Pergamon

Oral Oncol, Eur J Cancer, Vol. 31B, No. 5, pp. 346–347, 1995
Elsevier Science Ltd
Printed in Great Britain
0964–1955/95 $9.50 + 0.00

0964–1955(95)00043–7

Short Communication

Photodynamic Therapy and Lip Vermilion Dysplasia: a Pilot Study

G.F. Gregory, C. Hopper, K. Fan, W.E. Grant, S.G. Bown and P.M. Speight

PHOTODYNAMIC THERAPY (PDT) selectively destroys dysplastic skin or mucosa without scarring [1], and may be the ideal treatment for early tumours of the lips. One patient with a T_1 lip carcinoma and 3 patients with lip vermilion dysplasia were sensitised by infusion of Photofrin (2 mg/kg)*.

After 48 h, target lesions were illuminated by timed and measured pumped-dye laser light (wavelength = 628 nm). The first patient received 50 j/sq cm with a 100 mW beam, whilst the patients with dysplasia were treated with 400 mW, to give 100 j/sq cm in a shorter period, i.e.

$$\text{Energy(j/sq cm)} = \frac{\text{Beam power(j/s or watts)} \times \text{t(s)}}{\text{Spot area (sq cm)}}.$$

Postoperative discomfort was controlled with oral ibuprofen, and topical chloramphenicol ointment applied to prevent infection. Microbiopsy specimens were obtained postoperatively in the 3 cases of vermilion dysplasia. The same pathologist (PMS) examined the dysplastic lesions before and after PDT, and the results were collated (see Table 1). Natural porphyrin photosensitisers are "accumulated in tumor tissue after exogenous administration or endogenous synthesis" [2]. Prospective second generation sensitisers are activated by longer wavelength light than Photofrin (over 650 nm), conferring a gain in treatment depth with shorter duration of photosensitivity [3, 4]. PDT has direct tumoricidal action and a potent indirect effect on microvasculature causing rapid ischaemic necrosis [2, 4]. PDT photosensitisers cause dysplastic tissue to fluoresce when illuminated, and be more accurately targeted for phototoxic ablation [3] (Spectraphos CCD camera†). Although experimental in head and neck oncology, Photofrin/PDT is licensed in Canada for the prophylactic treatment of bladder cancer recurrence.

There is no evidence that PDT is mutagenic [5], although the mechanism of primary DNA disruption leading to mutation in solar cheilitis [6, 7], is very likely to be free radicals produced by the interaction of UV irradiation (295–400 nm), and native porphyrin. In PDT, the exposure parameters, both wavelength and porphyrin concentration, exert a lethal effect, rather than a genetic change [3, 4].

With preservation of connective tissue scaffolding, PDT ulceration heals without scar formation, if infection can be avoided. This is important where surgery would cause cosmetic or functional morbidity, such as the lips and periorbital skin. With primary treatment and biopsy monitoring controlled by a photo-detection camera, PDT may revolutionise current treatment.

A tingling sensation rather than pain was felt during PDT treatment of lip vermilion. A beam power of 400 mW illuminated a 16 mm diameter spot and produced a surface irradiance of 189 mW/sq cm. Hyperthermia does not contribute to tissue damage if irradiance is kept below the 200 mW/sq cm threshold [8]. Zhao *et al.* [9] measured the temperature of the lip skin during PDT and found that the surface temperature only began to exceed the core temperature when the irradiance power exceeded 400 mW/sq cm. Zhao's treatment durations were much greater (1800 s). Our patients developed painful ulcers after a few days, but healing without noticeable scarring was delayed up to 4 weeks. Biopsy, after PDT, demonstrated histological improvement in the degree of dysplasia. However, a normal clinical appearance could not be relied upon to exclude dysplasia. This finding agrees with Grant *et al.* [1], who treated intraoral cancers but found the native target mucosa still dysplastic, albeit up-graded histologically. Regular monitoring was necessary to anticipate the need for further intervention.

Presumably, PDT can be repeated, although there is evidence that repeated exposure to the porphyrin photosensitiser induces resistant cells [10, 11]. This might be overcome by using alternative photosensitising agents.

The macroscopic and microscopic appearance (see Figs 1 and 2) of dysplastic vermilion demonstrated a desirable response to PDT. Supporting a proposed mechanism of healing by replenishment from neighbouring epithelium, the normal-looking treated vermilion was shown, histologically, to be dysplastic, although up-graded.

Correspondence to G.F. Gregory.
G.F. Gregory, C. Hopper and K. Fan are at the Maxillofacial Surgery Unit, University College Medical School and the Eastman Dental Institute for Oral Healthcare Sciences; W.E. Grant, S.G. Bown and C. Hopper are at the University College Medical School, London and P.M. Speight is at the Department of Oral Pathology, Eastman Dental Institute for Oral Healthcare Sciences, London.
Received 14 Dec. 1994; provisionally accepted 26 Jan. 1995; revised manuscript received 14 June 1995.
*Photofrin QLT DP 73—A mixture of porphyrins purified by gel filtration chromotography of haematoporphyrin derivative (Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965, U.S.A.).
†Spectraphos CCD cancer photo-detection camera (Ideon S-223 Lund, Sweden).

Table 1.

History	Pre-biopsy	Dosimetry	Post-biopsy
Male 82 years. Smoker. Chronic lip ulcer (2 years). Radiotherapy for previous SCC (mandible).	Severe dysplasia.	Two spots, 10 mm, 12 mm, 100 j/sq cm, 400 mW, 200 s, 294 s.	Moderate dysplasia (4 months).
Male 51 years. Pipe smoker. Leucoplakia in lip angles. Diabetic.	Severe dysplasia.	Two spots, 16 mm, 16 mm, 100 j/sq cm, 400 mW, 510 s, 510 s.	(R) Angle no dysplasia at 6 months. (L) Angle moderate dysplasia at 4 months.
Female 67 years. Non-smoker. Chronic ulcer of lower lip (1 year).	Moderate dysplasia. Actinic cheilitis.	Four spots, 12 mm each, 100 j/sq cm, 400 mW, 294 s.	Mild dysplasia at 2.5 months.
Male 39 years. Pipe smoker. Keratosis of lower lip (4 years). SCC (lip) excised 10 years ago.	Well-differentiated squamous cell carcinoma (superficial).	One spot, 14 mm, 50 j/sq cm, 100 mW, 769 s.	Clinically cured at 12 months (biopsy refusal).

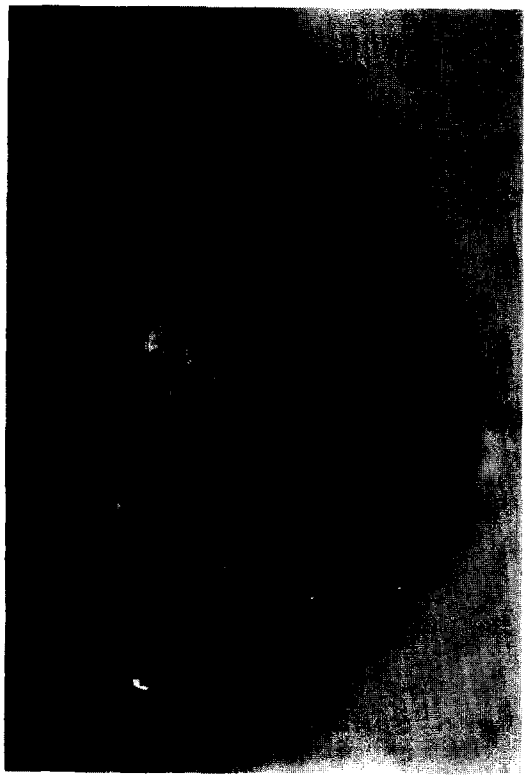

Fig. 1. Severe dysplasia pre-PDT.

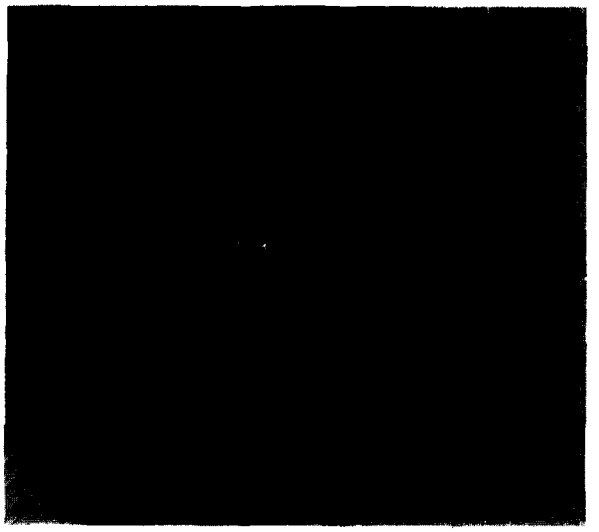

Fig. 2. Normal mucosa post-PDT.

1. Grant WE, Hopper C, Speight PM, *et al.* Photodynamic therapy of malignant and premalignant lesions in patients with "field cancerization" of the oral cavity. *J Laryngol Otol* 1993, **107**, 1140–1145.
2. Battle AM del C. Porphyrins, porphyria, cancer and photodynamic therapy: a model for carcinogenesis. *J Photochem Photobiol B Biol* 1993, **20**, 5–22.
3. Weiman TJ, Fingar VH. Photodynamic therapy. *Surg Clin North Am* 1992, 72(3), 609–622.
4. Pass HI. Photodynamic therapy in oncology: mechanisms and clinical use. *J Natl Cancer Inst* 1993, **85**(6), 443–445.
5. Gomer CJ, Rucker N, Banerjee A. Comparison of mutagenicity and induction of sister chromatid exchange in Chinese hamster cells exposed to haematoporphyrin derivative, ionizing radiation or ultra-violet light. *Cancer Res* 1983, **43**, 2622–2627.
6. Walker SL, *et al.* Effectiveness of UVB sunscreen 2-ethylhexyl-4-methoxycinnamate. *J Photochem Photobiol B Biol* 1994, **22**, 29–36.
7. Gilchrist BA. Sunscreens: a public health opportunity editorial. *N Eng J Med* 1993, **329**(16), 1193–1194.
8. Svaasand LO. Photodynamic response of malignant tumours. *Med Phys* 1985, **12**, 455–461.
9. Zhao FY, Zhang KH, Jiang F, Wu MJ. Photodynamic therapy for treatment of cancers in oral and maxillofacial region (72 cases). *Lasers Med Sci* 1991, **6**, 201–204.
10. Kessel D, Erickson C. Porphyrin photosensitization of multidrug resistant cell types. *Photochem Photobiol* 1992, **55**, 397–399.
11. Luna MC, Gomer CJ. Isolation and initial characterization of mouse tumour cells resistant to porphyrin-mediated photodynamic therapy. *Cancer Res* 1991, **51**, 4243–4249.

Acknowledgements—Grateful acknowledgement is accorded to Dr Giovanni Buonaccorsi for preparing the laser equipment. We also thank Dr Ingemar Jonsson for supervising the fluorescent imaging with the Spectraphos camera.