Lasers in Medical Science 1995, **10**:165–171

Development of an Alternative Light Source to Lasers for Photodynamic Therapy: 3. Clinical Evaluation in the Treatment of Pre-malignant Non-melanoma Skin Cancer

C.A. MORTON[a], C. WHITEHURST[b], H. MOSELEY[c], J.V. MOORE[b], R.M. MACKIE[a]

[a]*University Department of Dermatology, Western Infirmary, Glasgow, UK*

[b]*Laser Oncology Programme, Cancer Research Campaign Department of Experimental Radiation Oncology, Paterson Institute for Cancer Research, Christie Hospital, Manchester, UK*

[c]*Department of Medical Physics, Western Infirmary, Glasgow, UK*

Correspondence to Colin A. Morton, MRCP, Department of Dermatology, Western Infirmary, Glasgow, G11 6NT, UK

Paper received 27 September 1995

Abstract. The efficacy of a prototype non-laser light source for photodynamic therapy was assessed in clinical practice in the treatment of Bowen's disease and actinic keratoses. The light source, incorporating a 300 W short arc plasma discharge, was adjusted by appropriate filters to produce a bandwidth of 630 ± 15 nm. Topical 5-aminolaevulinic acid was applied 4 h before irradiation to permit production within the lesion of the active photosensitizer, protoporphyrin IX. Individual lesions received 94–156 J cm^{-2}. Twenty lesions of Bowen's disease and four actinic keratoses were treated in 12 patients. Patients were reviewed at monthly intervals and treatment repeated if residual disease was present. Clearance was achieved with a single treatment in 15 lesions and in all of the remaining nine lesions after a second treatment. The treatment was well tolerated, with pain absent or mild during treatment in 22 lesions, with only one lesion requiring local anaesthesia. Over the 10 days following treatment, no pain was associated with 21 treated lesions. During a 12 month follow-up period, two Bowen's disease lesions recurred. The overall complete response rate was 92%. Scarring was evident following PDT in only three lesions. Photodynamic therapy using this portable non-laser light source appears to be an effective and well-tolerated treatment for Bowen's disease and actinic keratoses.

INTRODUCTION

Photodynamic therapy (PDT) is an effective treatment for various cutaneous and non-cutaneous malignancies (1, 2). Certain pre-malignant and inflammatory cutaneous lesions appear also to respond to PDT, resulting in many potential clinical applications for this modality in dermatology (3, 4). Therapeutic response is achieved primarily via the activation of a photosensitizing drug by visible light to produce activated oxygen species, especially singlet oxygen, within the neoplastic/dysplastic tissue (5). Lasers have been the usual source of irradiation in PDT as they provide light of sufficient intensity at appropriate wavelengths for drug activation, with the opportunity of delivery to internal body surfaces via fibre optics. However, their cost, complexity and size, and the limited availability of lasers that can be used for PDT, has led to a search for alternative cheaper, yet effective, portable, light sources that can be used easily in clinical practice.

A recent development in light technology is a portable source incorporating a 300 W short arc plasma discharge. Initial in vitro assessment of this lamp demonstrated an efficiency of cellular photoinactivation close to that of the argon/dye laser and superior, at higher power densities, to the copper/dye laser (6). In an in vivo study using tumour regrowth delay to quantify the relative efficacy of the prototype with an argon/dye laser, there was no

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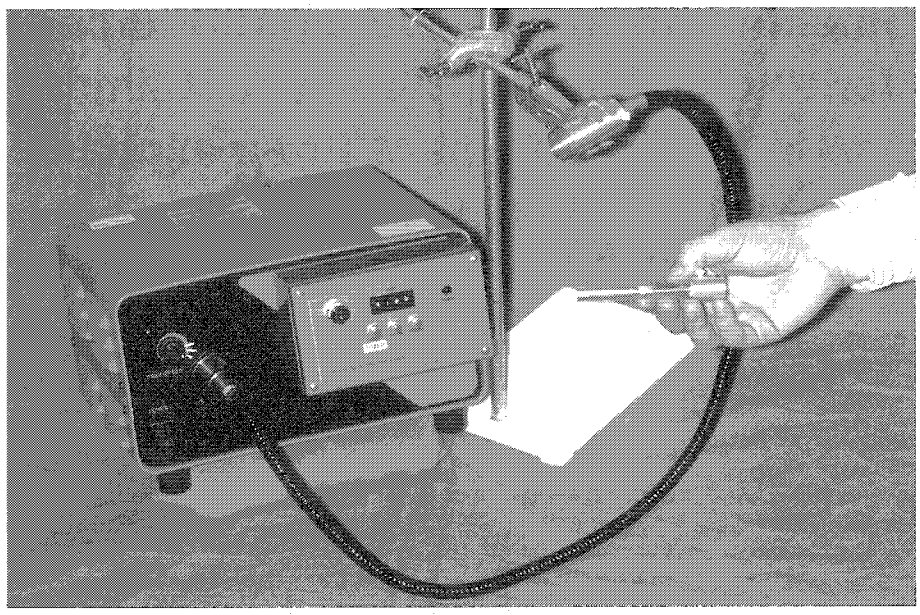


Fig. 1. Prototype lamp with timer unit and 5 mm flexible fibre bundle. The two attachments used on the end of the fibre are shown, the 11 mm perspex rod used to treat small lesions and the 25 mm collimating lens used for larger lesions (seen attached to fibre).

significant difference in the extent of tumour response between the two light sources (7).

The aim of the present study was to assess the efficacy of this prototype lamp in clinical practice in the treatment of pre-malignant non-melanoma skin cancer.

MATERIAL AND METHODS

Patients

Ethical committee approval was obtained for the treatment of patients with potential precursors to non-melanoma skin cancer, by photodynamic therapy. Patients presenting to the Dermatology Department of the Western Infirmary, Glasgow, with lesions of Bowen's disease (in situ squamous cell carcinoma) or actinic keratoses, 21 mm in diameter or less, were invited to participate in the study. No lesion had been previously treated. Histological confirmation of the diagnosis was acquired by performing a 4 mm punch biopsy on all lesions.

PDT light source

The prototype lamp (patent pending) incorporates a 300 W xenon short arc plasma discharge, producing a continuous wave broadband flat spectral output across the entire visible spectrum. The components of the light source are as described previously (6). The lamp used in this study can deliver 1 W directly or 0.5 W via a flexible light guide within a bandwidth of 30 nm which can be tuned to any wavelength from 300 nm to 1.1 μm. Infra-red emission from the source was totally blocked using a wideband dielectric heat filter and a non-infra-red transmitting light guide. Zero infra-red emission up to 35 μm wavelength was verified with a calorimeter. Using appropriate filters, the spectral output of the lamp was adjusted to a 30 nm bandwidth around 630 nm. To broaden the treatment field and produce uniform irradiation of lesions, an 11 mm perspex rod or 25 mm collimating lens was attached to the 5 mm fibre bundle (Fig. 1). The authors included at least a 10% margin around lesions in the field of irradiation permitting treatment of lesions up to 9 mm in diameter using the rod, and 21 mm in diameter using the lens. At fluence rates of 158 mW cm^{-2} for the rod and 55 mW cm^{-2} for the lens, lesions received 94–156 J cm^{-2}, the treatment dose centred on 125 J cm^{-2} as this dose has been shown previously to be effective in aminolaevulinic acid (ALA)-PDT using laser (8).

Photosensitizer

Topical 5-aminolaevulinic acid in an oil in water emulsion, 20% (w/w) 5-ALA (Sigma

Table 1. Clearance of lesions after a single treatment depending on light dose. Treatment times, depending on which end attachment to the fibre bundle was used, are also shown

Dose (J cm^{-2})	Total no. of lesions treated	No. of lesions treated		Treatment time (min)		Clear after one treatment
		Rod	Lens	Rod	Lens	
94	7	5	2	10	29	5
125	15	8	7	13	39	9
156	2	2	0	16	49	1

Chemical Co) in Unguentum Merck (E. Merck Ltd), was applied to lesions 4 h before illumination with the lamp. Surface crusts were removed from the lesions and the surface gently abraded prior to 5-ALA application. Approximately 50 mg of cream was applied per cm^2 to cover the entire irradiation field, thus including the clinically disease-free margin. The cream was then kept in place under an occlusive dressing (Tegaderm, 3M) for 4 h, after which the 5-ALA cream remaining on the skin surface was carefully removed. The patient was offered local anaesthetic (1% plain lignocaine by intradermal injection) during treatment.

Adverse effects, clearance and recurrence

Patients used visual analogue scales to record pain during and over the 10 days following PDT (with subsequent interpretation of $0<x\leq3$ as mild, $3<x\leq7$ as moderate and $7<x\leq10$ as severe). Lesions were examined on completion of therapy and 24–48 h later, then at increasing intervals during the following 2 months. Clinical response to the first application of PDT was determined at 2 months and a second treatment administered if lesions persisted. Monthly review of all patients was undertaken for 12 months following clearance to observe for recurrence and assess scarring potential of the therapy. Post-therapy punch biopsies were performed in lesions where doubt over clinical clearance/recurrence existed.

Statistics

Comparison of the size of lesions clearing and of those not clearing after a single PDT treatment, was performed by a Mann–Whitney U-test. Comparisons of clearance rates depending on dosage and the apparatus used to deliver the irradiation, were done using a Chi-squared test.

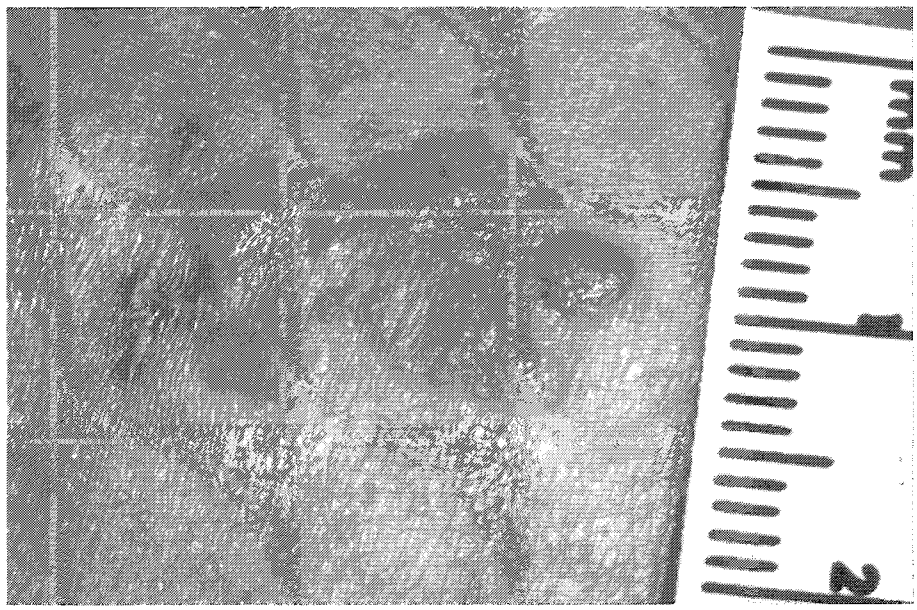
RESULTS

Clearance rates

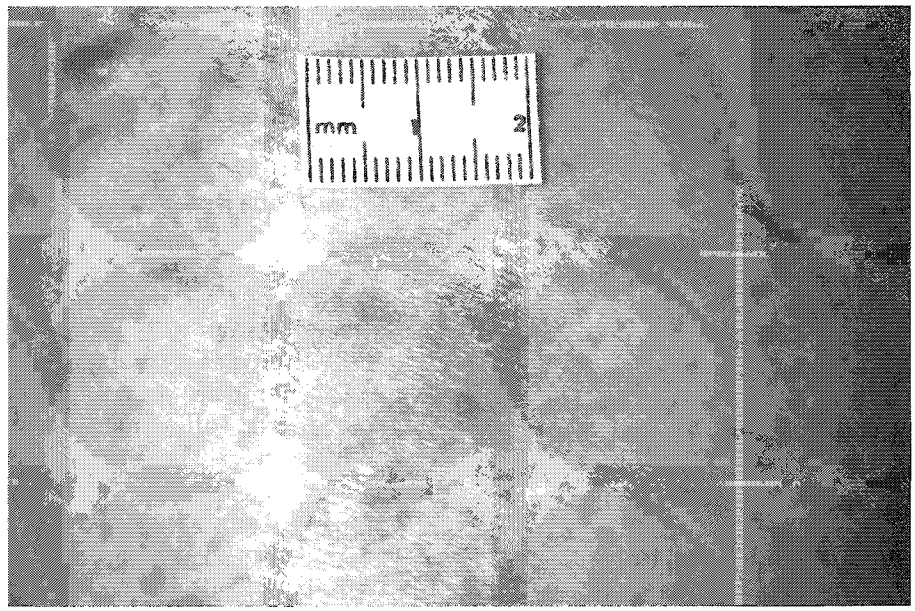
Twenty lesions of Bowen's disease and four actinic keratoses (AK), in 12 patients (three male, nine female, median age 65 years, range 43–95 years), received photodynamic therapy. Sixteen lesions were sited on the leg, six on the forearm or hand, and two on the scalp. The median surface area of all treated lesions was 60 mm^2 (range 9–400 mm^2).

Fifteen lesions (12 Bowen's and 3 AK) cleared after a single treatment with PDT using this non-laser source. All nine remaining lesions cleared following a second treatment, 2 months later. The median size of lesions clearing after one treatment was 56 mm^2 (range 9–400 mm^2), not significantly different from the size of those lesions requiring a second treatment (median 60 mm^2, range 9–380 mm^2). The clinical response of one area of Bowen's disease and one actinic keratosis is shown in Figs 2 and 3, respectively.

The effect of light dose on clearance after a single treatment is shown in Table 1. The first five lesions entered into the trial received 94 J cm^{-2}, 75% of the intended treatment dose in order to observe for side-effects. Subsequent lesions received 125 J cm^{-2} except, as one patient had seven lesions, two lesions received 94 J cm^{-2}, three 125 J cm^{-2}, and the remaining two, 156 J cm^{-2}. Three lesions in this patient did not clear with a single treatment, one from each of the three dose regimens used. Although overall a higher percentage of lesions treated with 94 J cm^{-2} cleared after one treatment, compared with those which



(a)



(b)

Fig. 2. Plaques of Bowen's disease on leg (a) before and (b) 2 months following a single treatment with ALA-PDT using the prototype lamp.

received 125 J cm^{-2}, this difference was not statistically significant.

The perspex rod, with the higher fluence rate of 158 mW cm^{-2}, was attached to the fibre bundle for the treatment of 15 lesions, of which 10 cleared (67%) on a single treatment. The collimating lens (fluence rate 55 mW cm^{-2}) was attached to the bundle for the treatment of the nine larger lesions, with five lesions clearing (56%) in this group after a single treatment. This difference in clearance rate, however, was not significant.

Adverse effects

As treatment of the initial lesions (with 94 J cm^{-2}) was well tolerated, the study proceeded with the increase in dose as described. Side-effects were similar in frequency and severity between the different dosage groups and are therefore listed together.

No pain was experienced by patients during the treatment of 12 lesions. Pain during PDT was described as mild in a further 10, moderate in one, and severe in one lesion which was an

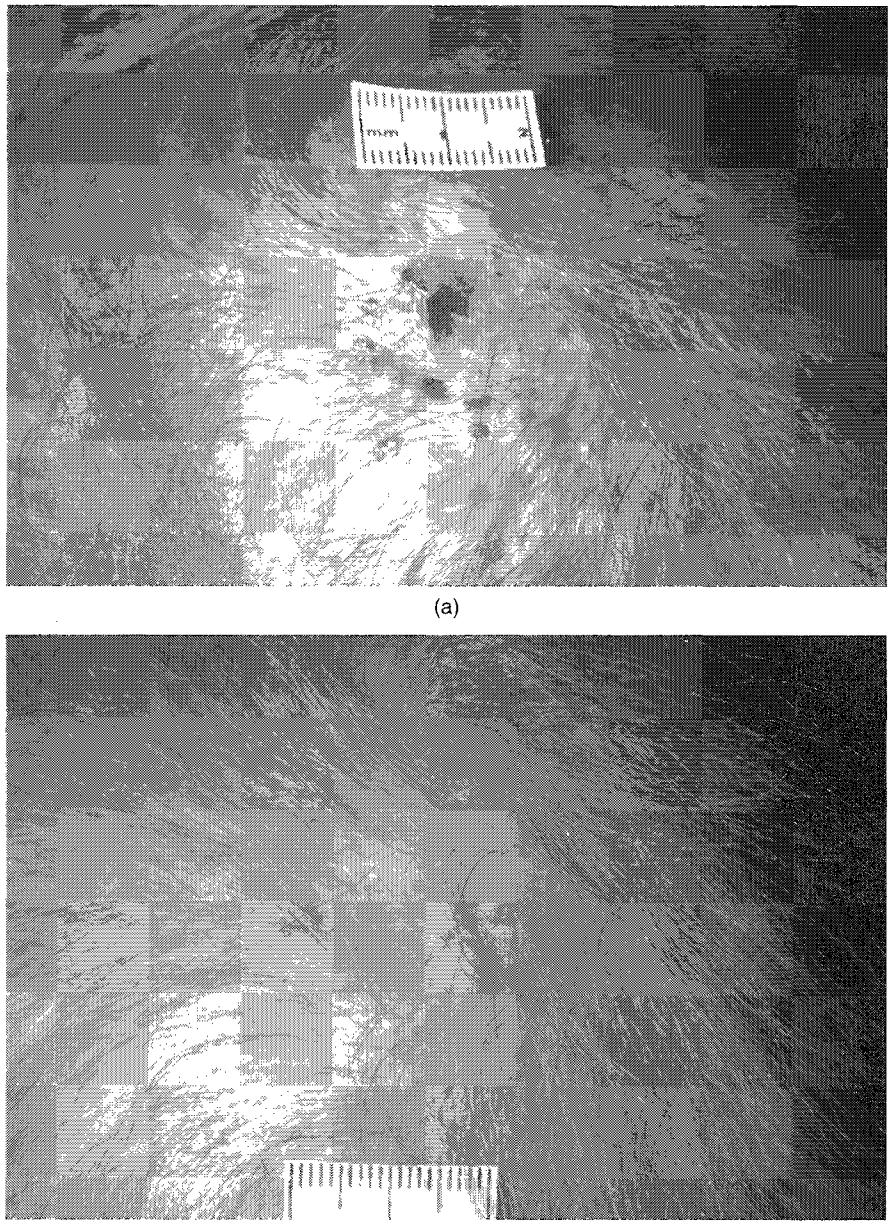


Fig. 3. Area of actinic keratosis on scalp (a) before and (b) 2 months following a single treatment with ALA-PDT using the prototype lamp.

area of Bowen's disease that had ulcerated prior to therapy. Only in this latter case was local anaesthesia administered. Over the 10 days following treatment, no pain was associated with 21 treated lesions, with mild discomfort lasting around 7 days described in the remaining three lesions. Whilst erythema and oedematous swelling of the treatment sites were evident on completion of irradiation, only three lesions proceeded to blister (by 2 days) with one area of Bowen's disease subsequently ulcerating. No photosensitivity reactions were evident following PDT.

A visible scar in the treatment field, outside diagnostic biopsy sites, was observed in only three treatment sites, all three areas of Bowen's disease treated on the ankle and overlying the Achilles tendon.

Recurrence rate

During the 12 months following clinical clearance of the 24 lesions, two areas of Bowen's disease recurred, both at 8 months in lesions treated with 125 J cm^{-2}. Clearance of these

two lesions was achieved with a further treatment session of PDT using the prototype lamp. This gives an overall complete response rate after 1 year of 92%.

DISCUSSION

This prototype non-laser source appears to be effective in facilitating ALA-PDT in clinical practice in the treatment of pre-malignant non-melanoma skin cancer. This paper reports a 100% initial clinical clearance, although two treatments with PDT were required to achieve clearance in 37% of lesions. The overall clearance rate at 1 year of 92% compares favourably with results from similar trials using laser light sources (8, 9). Cairnduff et al (8) reported an overall response rate of 89% at 18 months following a single treatment of 36 areas of Bowen's disease with ALA-PDT using a copper vapour/dye laser, irradiating lesions with 630 nm light at doses of 125–250 J cm^{-2}. Svanberg et al (9) treated 10 areas of Bowen's using ALA-PDT and 630 nm light from a pulsed frequency-doubled Nd-YAG laser. A complete response of 90% was obtained after a single treatment at a light dose of 60 J cm^{-2}, with the remaining lesion clearing after a second treatment, and no recurrence during a follow-up period of 6–14 months.

Whilst it is recognized that coherence of light is not required for effective photodynamic therapy, the development of effective incoherent light sources has been limited by difficulties in achieving an intensity of long wavelength light comparable to laser (10). Polychromatic light from modified slide projectors have been used by Kennedy and Wolf as the light source for ALA-PDT in the treatment of non-melanoma skin cancer (11, 12). However, such lamps, with relatively broad emission bandwidths, are inefficient sources of red light, which is considered to be optimal for PDT. Although other peaks of protoporphyrin IX exist (13) at shorter wavelengths (410, 510, 545 and 580 nm), light penetration in such spectral regions is significantly less, and light absorption by haemoglobin is greater. Karrer et al (14) recently described the successful treatment of basal cell carcinomas by PDT using a new incoherent light source, incorporating a 1200 W metal halogen light. This is a high intensity source designed to match that of lasers, although it has a bandwidth when filtered of 160 nm (580–740 nm).

The prototype lamp used in the present study was developed to provide many of the benefits of a laser, but at lower cost (approximately 10% the expense of a laser system) and in a portable, desktop package. The lamp showed negligible alteration in performance during the 6 months recruitment and treatment period. The ability to provide high intensity light within a narrow (and adjustable) 30 nm bandwidth, permitting the activation of photosensitizer at a given absorption peak, makes the prototype lamp a useful source with which to assess the efficacy of incoherent light in PDT. Unlike the non-laser sources described above, the prototype lamp can also deliver light down a fibre bundle, not only facilitating its potential use in endoscopic PDT, but permitting the easy and accurate alignment of the source over surface lesions. The lamp used in this clinical study was the first prototype constructed, a second more powerful version has now been evaluated in pre-clinical in vivo studies (7) and delivers twice the output of the original lamp (i.e. 1 W via the light guide), permitting shorter treatment times.

Acceptance of a new treatment, however, depends not only on efficacy and ease of operation, but on patient acceptance. ALA-PDT using the prototype lamp was well tolerated both during irradiation and in the follow-up period. The authors found a requirement for local anaesthesia only where the epidermis was not intact prior to irradiation. As expected, the majority of patients in this study were elderly, with lesions often on the lower leg, a poor site for healing. Therefore, the avoidance of ulceration following treatment in all but one lesion was encouraging. Avoidance of the prolonged photosensitivity reactions associated with previous systemic administration of photosensitizers (15, 16), permitted these patients to be managed easily on an out-patient basis.

The absence of clinically obvious scar formation, except in the three apparently site-dependent ankle lesions, is consistent with the good cosmetic results reported following laser-induced PDT for Bowen's disease (8, 9).

The wide variation in the dosimetry of light used in the treatment of Bowen's disease and actinic keratoses by ALA-PDT (8, 9, 11, 12), requires further study. Whilst the authors did not perform a dose ranging study, the present results would suggest 94 J cm^{-2} to be at least as effective as 125 J cm^{-2}. The

authors attempted to keep irradiance below thermal levels and noted no difference in outcome between those lesions treated at 55 mW cm^{-2} compared to 158 mW cm^{-2}.

Bowen's disease and actinic keratoses are intra-epidermal lesions, in contrast to the other non-melanoma skin cancers. Clearance rates reported for basal cell carcinomas treated by ALA-PDT (8, 9, 11, 12, 17) range from 34 to 91%, more variable than for Bowen's disease. Depth of penetration of activating light is likely to be important in influencing outcome, in addition to adequate absorption of photosensitizer (18, 19). Efficacy of ALA-PDT using this prototype lamp will therefore be important to establish in such lesions.

Following in vitro and in vivo assessment, this prototype lamp has now been shown to be an effective and practical desktop light source for use in ALA-PDT in Bowen's disease and actinic keratoses, although further research to optimize efficacy and define its clinical potential is required. A randomized comparison trial of ALA-PDT using this lamp, or cryotherapy in the treatment of Bowen's disease, is presently underway and the authors have also commenced a trial of the treatment of basal cell carcinomas using this light source.

ACKNOWLEDGEMENTS

The development of the lamp was supported by the Cancer Research Campaign (UK).

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Key words: Photodynamic therapy; Non-laser light source; 5-Aminolaevulinic acid; Non-melanoma skin cancer