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Is there an optimal irradiation dose for PDT: 37 Jcm^{-2} or 75 Jcm^{-2}?

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Topical photodynamic therapy (PDT) is widely used for the treatment of Bowen's disease (BD) and superficial basal cell carcinoma (BCC). The process involves oxygen-dependent light activation of the tissue-localised photosensitiser, protoporphyrin IX, three hours after pro-drug application to the lesion. Current approved and licensed regimens involve application of either methylaminolevulinate (MAL, Metvix, Galderma, Switzerland) or 5-aminolaevulinic acid in nanocolloid emulsion (ALA, Ameluz gel, Biofrontera, Germany) and subsequent light activation using narrow spectrum (630-635 nm) red light (typically light emitting diodes (LEDs)), at an unweighted radiant exposure ("dose") of 37 Jcm^{-2} (1-3).

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The original recommended use of topical PDT involved irradiation with a tungsten filament source (Photocure ASA, Norway), wavelength range 570-730 nm, delivering a dose of 75 Jcm^{-2} (4). This was our practice until 2004, when we changed to the recommended use of an LED source (Aktilite CL128, Photocure ASA, Norway) delivering a dose of 37 Jcm^{-2}. (3). However, we observed lower efficacy with this lower PDT irradiation dose, so we reverted to an LED dose of 75 Jcm^{-2}.

It is not known whether PDT outcomes for BD and BCC are influenced by light dose; specifically by 37 Jcm^{-2} or 75 Jcm^{-2}. It would be more efficient to use a lower light dose if efficacy was similar. Therefore, we compared the outcomes of two clinically utilised PDT regimens in order to ascertain whether total light dose affects treatment efficacy. Patients referred for PDT for BD or BCC were alternately treated with either 37 Jcm^{-2} or 75 Jcm^{-2} over a one-year period. A total of 62 lesions were treated, with 31 (15 BD and 16 SBCC) irradiated at 37 Jcm^{-2} and 31 (10 BD, 20 sBCC and one nodular BCC) irradiated at 75 Jcm^{-2}. Patients were reviewed three months following the first treatment cycle and a second treatment cycle was administered if partial lesional response was achieved at that time-point. Final review was 12 months following the initial treatment cycle.

The data obtained for these treatments are summarised in Table 1. Similar outcomes were achieved at three months after the first PDT cycle, with 64.5% and 67.7% lesion clearance for the 37 Jcm^{-2} and 75 Jcm^{2} treatment groups respectively. Similar proportions of each group (35.5%, 32.3%) received a second treatment cycle. The 12-month outcomes showed the most striking difference between the regimens, with clearance in 67.7% of those treated with 37 Jcm^{-2} versus 90.3% of lesions treated with 75 Jcm^{-2}.

These data provide evidence in support of improved outcomes for PDT for BD and BCC lesions when using a higher dose of 75 Jcm^{-2} of 630 nm red LED light than when using the lower dose of 37 Jcm^{-2} as recommended in the licensed PDT regimen.

It is unclear from the literature as to the reason for the recommended dose of 37 Jcm^{-2} when using the narrow spectrum red LED. Mathematical modelling shows that such an LED was more effective than a broadband light source for skin penetration depths greater than 1.5 mm, reaching a maximum ratio between light sources of 1.26 at a depth of 8 mm (4). In mouse skin, the authors also showed that the fluence required by the broadband source was 1.30 times higher than that of the LED source to produce 90% PpIX bleaching. In solution, this value was 2.24, indicating that the LED was proportionately more effective at inducing photobleaching in solution than in mouse skin. Monte Carlo simulations indicate that, at a 2mm depth, the photodynamic dose for the red LED source is more than twice that of a broadband lamp (5). However, these simulations also demonstrate that effective treatment depth is

increased at higher light dose and that singlet oxygen production still occurs at depth even after surface layers have been photobleached (6, 7). To our knowledge, there is no clinical study comparing the efficacy of the two red LED light doses (37 Jcm^{-2} and 75 Jcm^{-2}) for PDT in BCC or Bowen's disease.

In this study, the use of 75 Jcm^{-2} was associated with notably higher clearance rates at 12 month follow up after PDT when compared with the use of 37 Jcm^{-2}. Optimising PDT regimens in order to ensure improved longer-term outcomes is key to the efficacy and acceptance of PDT for patients with superficial non-melanoma skin cancer and pre-cancerous change. These data indicate that higher irradiation doses may be more effective, although further studies are required to determine the most efficacious quantity of light.

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Conflicts of Interest:

Professor Sally Ibbotson has received honoraria and travel expenses from Galderma, Ambicare, and Spirit Healthcare

Doctor Ewan Eadie has received travel expenses for conference attendance from Galderma

Doctor Paul O'Mahoney has received travel expenses for conference attendance from Galderma

Figures:

Table 1: PDT treatment outcomes at 3 and 12 month follow up following use of an irradiation dose of 37 J/cm^2 or 75 J/cm^2

	37 Jcm^{-2}		**75 Jcm^{-2}**	
	Number	Percentage	Number	Percentage
Lesions treated	31	100.0	31	100.0
Lesions clear at 3 month review	20	64.5	21	67.7
Lesions clear at 12 Month Review (single treatment)	16	51.6	18	58.1
Lesions requiring repeat PDT at 3 Months	11	35.5	10	32.3
Lesions clear at 3 month review (repeat treatment)	8	72.7	10	100.0
Lesions clear at 12 month review (repeat treatment)	3	27.3	10	100.0
Lesions clear at 12 month review (overall)	21	67.7	28	90.3