A randomised assessor-blinded comparison of low irradiance and conventional irradiance photodynamic therapy for superficial non-melanoma skin cancer

Protocol

Chief Investigator:

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Introduction

Skin cancer is the commonest malignancy in Caucasians and is a major cause of morbidity and burden on health services[1]. Patients with superficial non-melanoma skin cancer (NMSC) are frequently elderly and frail and surgery is often not appropriate or feasible and non–surgical approaches, such as topical photodynamic therapy (PDT), are ideally suited to treat these lesions. Topical PDT has been increasingly used to non-invasively treat superficial NMSC and dysplasia since its introduction in 1990 and this now has National and European Guidelines for use and NICE technology (http://guidance.nice.org.uk/IPG155) and Scottish Medicines Consortium approval (Methyl aminolevulinate (Metvix cream) - SMC approval for AK (50/03) and BCC (51/03) November 2003 http://www.scottishmedicines.org.uk)[2-4].

At present PDT is hospital-based and requires the patient to come up as a day case, wait for 3 - 6 hours (depending on the treatment regime), while the cream is in place and conversion to the photosensitiser occurs, before irradiation takes place over a further 15 - 20 minutes. Essentially, patients are at the hospital for most of the day. Treatment is repeated at one week, and these two treatments one week apart constitute a treatment cycle.

Subsequently, at three month follow-up, if complete resolution of the lesion is not apparent then a second treatment cycle is undertaken. Thus, this will require the patient to attend for four day case procedures, which is tiring and time consuming for elderly, frail patients and, because of the time involved, limits the number of patients that can be treated in one session at the hospital. Thus, there is a major demand for treatment to be more efficient and patient-orientated.

Furthermore, during the irradiation of PDT significant pain is experienced by most patients. In our Unit, 16% of PDT treatments (n=4717) were associated with severe pain. The mechanism of PDT-induced pain is not well understood and conventional methods of pain relief, such as topical anaesthetics are not very effective[5-7]. This can limit successful delivery of PDT and negatively impact on the patient's experience of treatment.

Low irradiance irradiation enhances photobleaching efficiency and the PDT effect when compared with higher irradiance light delivery, as oxygen depletion is less rapid when irradiation occurs over a longer time period[8], [reviewed in 9]). Furthermore, there is preliminary evidence that low irradiance PDT is less painful than conventional PDT, and indeed if this is the case, then this would significantly improve the patient's experience of PDT and successful delivery and wide acceptance of this therapy[10,11]. We will translate these findings into clinical practice by investigating low irradiance ambulatory PDT in the proposed clinical trial.

Results of pilot studies

A novel CE-marked portable red light LED source has been developed in the form of a "skin cancer plaster" (Ambulight, Ambicare Health). This is able to deliver a standard PDT light dose at very low irradiance over a prolonged time period. Thus, the Ambulight delivers light at low irradiance (7 mW/cm^2 as compared to 80-90 mW/cm^2 with conventional PDT), such that the total dose (75 J/cm^2) is delivered over 3 hours as compared to approximately 15 - 20 minutes for conventional hospital-based devices. The light source is small, light and compact and attached to a battery pack, such that patients can put the battery pack in a pocket and be mobile during treatment. This has been established in clinical practice in order for patients to receive treatment at home.

Initial studies of prototype devices in small numbers of patients showed that it could be successfully used for low irradiance topical PDT, and preliminary data suggested that treatment was less painful and of similar efficacy to conventional PDT[9,12]. Subsequently, the more portable and compact Ambulight device was developed and our preliminary clinical data using this in eight patients with multiple lesions of NMSC who were treated simultaneously with both conventional PDT and low irradiance Ambulight PDT showed a significant difference in pain experienced, with the VAS score for pain of conventional PDT being 5.2 (2 - 9) cm compared with 1.5 (0 – 3) cm for low irradiance Ambulight PDT (values given as median (range), $p<0.05$).

Study aims

The primary aim of this study is to examine whether the pain and discomfort of topical PDT is significantly different when using the low irradiance ambulatory LED device compared with conventional higher irradiance PDT and this is the first randomised controlled trial in this important clinical area. We will also examine possible differences in phototoxicity of the two

regimes and assess patient evaluation of treatment. The secondary end-point of efficacy of the two treatment regimes will be examined.

Research Questions

1. Is there a significant difference in pain and phototoxicity experienced with low irradiance ambulatory PDT compared with conventional higher irradiance PDT?
2. Is there a large difference in efficacy of treatments at one year follow-up?
3. Do patients prefer ambulatory or conventional PDT?

Clinical trial study design

a prospective, randomised, controlled, single-blind, comparison of low irradiance ambulatory MAL-PDT with conventional higher irradiance MAL PDT for patients with superficial NMSC.

Participants

Study details would be disseminated to local dermatology colleagues and plastic surgeons, as these are the sources of referral to the PDT Clinic in the Photobiology Unit. The PI will screen all referral letters for PDT and any patient with superficial basal cell carcinoma or Bowen's disease (diameter =/< 2 cm) will be sent out a Participant Information Sheet (PIS). They will be invited to participate in the study when they attend the PDT clinic. Exclusion criteria will be patients with lesions >2 cm diameter, patients unable to give consent, patients with lesions at sites where the portable device would be difficult to apply such as highly curved sites e.g. rim of ear. The aim will be to recruit 50 patients and they will be randomised to receive either low irradiance ambulatory PDT or conventional higher irradiance PDT. After obtaining written consent, demographic details and assessment of the lesion will be undertaken and the area will be mapped and photographed.

Randomisation

A blocked randomisation list will be computer generated. Randomisation codes will be concealed in opaque sealed envelopes and will only be opened at the time of entry of the patient to the study and this will be carried out by the Photobiology Technician. Patients will then receive their randomised treatment and this will also be undertaken by the Photobiology Technician as is the normal clinical practice in the PDT Unit.

Interventions

The study outline is shown in **Appendix 1**.

Treatment allocations will be:

Conventional PDT: Lesions will be gently scraped using a disposable ring curette (Stiefel®) and MAL cream (16% w/v, Galdema UK) will be applied to the lesion and occluded under Tegaderm® and Mepore® for three hours. Dressings and residual cream will then be carefully removed and irradiation of the lesion, including a 5 mm rim of clinically normal-appearing tissue, will be undertaken. Irradiation will be performed using the Aktilite 128/16 device (peak wavelength 636 nm, full width half maximum (FWHM) 18 nm) to deliver a total dose of 75 J/cm^2. Immediately after irradiation a dressing will be applied and the patient will go home.

Low irradiance ambulatory PDT: The lesion will be prepared and MAL cream applied as above. Immediately after cream application, the Ambulight device will be applied and will adhere to the

treatment site. This is automated to be in place and switched off for three hours and will then switch on and irradiate the lesion for a further three hours to deliver a total dose of 75 J/cm^2 (peak wavelength 640 nm, FWHM 25 nm). The Ambulight device has a green light displayed when device is active. A red light will be displayed if the device is not working properly. The green light will go off at the end of the planned automated treatment time. The patient will be free to go home once the cream and device are in place and will be advised about how to remove the plaster at the end of the irradiation period. The battery pack and used adhesive plaster are put in bags and then in the pre-paid envelope (supplied by the treatment centre) and posted back to the Photobiology Unit where the battery pack will be cleaned, recharged and re-calibrated and the dressing head sent back to the manufacturer for recycling.

Assessments (Appendix 1 and 2)

Re-treatment and assessment*:* Seven days later the patient will return for the second treatment, which will be repeated as per the first week and the treatment allocation. Prior to the second treatment, patients will be asked to complete a VAS score of 0 - 10 cm for the maximal recall of pain and discomfort experienced during the first PDT treatment. Additionally, the phototoxic reaction of the first treatment will also be assessed on a semi-quantitative scale for erythema (0-3), oedema (0-1), blistering (0-1), crusting (0-1) and ulceration (0-1) at this time point. This second treatment then completes the first treatment cycle.

Follow-up assessment at one week: The patient will return one week later and, again, pain and phototoxicity will be assessed as above.

Follow-up assessment at three months: Patients will be reviewed at three months and a clinical assessment of whether there is clearance (defined as absence of residual surface change, scale, infiltration or significant erythema) (CR), partial response (presence of residual surface change, scale, infiltration or prominent erythema) (PR) or no response (no change from baseline appearance) (NR) will be made. For patients with PR or NR a second treatment cycle will be performed according to the original randomisation. Again, pain recall and phototoxicity will be assessed one week after each of these treatments as per the first treatment cycle.

Follow-up assessment at six months: All patients will receive a follow-up assessment at 6 months. Those who do not exhibit a complete response on clinical assessment (after one or two treatment cycles) will receive an alternative treatment at the doctor's discretion and the patient will have completed the study. An overall assessment of the patient's evaluation of treatment will also be recorded in all patients's notes at this time point. This evaluation will take into account the patient's perception of efficacy, adverse effects and convenience of treatment and their overall satisfaction with the PDT regime they received.

Follow-up assessment at 12 months: All patients remaining in the study (i.e. those with CR at 3 months and/or 6 months) will undergo final clinical assessment of efficacy of treatment (clear or not clear) at 12 months after the first PDT treatment cycle. Histological analysis will not be undertaken as part of the study as these patients will usually have been selected for PDT on the basis that surgery was not considered appropriate.

Data processing and statistical analysis

Stastistical power*:* From our original published data with the prototype device, the mean pain score of patients treated with ambulatory low irradiance PDT (n=12) was 1.25 (standard deviation 0.4) and was 5.26 (standard deviation 2.38) for a historical cohort of patients treated

with conventional PDT (n=50) (10). Based on this we estimated that to give 90% power to detect as significant at the 5% level ($p<0.05$ as significant), a difference in mean pain score in one group of 2 compared with the mean pain score of 4 in the other group, assuming two-sided testing, a minimum of 36 subjects would be needed. Therefore, we plan to incorporate a safety margin recruiting 50 subjects given the old and frail nature of patients as this would account for any drop-outs. Over the last 2 years, we have treated 60 - 80 new patients per year with topical PDT. 82% of these were patients with Bowen's disease or superficial basal cell carcinoma and we estimate that of these at least 50% should fit the eligibility criteria for the study. Therefore, we estimate that recruitment will be finished within 2 years, and with a one year follow-up, the overall study will be completed within 3 years.

Blinding*:* Blinding of the patient and the Photobiology technician will not be possible. The study will remain blinded to the CI and co-investigators until database lock, after which the study statistician will be unblinded. Any necessary clinical communications will be carried out by a Photobiology Unit clinician unrelated to the study. These clinicians will be the photodermatology Specialist Registrars.

Data recording and analysis: Analyses will involve assessment of tabulated and graphical data and this will be followed by use of appropriate statistical tests comparing the pre-planned outcome measures. Analysis will be on an intention-to-treat basis, where possible. Reporting of study data will be based on CONSORT guidance.

Timetable of work

Patient recruitment will be completed by the end of year 2 and follow up by the end of year 3.
Final analysis of outcome measures will be undertaken in year 3.

Key references

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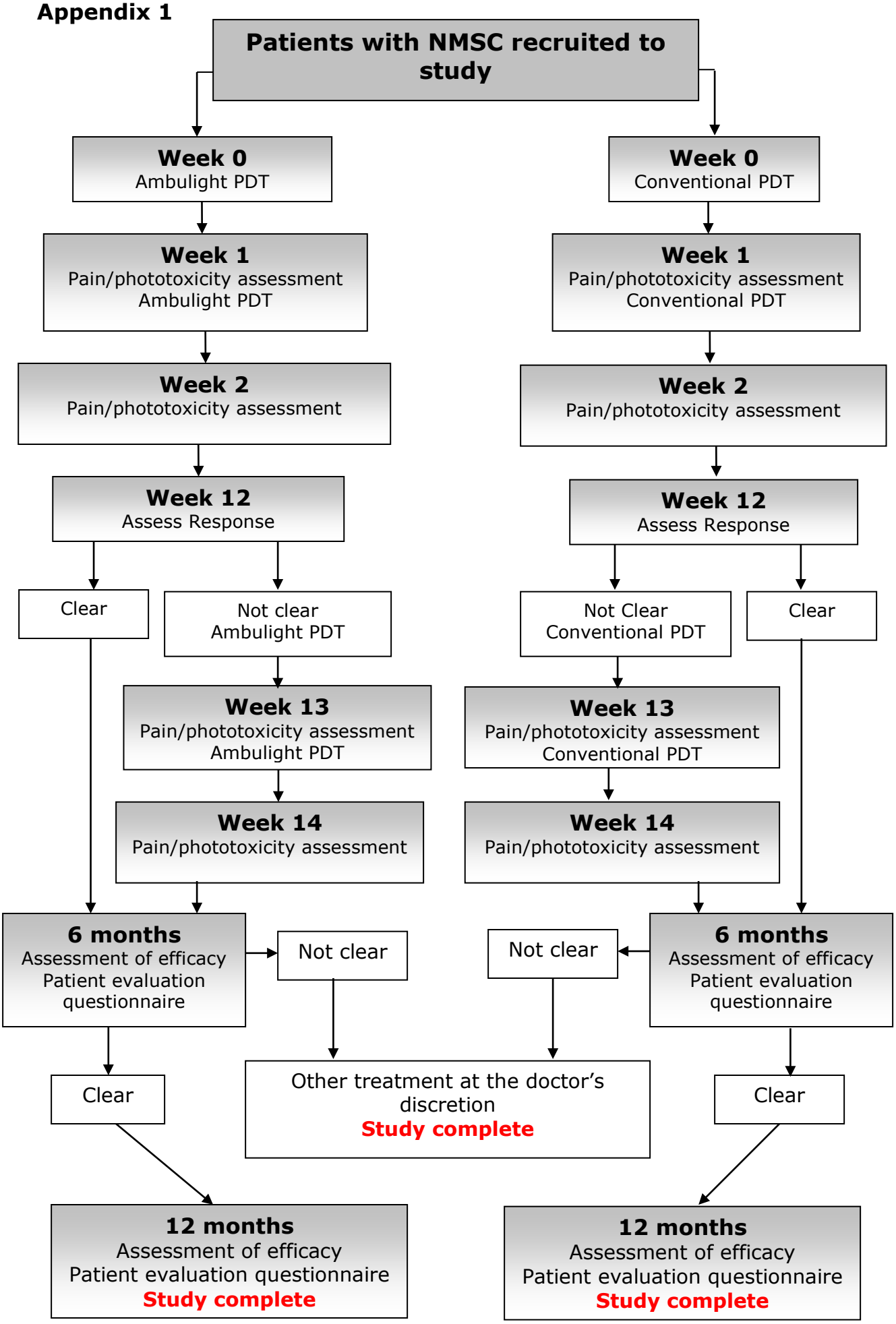
Appendix 1


Patients with NMSC recruited to study
Week 0
Ambulight PDT
Week 0
Conventional PDT
Week 1
Pain/phototoxicity assessment
Ambulight PDT
Week 1
Pain/phototoxicity assessment
Conventional PDT
Week 2
Pain/phototoxicity assessment
Week 2
Pain/phototoxicity assessment
Week 12
Assess Response
Week 12
Assess Response
Clear
Not clear
Ambulight PDT
Not Clear
Conventional PDT
Clear
Week 13
Pain/phototoxicity assessment
Ambulight PDT
Week 13
Pain/phototoxicity assessment
Conventional PDT
Week 14
Pain/phototoxicity assessment
Week 14
Pain/phototoxicity assessment
6 months
Assessment of efficacy
Patient evaluation questionnaire
Not clear
Not clear
6 months
Assessment of efficacy
Patient evaluation questionnaire
Clear
Other treatment at the doctor's discretion
Study complete
Clear
12 months
Assessment of efficacy
Patient evaluation questionnaire
Study complete
12 months
Assessment of efficacy
Patient evaluation questionnaire
Study complete

Appendix 2 **Study I.D.** [ ]

A randomised controlled trial of ambulatory low irradiance PDT and conventional PDT for superficial non-melanoma skin cancer

Questionnaire: Patient evaluation of treatment regime

A. Effectiveness of treatment
1. NR – No response, not effective
2. PR – Partial response, partially effective
3. CR – complete response, completely effective

B. Side effects of treatment – e.g. pain and inflammation
1. Severe
2. Moderate
3. Mild
4. None/minimal

C. Practicalities of treatment – e.g. ease of use, travel, time, inconvenience
1. Very disruptive and difficult
2. Moderately disruptive and difficult
3. Minimally disruptive and difficult

Total minimum score: 3
Total maximum score: 10

Overall patient evaluation:

How would you rate treatment overall?

Please indicate by scoring across the line below between 0 to 10

0 ——————————————————————————— 10

Treatment very poor and I would not have again

Treatment excellent and I would have again