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SHORT RESEARCH ARTICLE

Photodynamic therapy with new sublingual sensitiser

Photosoft®E4 for cancer: a case series [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: An increasing number of patients seek complementary therapies for cancer treatment, the leading cause of death in the developed world. Photodynamic therapy (PDT), the combination of light and a photosensitiser agent, has provided some promising results in cancer therapy. New photosensitiser agents are continuously being developed to improve tolerability and effectiveness. There is a need to objectively evaluate clinical data from PDT patients.

Methods: Here we report a case series using the new sublingually administered, chlorophyll-based photosensitiser Photosoft®E4 and an external laser light in a group of ten adult cancer patients not undergoing other concurrent therapies. PDT was administered for three treatment cycles with an average of 14 light treatments per patient, consisting of agent administration and laser treatment on alternate days over 3 months. Safety, tolerability and effectiveness on tumour palliation were monitored.

Results: Patients in this study presented with a variety of cancer types and stages; half of the patients had breast cancer, and 40% had metastases. We found Photosoft®E4 to be safe and highly tolerable. However, overall disease status was not improved in our group of patients.

Conclusions: Future research is required to determine the bioavailability of Photosoft®E4 and its uptake in tumour tissue, pharmacokinetics and dosing regimen, as well as the best mode of light delivery for the *in vivo* sensitiser activation.

Open Peer Review**Approval Status**

	1	2
version 1 26 Jul 2013	view	view
1. Michael Hamblin , Harvard Medical School, MA, USA		
2. David Kessel , Wayne State University School of Medicine, Detroit, MI, USA		
Any reports and responses or comments on the article can be found at the end of the article.		

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Introduction

Cancer is the leading cause of death in the Western world, accounting for 13% of all deaths worldwide, and about three in ten deaths in Australia^{1,2}. It is estimated that 800,000 Australians (3.3%) were living with cancer in 2007, and an additional 100,000–125,000 are expected to be diagnosed every year, contributing 19% of the total disease burden in 2012³.

An increasing number of patients seek complementary and unconventional cancer therapies. While in 1998 an average of 31.4% of patients in Western countries sought complementary and alternative medical (CAM) therapies⁴, three-quarters of the patients in a cancer centre in the United States used at least one CAM modality in 2005, and the majority of those (58%) were initiated after cancer diagnosis⁵.

The main CAM modalities sought in addition to conventional cancer therapies include special diets, dietary supplements and herbs, psychotherapy, movement therapy, mind-body therapies and spirituality based interventions^{4–7}. More recently, photodynamic therapy (PDT) has become an acceptable adjunct cancer therapy, providing some promising results. A systematic review of the effect of PDT-alone or in conjunction with conventional therapy-on patients with non-small cell lung carcinoma, showed a response rate of 30.8–84.8% on mainly inoperable disease, with a 5-year survival rate of 43.4–72%, a considerable improvement to the survival rate of 15–35% for inoperable and metastasised cancers using conventional treatment alone⁸. Other types of cancers treated with PDT such as head and neck cancer showed an 89% 5-year survival rate for superficial cancers, compared with 75% using conventional therapies alone^{1,9,10}.

PDT combines a photosensitiser and light to cause selective damage to the target tissue^{10–13}. Laser light of a specific wavelength of maximum absorbance matched to the photosensitiser is directly toxic to the cell and also interacts with local intracellular oxygen molecules to activate singlet oxygen, which in turn destroys the target tissue¹⁴. Cancer cells accumulate a higher concentration of the photosensitiser than surrounding healthy tissue, and therefore are a selective target for light treatment^{10–13}.

A range of photosensitisers are available for malignant tumours. Early drugs were based on haemato-porphyrin derivatives, while newer drugs based on porphyrin, chlorin or chlorophyll derivatives have been developed to reduce the phototoxic effects of the early photosensitisers¹⁵. Pharmacokinetic *in vitro* studies on chlorophyll-based photosensitisers have demonstrated uptake in tumour cells with a range of clearance times¹⁶, and the safety of similar chlorophyll-based photosensitisers, such as Radachlorin® or Sonoflora/Sonnemed® has been demonstrated in animal studies and high tolerability has been observed in small human trials^{17–19}.

While most photosensitisers are administered intravenously, the new chlorophyll-based sensitiser Photosoft®E4 was developed to be taken sublingually²⁰. A similar chlorophyll-based and sublingually administered photosensitiser Sonoflora® was found to be safe and effective in the sonodynamic treatment (a combination of light and ultrasound) of breast cancer patients¹⁹.

As patients are increasingly seeking and accessing information on complementary treatment options for their cancer treatment, there is a need for the objective evaluation and dissemination of current clinical data on available therapies such as PDT, to help with decision making²¹.

Recently, a new generation photosensitiser has become available in Australia, Photosoft®E4. While there is extensive clinical experience with this sublingual photosensitiser in China where there have been several promising case study reports²², concerns have been expressed about the effectiveness of the modified technology by others^{23,24}.

For these reasons, there is a need to evaluate clinical experiences with PDT in other countries, including Australia. Here we report on the safety and tolerability of Photosoft®E4 and gauge the effect of the PDT treatment in a group of cancer patients not undergoing any concurrent therapies.

Methods

Study design

Data for this case series report was collected at the National Institute of Integrative Medicine, Melbourne between January and November 2012. The aims of this pilot study were to determine the safety and tolerability of sublingual administration of a new chlorophyll-based photosensitiser and external laser treatment, and to ascertain the effectiveness of PDT and tumour palliation.

Patients

Ten patients (8 women, 2 men) were enrolled (mean age 56.6 years, range 35–81 years), representative of the common clinical population. Inclusion criteria were: adults with primary or metastatic cancer, no concomitant other therapies during PDT treatment (including chemo- or radiotherapy, sublingual or intravenous medical therapy, as per patient's request), ability to take medication sublingually, compliance with study protocol, and informed written consent. Patients were excluded if tumours were close to large blood vessels, or invading the trachea, if patients were pregnant or lactating, or with mental impairment. Participating patients were treated with PDT free of charge.

The pilot study was approved by the Human Research Ethics Committee at the National Institute of Integrative Medicine. Clinical Trial Notification (CTN) numbers for equipment and the photosensitiser were obtained from the Therapeutic Goods Administration Australia.

PDT treatment

The protocol was based on the protocol used at clinics in China at the time of the start of our trial²². The photosensitiser PhotoSoft®E4 (Chlorin-e6-Chlorophyllin-A-Zinc-complex, The Cho group, supplied by Sekhsaria Chemicals Ltd, CTN 050/2012), was administered sublingually at a dose of 5 mg/kg body weight.

A multi-frequency laser model PDT630II (The Cho group, Guilin Xingda Photoelectricity Medical Equipment Co Ltd, CTN 062/2012) emitting blue, red and infra-red laser light with peak wavelengths at 460 nm, 660 nm, and 870 nm with a total light-dose

of 45 J/cm² and a fluence-rate of 25 mW/cm² was used to irradiate each tumour site for 30 min (Figure 1). After the external focused laser, all patients were treated in a whole-body LED-light-bed model NGPDT (The Cho group, Guilin Xingda Photoelectricity Medical Equipment Co Ltd) emitting the same wavelengths as the external laser for 30 min to target any circulating tumour cells (Figure 2).

Figure 1. External focussed multi-frequency laser.

Figure 2. Full LED light bed.

The treatment comprised of three cycles, with each cycle consisting of 4–5 laser treatments on alternate days over the course of nine days, followed by a 4–5 week break. The photosensitiser was taken sublingually 18–26 hours prior to each laser treatment. In total, patients who completed the three treatment cycles received 12–15 light treatments (mean=14) over three months.

Safety and tolerability

Safety and tolerability were assessed during and after each treatment session by the treating physician. A semi-structured questionnaire assessed whether patients had any unusual sensations, including gastrointestinal symptoms, feeling of tiredness or malaise, pain, or elevated temperature between treatment sessions (see [Supplementary material](#)).

Tumour size

The appearance and size of the primary tumour site and the presence and extent of any metastases were assessed clinically and by Computer-Tomography (CT), Magnetic-Resonance-Imaging (MRI), or ultrasound scan before baseline and at three months after completion of treatment.

Results

Half of the patients (n=5) had breast cancer, three of which had declined surgery and were without metastases, and two had local recurrence and/or metastases after mastectomy (Table 1). Other types of cancer were basal salivary (n=1), neck (n=1), both of whom had no prior mainstream cancer treatment, and stage-IV cervical (n=2) and stage-IV pancreatic cancer (n=1) who had all undergone surgery and/or chemotherapy and radiotherapy previously (Table 1).

All breast cancer patients completed the full course of 3x4 treatments (n=5); other patients underwent 1–2 cycles of treatment before withdrawal due to disease progression (n=3) or uptake of other therapies (n=2).

Patients were treated with a 30 min external laser per tumour site plus 30 min exposure in the light bed, ranging from 1–2 hour-sessions for primary non-metastatic cancers (n=5), and 2–4 hour-sessions for patients with metastasis (n=5).

All patients tolerated the sublingual administration of the photosensitiser well and did not report any side effects other than unpleasant taste (n=10). Laser treatment caused localised sensations such as tingling in some patients (n=5). No phototoxic reactions were experienced. Some patients (n=3) reported localised tingling of variable intensity at the tumour site 1–2 weeks after treatment, lasting between 30 min to overnight.

One patient with a superficial breast tumour showed some localised reduction of tumour size (Table 1, ID4). Diagnostic imaging by CT, MRI or ultrasound scans showed evidence of disease progression in all patients after three months regardless of the type or stage of cancer (Table 1). However, one patient (ID1, breast cancer) who continued with PDT treatment reported clinically stable disease at six months after study completion (tumour-size 3.6 cm³).

Discussion

In our study, the photosensitiser PhotoSoft®E4 taken sublingually at a dose of 5 mg/kg up to 15 times over three months was tolerated

Table 1. Patient characteristics and outcomes.

ID	Gender	Age (years)	Type of cancer	Treatment* prior to study	Scan at baseline		Scan at end of study		Completed treatment** schedule
					Tumour size	Time (days) before first treatment	Tumour size	Time (days) after last treatment	
1	F	47	Breast	None	2.3 cm ³ (U)	21	3.6 cm ³ (U)	37	Yes (14x)
2	F	46	Breast	None	7.3 cm ³ (U)	28	14 cm ³ (U)	35	Yes (15x)
3	F	80	Breast	None	3.3 cm ³ (CT)	42	4.9 cm ³ (CT)	39	Yes (12x)
4	F	41	Breast superficial	Surgery	18 cm ² (CP)	0	11.6 cm ² (CP), Bone metastasis (CT)	0 (CP), 6, 12 (CT, after cycle 1; 1 after cycle 3)	Yes (13x)
5	F	68	Liver stage IV (primary breast, mastectomy)	Surgery	16 lesions, Largest: 95 cm ³ (CT)	1	20 lesions, Largest: 103 cm ³ (CT)	19	Yes (15x)
6	F	55	Basal salivary	Biopsy	Not detectable (CT), but pain, tinnitus, visible growth	1	Disease progression (CT), other treatment	10	Withdrew after 2 cycles (10x)
7	M	54	Neck	None	3.9 cm ² (CT)	42	Disease progression (CT), other treatment	30	Withdrew after 2 cycles (8x)
8	M	64	Pancreatic, lymph metastasis	Surgery, chemo-, radiotherapy	Lymph 2.1 cm (CT)	35	Disease progression (CT)	28	Withdrew after 1 cycle (5x)
9	F	35	Cervical stage IV	Surgery, chemo-, radiotherapy	32 cm ³ (U, CT)	6	Disease progression (U, CT)	10	Withdrew after 2.5 cycles (10x)
10	F	75	Cervical stage IV	Chemo-, radiotherapy	1287 cm ³ (MRI)	9	Disease progression (MRI)	29	Withdrew after 1 cycle (5x)

*Mainstream treatment, including surgery, chemotherapy, radiotherapy.

** 1 cycle consisted of 4–5 laser treatment sessions.

CP = Clinical Photoimage; CT = Computer Tomography; F = Female; M = Male; MRI = Magnetic Resonance Imaging; U = Ultrasound; x = times laser treatment.

well by all cancer patients and no phototoxic effects were observed. The high tolerability of the photosensitizer is in line with international reports from clinical centres using similar agents¹⁹. However, photodynamic therapy of the sublingually administered photosensitizer with external laser light did not improve the overall disease status in our group of patients.

To date, most photosensitizers are administered intravenously, and the pharmacokinetics of sublingually administered photosensitizing agents has not been studied extensively. However, one study found that biodistribution and pharmacokinetics of another photosensitizer 5-aminolaevulinic-acid (ALA) in the human gastrointestinal tract and urinary bladder was comparable if administered sublingually or intravenously²⁵. In addition, sublingual administration of Photosoft®E4

was shown to be taken up selectively by tumour cells in prostate cancer patients²⁶. However, more research is needed on the bio-distribution, uptake in different types of tumour tissue²⁷, and pharmacokinetics of the photosensitizer PhotoSoft®E4. Pharmacokinetic data would also ascertain the optimal time interval between drug intake and light administration²⁸. In our study, we used a 24-hour-interval, which is in line with intervals used in studies with early photosensitizers such as Photofrin®, as well as the chlorophyll-based photosensitizer Sonoflora®^{19,29,30}. Interestingly, a fractionated drug-dose (the administration of the photosensitizer at multiple time intervals before light activation) ranging between 15 minutes to four hours prior to light therapy has resulted in superior therapeutic effects for a variety of chlorophyll-based photosensitizers^{11,29,31}. Fractionated drug-dosing has been shown to target tumours by

different mechanisms, involving either vascular damage with a short-interval laser treatment or direct tumour-cell apoptosis with a long-interval laser treatment²⁹. Furthermore, sonodynamic therapy has provided promising results with sublingually administered chlorophyll-based photosensitisers similar to PhotoSoft®E4¹⁹.

Our study had a few limitations, including the small number of patients, and the diverse range of cancer types and stages. However, patients were representative of the common clinical population seeking alternative options for their cancer treatment. In addition, the number of patients was sufficient to elucidate the potential effect of the treatment following the protocol as outlined.

A limitation of the protocol was that we used external laser equipment emitting wavelengths between 460–870 nm. Light penetration through skin or muscle increases with wavelength, and is estimated to reach with 37% density between 2.5 and 9 mm of tissue^{32,33}. Interstitial administration of laser light facilitates penetration and reach of deeper tumours³⁴, but may be too invasive for most patients.

Conclusions

This clinical study indicates the safety and high tolerability of the photosensitiser PhotoSoft®E4, if taken sublingually at a dosage of 5mg/kg up to 15 times within a three month period. However, the protocol for the photodynamic therapy used in this trial as well as in clinical settings by others previously provided no benefit to

treatment-related outcomes. More research is required to determine the bioavailability and uptake in tumour tissue, pharmacokinetics and dosing regimen, as well as the best mode of light delivery for the activation of the *in vivo* sensitiser.

Author contributions

AS conceptualised the study, secured support, and developed study design with contributions from all authors. MW was responsible for enrolment of patients, application of PDT treatment, and data collection. MW and KR analysed and interpreted data. KR prepared the manuscript with feedback from all co-authors. All authors approved the final version of the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

Village Roadshow provided financial support for the study.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary material

Tolerability of PDT treatment

1) Did you experience any side effects **during** the PDT treatment?

Yes []

No []

If yes, please give details:

2) Did you experience any side effects **since the last** PDT treatment?

Yes []

No []

If yes, please give details (in your own words):

	Since the last PDT treatment....	Yes*	If yes, what did you do?	No
2b	...did you have any unusual sensations?			
2c	...did you feel unwell?			
2d	... did you feel unusually tired?			
2e	...did you feel any pain?			
2f	...did you have an elevated temperature?			

*If yes, please give more detail including when and for how long.

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Reviewer Report 23 October 2013

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David Kessel

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It is not clear what information this report is designed to convey. PDT is not 'alternative' therapy, having been approved by the FDA for some indications and showing evidence for effective cancer control. The approach described here seems to be based on a random trial & error method with no consideration for pharmacokinetics, biodistribution or dosimetry. There has been some enthusiasm for publication of negative reports so as to tell future investigators what not to do, so in that sense, this report qualifies.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 03 October 2013

<https://doi.org/10.5256/f1000research.1823.r1947>

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Michael Hamblin

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This paper reports a case series of 10 adult cancer patients treated with a procedure involving sublingual administration of a "photosensitizer" called PhotosoftE4 and illumination of tumors with a laser and the whole body with a "LED bed". Not surprisingly there was no real therapeutic

effect.

Using a sub-optimal PDT regimen such as that described in this report and describing it as “*complementary and alternative medicine, CAM*” is analogous to snipping at a tumor with nail scissors and calling it “CAM surgery”, or using a diagnostic X-ray machine and calling it “CAM radiotherapy”. Of course PDT performed with this bizarre methodology didn’t work; the question is more why would one think it possibly could?

PDT treatments for cancer using chlorophyll-based photosensitizers (PS) such as HPPH, ce6 or TOOKAD work perfectly well when the PS is injected IV ¹. If the investigators in this study were intent on only using an orally delivered PS they could have used oral 5-aminolevulinic acid (ALA) ². While this has some problems in terms of side effects such as blood pressure changes, it has been shown to work. Putting this type of ce6 preparation under the tongue would not be expected to lead to any appreciable systemic absorption and therefore no therapeutic effect. The assertion that a whole-body illumination procedure could eradicate “circulating tumor cells” is frankly laughable.

PDT is a perfectly respectable but not yet mainstream medical procedure and I am concerned that flawed studies such as this one could affect the reputation of this potentially useful therapeutic technique and offer false hope for desperate cancer patients.

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 08 Oct 2013

Karin Ried, National Institute of Integrative Medicine, Melbourne, Australia

In this trial we tested reproducibility of a protocol previously used by others, and are the first, to our knowledge, to have objectively evaluated and reported on the safety (primary outcome) and effectiveness (secondary outcome). We agree with the referee that our findings suggest that the PDT regime used in this trial is sub-optimal. Therefore we consider it important to have published our findings to inform patients and practice, and to counteract publication bias and indeed false hope. Our article discusses potential improvements of PDT to be considered for future applications.

Competing Interests: No competing interests.

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