no advantage in using the horizontal Mohs' technique, as serial sections would still have been required to examine all tissue. Furthermore, tumors that would normally have been treated by Mohs' surgery were excluded from these studies.

In each study, the histologic lesion response was evaluated at an independent central laboratory (Skin and Cancer Foundation, Darlinghurst, NSW, Australia and the Division of Dermatopathology, Mayo Clinic, Rochester, MN, USA), blind to study treatment, as either complete (no residual BCC) or noncomplete.

The clinical response of each lesion was assessed at each relevant time point as complete response (complete disappearance of a lesion), partial response (≥ 50% reduction in the longest diameter of the lesion), no response (< 50% reduction in the longest diameter of the lesion), or progression (≥ 20% increase in the longest diameter of the lesion). In addition, cosmetic outcome was assessed for each lesion that had responded completely (on clinical and histologic evaluation) using a four-point scale ranging from "excellent" (no scarring, atrophy, or induration, and no or slight occurrence of redness or change in pigmentation compared with adjacent skin) to "poor" (extensive occurrence of scarring, atrophy,

or induration), as described previously.[17,20] Patients were also asked to assess the cosmetic outcome of the responding lesions as excellent, good, fair, or poor. Subjective patient satisfaction with the study treatment relative to previous treatments was also documented.

Local skin reactions and/or phototoxicity reactions during and after cream application and illumination were documented. Adverse events were noted at each follow-up visit, together with their severity (mild, moderate, or severe), duration, and need for additional therapy. The causal relationship of the event to the study treatment was assessed by the clinician as related, uncertain, or not related.

Statistical analysis

The variable patient histologic complete response rate (i.e. all patients with 100% of lesions showing complete response 6 months after last treatment) was the basis for sample size calculations, using the formula proposed by Fleiss[22] without continuity correction. Assuming patient response rates of between 50% and 70% with MAL PDT and 10% with placebo (based on previous clinical studies), between 31 and 15 patients, respectively, were required per treatment group to demonstrate a treatment difference at a significance level of 0.05 (two-sided) and a power of 95%. Recalculation of the sample size using the response rates observed in the study indicated that 28 patients were required per treatment group to achieve a power of 98%.

The primary variable of interest in this paper was histologically verified lesion complete response at 6 months after last treatment. Data were analyzed on an intention-to-treat basis, including all randomized and treated patients. The Breslow–Day test was performed to assess homogeneity of response across the treatment centers. Analyses were performed independently by PAREXEL International GmbH using SAS software (SAS Institute Inc., Cary, NC, USA).

Results

Population

In total, 131 patients with 160 lesions were randomized; 66 patients with 81 lesions were enrolled in the Australian study and 65 patients with 79 lesions were enrolled in the US study. Ten lesions, six in the MAL PDT group and four in the placebo PDT group, were histologically not nodular BCC and were therefore not treated. Thus, 66 patients with 75 lesions were treated with MAL and 65 patients with 75 lesions were treated with placebo prior to illumination. Three patients did not complete the study: two patients in the MAL PDT group [one who withdrew consent for excision (he showed a complete clinical response with excellent cosmetic outcome and did not want the excision of ''normal'' skin as he was convinced the lesion had cleared) and one who experienced a nontreatment-related serious adverse event (death caused by cholangiocarcinoma before the final assessment)], and one patient in the placebo group (who was lost to follow-up). All lesions were included in the analysis of the histologic and clinical response.

Table 1 Baseline patient characteristics

Characteristic	Methyl aminolevulinate ($n = 66$)	Placebo ($n = 65$)
Male : female (*n*)	47 : 19	52 : 13
Age (years)	66 (28–88)	67 (39–88)
Fitzpatrick skin phototype, *n* (%)‡		
I	27 (41)	19 (29)
II	26 (39)	28 (43)
III/IV	13 (20)	18 (28)
Number of lesions	75	75
Lesion location, *n* (%)		
Face/scalp	19 (25)	23 (31)
Neck	9 (12)	1 (1)
Trunk	32 (43)	34 (45)
Extremities	15 (20)	17 (23)
Largest lesion diameter (mm)	8.8 (6–20)	9.0 (6–22)
Lesion depth (mm)*	1.3 (0–5.0)	1.2 (1–3.0)
Lesion depth (mm), *n* (%)†		
< 0.7	16 (22)	16 (22)
0.7 to < 1.0	15 (21)	15 (20)
1.0 to < 2.0	31 (42)	31 (42)
2.0–5.0	11 (15)	12 (16)

Data given as mean (range), except where indicated otherwise.
*Lesion depth confirmed by punch biopsy.
†Data missing for two lesions treated with methyl aminolevulinate and one lesion treated with placebo.
‡Significant difference between groups in the distribution of Fitzpatrick skin phototype, $P < 0.05$.

The baseline characteristics of the two groups were generally similar. There was, however, a significant difference between the groups in the distribution of Fitzpatrick skin phototype ($P < 0.05$), largely caused by a greater proportion of patients with type I skin in the MAL group (Table 1). Most patients [89% (117/131)] had one lesion only treated.

One complete treatment cycle (comprising two treatment sessions) was administered to 78% (117/150) of the lesions, 55 in the MAL group and 62 in the placebo group. Of these lesions, 71% (39/55) in the MAL group and 23% (14/62) in the placebo group showed a complete response. Two lesions in the MAL group received only one treatment session because of local adverse events or withdrawal of consent (one lesion each), and the remainder of the lesions [21% (31/150)] received two treatment cycles (18 with MAL, 13 with placebo). The treatment procedures were similar in each group and in accordance with the specified schedule, with a mean cream application time of 3 h and 4 min (range 2 h 50 min to 4 h) and a mean light dose of 77 J/cm^2 (standard

Table 2 Histologic lesion complete response rate at 3 or 6 months after last treatment [number (%) of lesions]

	Methyl aminolevulinate	Placebo
No. of patients	66	65
No. of lesions treated	75	75
Overall complete lesion response rate	55 (73)	20 (27)
Lesion response by location		
Face/scalp	16/19 (84)	5/23 (22)
Neck	5/9 (56)	0/1 (0)
Trunk	24/32 (75)	10/34 (29)
Extremities	10/15 (67)	5/17 (29)
Lesion response by baseline depth (mm)		
< 0.7	14/16 (88)	5/16 (31)
0.7 to < 1.0	12/15 (80)	4/15 (27)
1.0 to < 2.0	18/31 (58)	7/31 (23)
2.0–5.0	9/11 (82)	4/12 (33)
Lesion response by baseline diameter (mm)		
< 10 mm	49/64 (77)	18/61 (30)
10 to > 20 mm	6/11 (55)	2/14 (14)

Lesions excised at 3 months were evaluated clinically as nonresponse at 3 months after last treatment; lesions excised at 6 months were evaluated clinically as complete response (CR) at 3 months after last treatment. Three lesions in the methyl aminolevulinate group – one on the face, one on the neck, and one on the extremities – were not excised and were included as non-CR.

deviation, 4 J/cm^2) (reflecting the variation in lesion diameter, see Table 1).

Efficacy

Histologically verified lesion complete response rates following PDT were superior after treatment with MAL compared with placebo (73% vs. 27%) (Table 2). Lesion complete response rates were generally similar in the individual studies (78% vs. 33% with placebo in the US study and 68% vs. 19% in the Australian study) (data not shown). The superiority in treatment response was also apparent in lesions treated with only one treatment cycle [72% (41/57) vs. 23% (14/62)]. The Breslow–Day test for homogeneity of the response rates across centers revealed no statistically significant difference, suggesting a lack of treatment center-related bias.

In the MAL group, treatment was most effective in facial lesions, even after one treatment cycle, as shown in Fig. 2. The response tended to be lower in larger lesions (≥ 10 mm in diameter) and in lesions with a baseline depth of > 1.0 mm. It is, however, worth noting that 82% (9/11) of lesions of 2.0–5.0 mm in depth responded completely to MAL PDT (Table 2); moreover, the deepest lesion treated with MAL PDT (5.0 mm) showed a complete response after one treatment cycle. Lesion complete response rates based solely on clinical evaluation were similar to the histologic complete response rates, although the placebo response was higher [81% (61/75) in the MAL group vs. 39% (29/75) with placebo]. The Fitzpatrick skin type had no effect on outcome.

Twenty lesions in the MAL group did not show a histologic complete response to PDT. The baseline depth of these lesions ranged from 0.69 mm to 4.0 mm, with 15 lesions of at least 1.0 mm in depth. Data for the 11 lesions (histologic noncomplete response) with a clinical complete response after one or two treatment cycles, and without clinical recurrence, are summarized in Table 3. Six of the nine lesions assessed clinically as complete responses at 3 months (and therefore receiving only one treatment cycle), but showing residual disease histologically, exhibited relatively superficial disease at excision, of a shallower depth than on pretreatment biopsy (Fig. 3). On the available evidence, the reasons for the lack of histologic response in these lesions remain unclear.

Cosmetic outcome, as assessed by the investigator, was excellent or good in 42 of the 43 (98%) completely responding lesions treated with MAL (Fig. 4), and in 14 of the 15 placebo lesions (93%) with clinical and histologic complete response assessment.

Of the 64 MAL PDT-treated patients with information available, 48 patients had received at least one previous therapy for BCC: 45 had been treated with surgery, 29 with cryotherapy, four with topical 5-fluorouracil, one with ALA

Table 3 Histopathology results in lesions treated with methyl aminolevulinate photodynamic therapy (MAL PDT) and assessed as clinical complete response at 3 or 6 months but histologic noncomplete response in the final assessment

	Case number										
Lesion size (mm)	**1004**	**2005***	**2008**	**2010**	**2012**	**2013**	**4005A***	**4005B***	**6001**	**6008**	**7001**
Baseline depth	1.4	1.3	0.5	0.69	1.54	1.7	1.1	1.0	1.3	0.9	1.2
Baseline diameter	18	6	6	6	10	7	10	12	12	10	6
Depth at excision	Missing	0.64	2.8†	0.59	0.79	1.05	1.68	2.54	0.4	Missing	0.95

*Three lesions (case numbers 2005, 4005A, and 4005B) received two treatment cycles. Patient 4005 had three lesions treated with MAL PDT.
†Micronodular histology on review at baseline and excision.

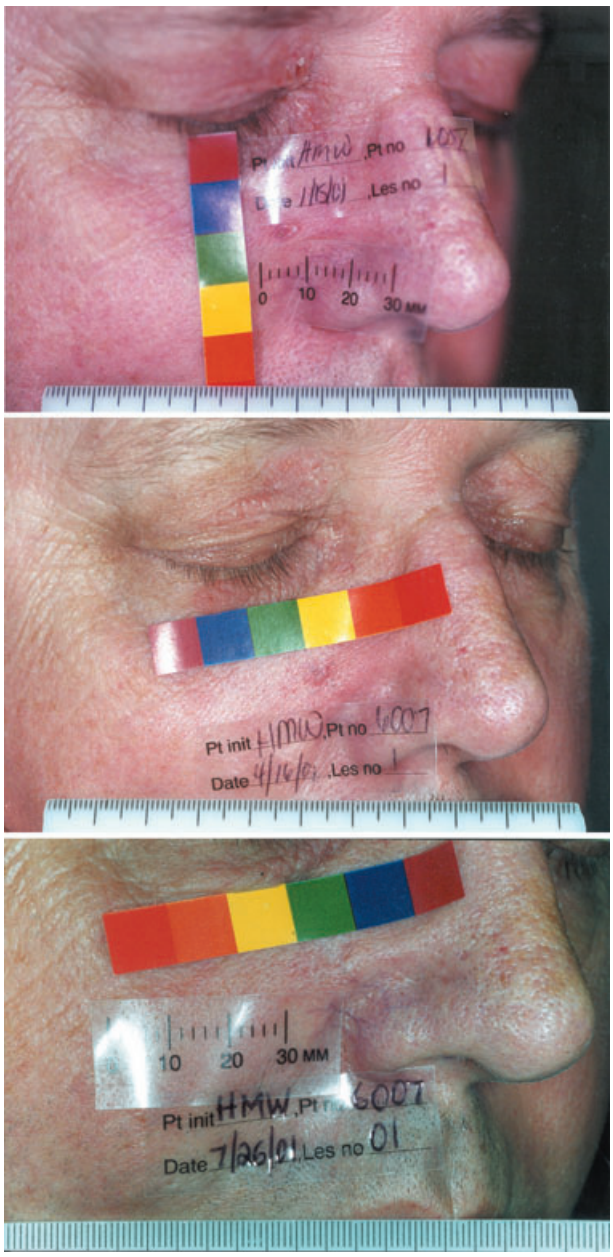

Figure 2 Male patient, aged 54 years. Lesion of 6 mm in diameter, 1.3 mm deep, located on the face. Top panel shows baseline. Middle panel shows partial response after one treatment cycle with methyl aminolevulinate photodynamic therapy (MAL PDT). Bottom panel shows clinical result after two treatments. Histology showed complete response. Cosmetic outcome was assessed as good by both patient and investigator. It is acknowledged that Mohs' surgery is currently the treatment of choice for such lesions, with other treatments only considered if surgery is contraindicated

PDT, and six with other forms of therapy. MAL-based PDT was preferred by 64% of patients previously treated with excision surgery, cryotherapy, and/or topical 5-fluorouracil, and only 18% considered previously received treatment to be better than MAL PDT.

Table 4 Profile of commonly reported treatment-related local adverse events*

	Methyl aminolevulinate ($n = 66$) No. (%)	Placebo ($n = 65$) No. (%)
Any local adverse event	49 (74)	30 (46)
Treatment-related local events		
Burning sensation of skin	19 (29)	8 (12)
Erythema	14 (21)	4 (6)
Skin pain	12 (18)	3 (5)
Stinging of skin	10 (15)	5 (8)
Crusting	5 (8)	3 (5)
Bleeding skin	4 (6)	–

*Adverse events assessed as related or of uncertain causality by the investigator, and reported by more than 5% of patients in either treatment group.

Adverse events

The incidence of adverse events was higher in the MAL group than in the placebo group [91% (60/66) vs. 66% (43/65)]. In each group, local adverse events were most commonly reported (Table 4). In the MAL group, burning sensation of the skin was the main treatment-related adverse event. All treatment-related local adverse events were of mild to moderate intensity, and usually resolved within 1 day, although commonly reported events of bleeding, crusting, and erythema (reported for 4, 5 and 14 patients, respectively) persisted for longer (median duration of 3, 5 and 32 days, respectively).

Nine serious adverse events were reported by six patients, two treated with MAL PDT and four treated with placebo PDT. In all cases, the adverse events were not considered to be related to the study treatment. In the MAL PDT group, one patient died of metastatic cholangiocarcinoma, and one patient developed carotid stenosis. In the placebo PDT group, one patient developed cholelithiasis, one patient underwent femoral artery surgery, one patient had pulmonary edema and acute myocardial infarction, and one patient had an abdominal aneurysm and developed a new melanoma (first evident at baseline before the start of treatment). This patient was treated for a BCC on the front of the left ear and a melanoma appeared on the left forearm.

Discussion

The results of these Phase III studies provide short-term data to support MAL PDT as a possible treatment alternative for nodular BCC (up to 5 mm in depth). Our findings are consistent

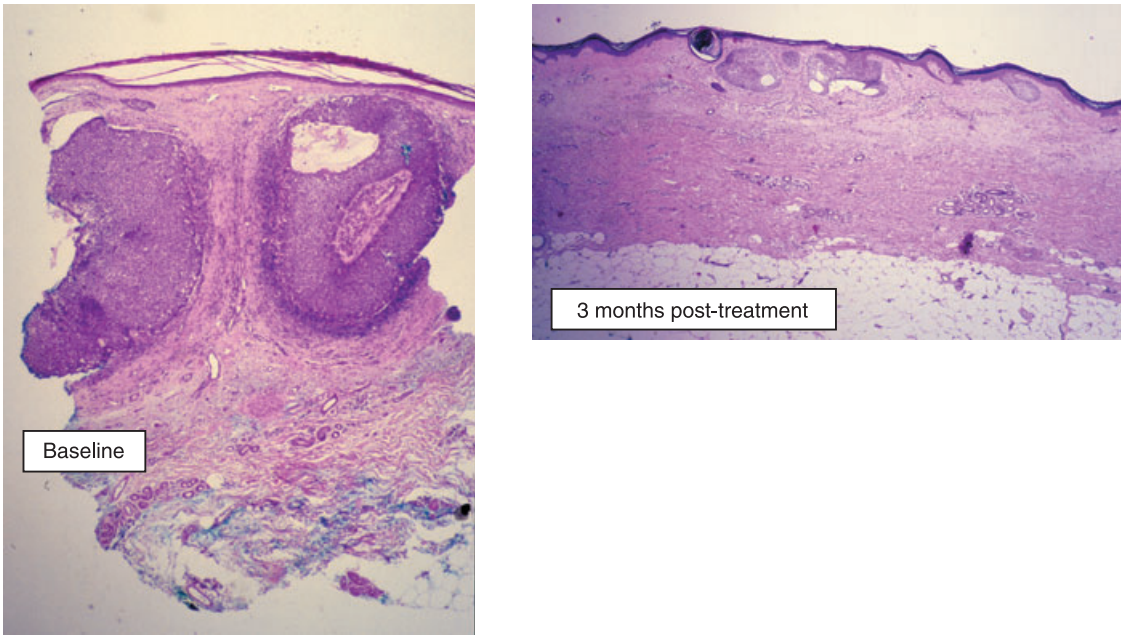

Figure 3 Example of histologic sections from a nonresponding lesion which was excised 3 months after treatment. Baseline depth, 1.3 mm; depth at excision, 0.4 mm. Left: pretreatment (×40); right: post-treatment (×25). Hematoxylin and eosin

with data from recent randomized studies in nodular BCC, with identical inclusion criteria, comparing MAL PDT and surgery (clinically assessed lesion complete response rate of 83% for MAL PDT at 12 months),[18] and PDT using topical MAL or ALA (histologically verified lesion complete response rate of 72% at 8 weeks).[23] Although MAL PDT was less effective in larger lesions (≥ 10 mm in diameter), as well as those between 1.0 and 2.0 mm in depth, it was noted that, in 11 lesions with a baseline depth of 2.0–5.0 mm, the histologic response rate was 82%, and, in the deepest lesion treated (5.0 mm), there was histologic complete response.

The overall placebo effect observed in our studies was higher than expected (27% histopathologically verified lesion complete response compared with 10% expected). A similar effect has been noted in another placebo-controlled study investigating MAL PDT for the treatment of actinic keratosis.[24] At the wavelengths, fluences, and irradiances employed in our studies, red light in the absence of photosensitizer would not be expected to cause any significant tissue effect. This suggests that the lesion response rate, as well as local adverse effects in the placebo group, are related to the use of tumor surface debridement, and would therefore be expected to be enhanced in those tumors undergoing two PDT cycles (four cream applications, i.e. 24% of placebo-treated tumors). Repeat curettage alone has been used to treat nodular BCC,[25] which may partly explain the high placebo response rate in our report. Nevertheless, it should be noted that, in our studies, curettage was used to debulk rather than remove the tumor. In addition, it is possible that inflammation associated with the debridement procedure may have contributed to the lesion response, although data suggest that this is unlikely.[26] In retrospect, an additional arm with active comparator treatment (such as excisional surgery) may have been preferable in our studies, although, if used, a blind study design would not have been feasible.

The most commonly reported treatment-related adverse event with MAL PDT, observed in our study, was a burning sensation of the skin (Table 4). This descriptor is consistent with reports of pain, i.e. burning, stinging, or prickling sensation, in the treatment area during illumination with this treatment modality,[27] including in studies using topical MAL.[15,18–21,24,28] Pain probably is a consequence of nerve stimulation or damage by reactive oxygen species produced during illumination.[29] The ensuing inflammatory reaction may also contribute to pain perception. As observed in our study, the intensity of pain varies considerably between patients. Some studies have described an increase in patient self-reported pain intensity from the first to second PDT treatment, especially if there is a low experience of pain during the first PDT.[30] Wiegell *et al.*[31] showed that pain during PDT is associated with protoporphyrin IX fluorescence in the treatment area prior to illumination. This is consistent with the study findings in patients receiving MAL PDT for the treatment of actinic keratoses or facial acne, where protoporphyrin IX fluorescence and reported pain were significantly lower in the second PDT treatment than in the first.[31] Curettage prior to cream application also appeared to increase protoporphyrin IX fluorescence and, consequently, pain intensity.[31]

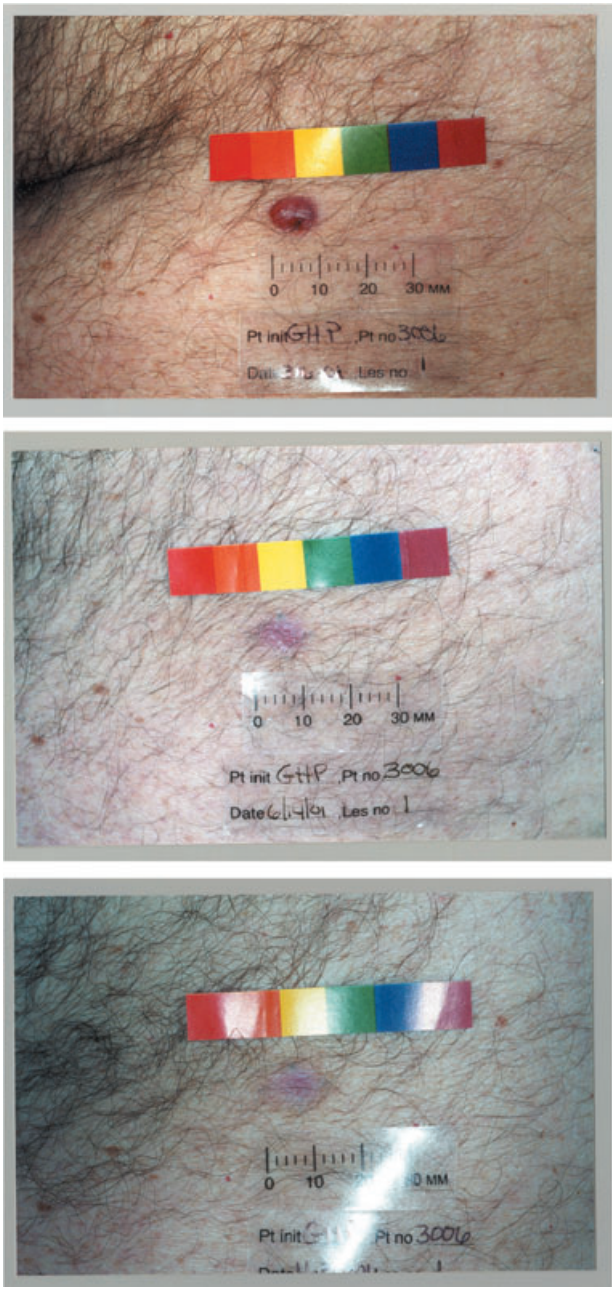

Figure 4 Male patient, aged 69 years. Lesion of 10 mm in diameter, 0.99 mm deep, located on the back. Top panel shows baseline. Middle panel shows partial response after one treatment cycle with methyl aminolevulinate photodynamic therapy (MAL PDT). Bottom panel shows clinical result after two treatments. Histology showed complete response. Cosmetic outcome was assessed as excellent by both patient and investigator

Both the current report and previous studies have indicated that MAL PDT appears to offer favorable cosmetic outcome in the treatment of nodular BCC. Between 82% of lesions at 3 months[18] and 98% of lesions at 6 months showed an excellent or good cosmetic outcome following MAL PDT. It is, however, recognized that cosmetic outcome, even when assessed in a blind manner as in this study, is a subjective measure. A recent pharmacoeconomic analysis has indicated patient preference for MAL PDT over excision surgery in the treatment of BCC, largely driven by better cosmetic outcomes with this treatment modality.[32]

In the context of the range of available treatments for nodular BCC, we acknowledge that these data involve a relatively short follow-up period, as the primary outcome of the studies was the histologic lesion complete response rate. From a clinical perspective, longer follow-up data are needed to support the use of MAL PDT as a treatment alternative to conventional modalities for nodular BCC. Current modalities in this setting include excisional surgery (5-year recurrence rates of less than 10%),[33] electrodesiccation and curettage (5-year recurrence rates of 6–19%),[33] and radiation therapy (5-year clinical recurrence rate of 7.4% for primary BCC);[34] however, radiation therapy is not recommended in younger patients (< 50 years) because of the less favorable cosmetic outcome over time,[34] as well as the potential risk of further lesions in the radiation field in the longer term.[35]

The results with MAL PDT, observed in our report, suggest that this procedure may have applicability as a treatment option for nodular BCC, particularly in patients who may be resistant to invasive treatment, or in whom surgical modalities may be contraindicated. A burning sensation of the skin/pain is the main drawback of therapy, although reports indicate that this is less problematic than with PDT using ALA.[36] Pain intensity also varies considerably between patients.[30] In the minority of patients reporting severe pain, subcutaneous infiltration anesthesia may be an effective means of controlling PDT-associated pain, without any impairment of clinical outcome.[37]

Clearly, longer follow-up for recurrence is essential for a full evaluation of the efficacy of any new prospective treatment in this indication.[29,38] With this in mind, although histologic complete response data at 6 months are promising, longer follow-up is required to confirm the suitability of MAL PDT within the range of clinical scenarios and therapeutic options for the management of nodular BCC.

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Conflict of interest

Dr Tope is a paid clinical consultant of PhotoCure ASA, Oslo, Norway. In the past, he has been a paid clinical consultant, a paid investigator, and/or received free drug or temporarily

loaned light sources from competitors in photodynamic therapy: QLT Inc. (Vancouver, BC, Canada), Miravant Inc. (Santa Barbara, CA, USA), and DUSA Pharmaceuticals (Wilmington, MA, USA). Dr Foley has been paid as an investigator for PDT trials sponsored by PhotoCure ASA, Galderma R&D (Sophia Antipolis, France), and QLT Inc., as well as for non-PDT studies on nonmelanoma skin cancer by Peplin Ltd. (Qld, Australia) and 3M (St Paul, MN, USA). He has received honoraria and travel bureaux from PhotoCure and Galderma for presentations at national and international congresses and scientific meetings. He receives honoraria for attending meetings as a member of Galderma Australia's Metvix Medical Advisory Board, and as a member of Medical Advisory Boards for Peplin and CSL Solaraze.

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