Phototherapy of posterior uveal melanomas

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Abstract

The results of phototherapy on a small series of 19 patients with uveal melanomas are presented. Laser radiation at a wavelength of 620 to 630 nm was used in conjunction with a 5 to 7.5 mg/kg dose of haematoporphyrin derivative administered 24 hours before treatment, with total doses/treatment averaging 960 J/cm². Eleven patients received two treatments, and one received a third. The longest duration of tumour control to 30 September 1990 was 31 months. Of the 19 patients treated six had complete regression of the tumour, while another five had minor to significant regression. A strong correlation between degree of regression and degree of tumour pigmentation was found, the lighter tumours responding much better than darker tumours. There were also strong indications that if a tumour did not respond to the initial phototherapy it was very unlikely that subsequent phototherapy would provide any further benefit.

For over a hundred years enucleation has been the traditional method of treatment for posterior uveal melanomas, particularly for large tumours. However, its singular lack of success in increasing life expectancy¹ has led to alternative methods of treatment, with radiotherapy being the most effective and widely used.²⁻⁴ Since recent reports have shown that enucleation and radiotherapy have essentially equivalent survival rates,⁵⁻⁷ new forms of therapy such as phototherapy need to be evaluated.

Phototherapy (PT) has been shown to destroy implanted melanomas and retinoblastomas in animals, with few adverse effects.^{8,9} The operation of PT is based on the fact that malignant tissue selectively retains a photosensitiser such as haematoporphyrin derivative (HpD). If the sensitiser is subsequently activated with light of an appropriate wavelength, it releases high-energy radicals which cause tumour cell destruction.¹⁰ Although the use of light-sensitive substances in the treatment of disease was described as early as 4000 BC,¹¹ it was first used successfully to treat basal cell carcinomas in 1905.¹² Since then it has been used to treat many different forms of cancer with varying degrees of success and with minimal side effects.^{13,14}

The few reports of phototherapy for posterior uveal melanomas in humans have been encouraging, despite the small numbers, short follow-up, and varied response. In one series seven posterior uveal melanomas were treated with one complete response in an amelanotic melanoma of 9.4 mm height at the posterior pole followed up for four years, with varied to zero response in the others.¹⁵ In another report, of 23 patients, the greatest tumour reduction occurred in melanomas of less than 1000 cm³ volume, with

no adverse systemic side effects from HpD.¹⁶ Marked necrosis extending to the base of the melanoma has been reported in enucleated specimens following PT.¹⁷

HpD has been the photosensitiser most widely used. It binds tightly to serum proteins, including lipoprotein carriers, and there is a linear relationship between cell volume and uptake.¹⁸ Animal experiments have shown that it localises in vascular structures of the eye (choroid, iris, retina) within 48 hours of intravenous administration, with lower concentrations in the sclera, and with none located within the cornea and lens.¹⁹ In experimental tumours it is concentrated in the vascular stroma (macrophages, mast cells, and possibly fibroblasts), with a lower concentration in the cells, and the earliest histological change following PT is bleeding of tumour cells adjacent to the microvasculature.²⁰ The actual mechanism by which tumour cells are destroyed is not clear, though ischaemia,^{21,22} destruction of cell membrane functions, intracellular enzyme inhibition, and DNA damage probably initiated by singlet oxygen production²³ and other radicals have been reported.²⁴ Ocular toxicity studies have shown that its acute effects are confined to the treated area, and the chronic changes are non-progressive.¹⁹ Its major side effect is skin photosensitisation for up to 80 days following administration.

This report describes the effects of PT on a small series of choroidal melanomas.

Materials and methods

Under a management protocol approved by the Research (Advisory and Ethics) Committee at Prince Henry's Hospital, Melbourne, and with informed consent, 19 patients with posterior uveal melanomas diagnosed by ophthalmological examination, fluorescein angiography, and ultrasonography were treated with PT after growth had been demonstrated by an increase in volume in consecutive measurements (17 patients), or at the patient's request (patients 76 and 80). Tumour size was assessed by volume in accordance with previously reported methods by a 'blind' observer.^{25,26} Location of the anterior margin of the tumour was graded as posterior to the equator, equatorial, or anterior to the equator, and tumour pigmentation was graded as deeply, moderately, or lightly pigmented as determined by indirect ophthalmoscopy and colour photographs. All patients were examined by an oncologist and received whole body CT scans. A full blood examination and renal and liver function tests were performed prior to treatment. Exclusion criteria were the presence of clinical porphyria, metastases, pregnancy, allergic reactions to HpD, and tumours more than 10 mm in height.

Patients were treated with a pulse-injected

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Table 1 Degree of pigmentation, position, pretreatment height and volume, PT dose, degree of regression, and other details for 19 patients treated with PT

Patient no.	Colour pigment	Position of tumour	Pretreatment size		First treatment (months)			Second treatment (months)			Third treatment (months)			Degree of regression overall	Enucleated eye cell-type
			Height mm	Volume mm ³	Total dose J/cm ²	To 30 Sept 90 or to 2nd treatment	Deg reg	Total dose J/cm ²	To 30 Sept 90 or to 3rd treatment	Deg reg	Total dose J/cm ²	To 30 Sept 90 or since 3rd treatment	Deg reg		
2	Dark	Post	4.1	111	1490	7.8	NR	1150	12.9	NR				NR	Spindle cell
22	Dark	Post	6.6	255	1300	13.3	NR	1410	12.6	NR	1300	6.5	NR	NR	Spindle cell
58	Dark	Post	3.3	175	1000	23.6	NR							NR	
1	Dark	Post	3.3	129	130	9.2	NR	2200	31.3	NR				NR	
64	Dark	Equ	4.4	167	920	9.5	MR	674	2.4	NR				NR	Spindle cell Epithelioid
125	Dark	Post	2.0	29	1190	5.4	SR							SR	
9	Moderate	Post	2.6	76	980	21.4	NR	720	13.7	NR				NR	
11	Moderate	Post	5.3	100	1100	5.1	NR	1280	22.1	NR				NR	Spindle cell Epithelioid
112	Moderate	Equ	5.2	193	920	9.0	NR	710	2.8	NR				NR	
7*	Moderate	Post	4.4	211	780	7.8	NR	1180	27.0	MR				MR	
16	Moderate	Post	5.5	649	260	6.2	NR	770	31.3	SR				SR	Spindle cell Epithelioid
116	Moderate	Ant	4.0	55	595	6.7	MR							SR	
25	Moderate	Post	4.7	151	1120	17.8	SR							SR	
76	Moderate	Post	1.2	13	320	9.0	SR	740	16.4	CR				CR	Spindle cell Epithelioid
72	Moderate	Post	3.9	93	790	18.4	SR	992	6.0	CR				CR	
77	Moderate	Post	4.7	82	1140	11.3	CR							CR	
8	Moderate	Post	2.6	111	960	27.2	CR							CR	Spindle cell Epithelioid
80	Light	Equ	5.0	145	960	23.5	CR							CR	
132	Light	Equ	8.9	NA	760	1.9	CR							CR	

NR=no regression. MR=minor regression. SR=significant regression. CR=complete regression. Deg reg=degree of regression. *Patient dead.

intravenous infusion of HpD obtained from the Queen Elizabeth Hospital, South Australia, dosage 5–7.5 mg/kg body mass. For all patients, monochromatic light of 620–630 nm wavelength and 1000 µm beam width from a coherent argon/dye laser was delivered through the pupil on to the surface of the melanoma via a Rodenstock panfunduscope lens and/or Goldman three-mirror lens, in two sessions 24 and 48 hours after administration of HpD. For three patients additional light was delivered transclerally by a 1 mm diameter fibreoptic bundle applied to the tumour base. The total dose in J/cm² received by each

tumour was calculated from its basal surface area measurement, or best estimate, and is listed in Table 1.

Eight patients with posterior uveal melanomas which showed either zero or insufficient response received a second treatment (mean 10 months, ranging from 5 to 21 months following the initial treatment). One patient received three treatments. All patients received systemic prednisolone 10 mg/day, topical atropine 1%, and prednisolone 1% for four weeks following treatment.

All patients wore protective clothing,

Figure 1 Fluorescein angiogram prior to PT (patient 8): early, middle, late frames.

Figure 2 Fluorescein angiogram following PT (patient 8): early, middle, late frames.

ultraviolet-block skin creams, and avoided direct sunlight for a minimum period of 45 days following treatment. They were regularly reviewed, with measurement of visual acuity with and without pinhole, slit-lamp biomicroscopy, clinical photography, and serial measurement of the melanoma volume.

Results

Tumour response to treatment was classified into four grades:

- (1) Complete regression (CR): no evidence of tumour macroscopically to end of the current follow-up period (30 September 1990).
- (2) Significant regression (SR): more than 50% reduction of original tumour size to the end of the current follow-up period.
- (3) Minor regression (MR): up to 50% reduction of original tumour size to the end of the current follow-up period.
- (4) No regression (NR): no change or continued growth after treatment.

Apart from one patient who died, none was lost to follow-up. The results are summarised in Table 1. To illustrate the relation between the degree of pigmentation and the level of regression the table is sorted in order of pigmentation (from dark to light) as the primary sort condition, with regression (from none to complete) as a secondary criterion.

After one session of PT a complete response was seen in four of the 19 patients (21%), while a further six showed a partial response (31%). After a second application of PT the number of cases showing a complete response increased to six (31%), while the number showing a partial response remained at six (31%). As of 30 September 1991 there was no sustained regression or continued growth of tumour in eight patients (42%).

The longest duration of tumour control was 31 months to 30 September 1990. The average PT dose per treatment was 960 J/cm² for the 31 treatments given. One patient (patient 7) who had MR following treatment died as a result of hepatic metastases three years after diagnosis and two years after PT.

The posterior uveal melanomas which regressed following PT exhibited fluorescein angiographic evidence of tumour and choroidal vascular occlusion and elimination of fluorescein leakage (Figs 1, 2).

Of the eight patients showing NR, six received two treatments, and one received three. No patient experienced any adverse side effect as a result of multiple treatments. For those tumours that showed either NR or MR as a result of PT, neither a second nor third treatment produced further improvement except in one patient (patient 16). We now believe that tumour regression occurred in this patient following the first treatment but was masked by a large overlying serous retinal detachment. Two patients with an initial CR of melanomas at the posterior pole received a second treatment resulting in CR for recurrences arising from the tumour edge, and extending into the macular area which had been deliberately avoided in the initial treatment. Four eyes which showed NR, of which three had

Table 2 Spearman rank correlation analysis parameters: relationship of degrees of regression of choroidal melanomas with pre-PT treatment height, volume, initial dose, cumulative dose, and degree of pigmentation

Parameter (correlated with four levels of degree of regression)	Corr. coeff.	Significance
Height (1 mm inc.)	-0.03	0.91 (NS)
Volume (100 mm ³ inc.)	-0.18	0.48 (NS)
Initial PT dose (500 J/cm ² inc.)	-0.07	0.79 (NS)
Cumulative PT dose (500 J/cm ² inc.)	-0.59	0.006 (S)
Degree of pigmentation (3 levels)	0.71	0.0005 (S)

inc. = increment. NS = not significant at 5% level. S = significant.

second treatments, were enucleated. Histo-pathology, including transmission electron microscopy, showed active tumour cell growth in all eyes with extrascleral extension in one (patient 9).

Table 2 lists Spearman's rank correlation coefficients and significance levels for the relationship between degree of regression with tumour height, volume, initial and cumulative PT doses, and degree of pigmentation. There was no significant correlation with height, volume, or initial PT dose. Cumulative dose showed a strong negative correlation with degree of regression, which implies that if a tumour does not respond to initial PT it probably will not respond to further treatment. Very strong correlation was found between degree of regression and degree of pigmentation; the less the pigmentation, the greater the degree of regression.

Discussion

Despite the small size of this series the short-term results following PT were encouraging. The lack of correlation between tumour response and its physical attributes, apart from the degree of pigmentation, highlights the unpredictability of the PT response owing to multiple factors including photosensitiser type, dosimetry and tissue uptake, and the total dose of light energy. Although HpD is the most commonly used sensitiser for PT, it is not ideal. It maximally absorbs light at 390 nm wavelength; but because this wavelength has poor tissue penetration, the minor absorption peak at 630 nm wavelength, which penetrates tissues more effectively, but requires relatively more energy, is generally used. The poor response of the six deeply pigmented melanomas suggests that they may have received a lower than calculated total light energy dose. Transcleral delivery of light energy in addition to transpupillary delivery may overcome the problems of light absorption by these deeply pigmented melanomas.

Unfortunately, there is no satisfactory quantitative method of determining in vivo the concentration and localisation of HpD in tumour tissue. Porphyrins are usually measured by the level of fluorescence emission; however HpD is not particularly fluorescent.²⁷ Experimental work has shown that the concentration of HpD is of the order of several micrograms per gram of tumour tissue at dosages of 3.0 mg/kg at 48–72 hours after injection. It may peak after a few hours and remain essentially constant for days. Variation occurs between different tumours in one patient and between different patients with

the same kind of tumour. Moreover it may decrease with irradiation.²⁸ The poor correlation between tumour response to PT and volume, height, and energy dose may be due to variable uptake of HpD by tumour tissue. Newer photosensitisers may prove to be more suitable and overcome some of the problems of HpD.

At present there is no reliable method of calculating the most appropriate dose of light and HpD to obtain maximal tumoricidal activity with minimal damage to normal tissue. The effective absorbed dose depends on the light energy density at the dose point, the concentration of the photosensitising drug, and the concentration of molecular oxygen.²⁸ There is experimental evidence that the depth of tumour kill is directly related to the dose of light energy, rather than the concentration of HpD.²⁹ In this series higher doses of HpD (5–7.5 mg/kg) than previously reported for posterior uveal melanomas¹⁶ were used, and all tumours were treated initially 24 hours after administration, as laboratory data indicated this to be the optimal time.²⁸ Because light energy densities above 200 J/cm² significantly increase the depth of tumour kill,³⁰ and eradication of posterior uveal melanomas by light energy densities in excess of 1500 J/cm² has been reported,¹⁶ we aimed at about 1000 J/cm²; total light energy levels averaged 960 J/cm² in our series.

The fluorescein angiographic evidence of tumour and choroidal vascular occlusion and elimination of fluorescein leakage for those melanomas which showed regression have also been observed following radiotherapy.³¹ This supports the concept that ischaemia due to endothelial cell damage of tumour blood vessels is a possible mechanism of action of PT.³²

Sunburn persisting for one or two days and presenting as an erythematous swelling of the skin, mainly of the face and hands, has been the major side effect in all patients. The commonest ocular complication in 14 patients (74%) following PT was a transient serous retinal detachment overlying the tumour, nine of which resolved in six weeks. This probably reflects the inflammatory response to the high laser energy levels used, and, in the five patients (26%) in whom the localised retinal detachment persisted, overlying vitreous traction was associated. Two patients (10%) developed anterior uveitis which resulted in pupil block glaucoma and subsequent cataract in one and an associated posterior scleritis in the other. A transient vitreous haemorrhage immediately following PT occurred in three patients (16%), all of which resolved without complication. Four eyes (21%) which showed no response to PT were enucleated, though no eye was enucleated for complications of PT. The post-treatment visual function was worse in 15 patients (79%). However, in 13 patients (68%) the tumour was located posteriorly and involved

the macula, and in two patients (10%) the tumour was located in the temporal equatorial position, and the macula was involved secondarily from the retinal and choroidal vascular occlusion which followed PT.

At present no globe preserving treatment is entirely successful. The obvious advantages of PT are its non-invasiveness and repeatability. At this stage of development phototherapy may be a satisfactory treatment for small and medium size light to moderately pigmented posterior uveal melanomas, and as a supplementary treatment following recurrences with other methods.

- Zimmerman LE, McLean IW. An evaluation of enucleation in the management of uveal melanoma. *Am J Ophthalmol* 1979; 87: 741–60.
- Stallard HB. Radiotherapy for malignant melanoma of the choroid. *Br J Ophthalmol* 1966; 50: 147–55.
- Shields JA, Augsberger JJ, Brady LW, Day JL. Cobalt plaque therapy of posterior uveal melanoma. *Ophthalmology* 1982; 89: 1201–7.
- Char DH, Castro JR. Helium ion therapy for choroidal melanoma. *Arch Ophthalmol* 1982; 100: 935–8.
- Augsberger JJ, Gamel JW, Lauritzen K, Brady LW. Cobalt-60 plaque radiotherapy vs enucleation for posterior uveal melanomas. *Am J Ophthalmol* 1990; 109: 585–92.
- Adams KS, Abramson DH, Ellsworth RM, et al. Cobalt plaque versus enucleation for uveal melanoma. Comparison of survival rates. *Br J Ophthalmol* 1988; 72: 494–7.
- Lommatzsch PK. Results after β -irradiation (⁹⁰Ru/⁹⁰Rh) of choroidal melanomas: 20 years' experience. *Br J Ophthalmol* 1986; 70: 844–51.
- Sery TW, Dougherty TJ. Photoradiation of rabbit ocular malignant melanoma sensitised with haematoporphyrin. *Curr Eye Res* 1984; 3: 229–37.
- Dougherty TJ. In: Kessel D, ed. *Methods in porphyrin sensitisation*. New York: Plenum, 1985: 313–28.
- Dougherty TJ, Kaufman JE, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumours. *Cancer Res* 1978; 38: 2628–35.
- Forrest JB, Forrest HJ. Case report. Malignant melanoma arising during therapy for vitiligo. *J Surg Oncol* 1980; 13: 337–40.
- Jesionek A, Tappeiner HV. Zur Behandlung der Hautcarcinome mit fluoreszierenden Stollen. *Dtsch Arch Klin Med* 1905; 82: 223–7.
- Lipson RL, Blades EJ, Gray MJ. Haematoporphyrin derivative for detection and management of cancer. *Cancer* 1967; 42: 623–9.
- Forbes IJ, Ward AJ, Jacka AJ, et al. Multidisciplinary approach to phototherapy of human cancers. In: Andreoni A, Cubeddu R, eds. *Porphyrin localization and treatment of tumours*. New York: Plenum, 1984.
- Murphree AL, Cote M, Gomer CJ. The evolution of photodynamic therapy in the treatment of intraocular tumours. *Photochem Photobiol* 1987; 46: 919–23.
- Bruce RA. Evaluation of haematoporphyrin photoradiation therapy to treat choroidal melanomas. *Lasers Surg Med* 1984; 4: 59–64.
- Tse DT, Dutton JJ, Weingeist TA, Hermens VM, Kersten RC. Haematoporphyrin photoradiation therapy for intraocular and orbital malignant melanoma. *Arch Ophthalmol* 1984; 102: 833–8.
- Bohmer RM, Morstyn G. Uptake of HpD by normal and malignant cells: effects of serum pH, temperature and cell size. *Cancer Res* 1985; 45: 5328–34.
- Gomer CJ, Jester JV, Razum NJ, Szirth BC, Murphree AL. Photodynamic therapy of intraocular tumours. Examination of haematoporphyrin derivative distribution and long term damage in rabbit ocular tissue. *Cancer Res* 1985; 45: 3718–25.
- Bugelski PJ, Porter CW, Dougherty TJ. Autoradiographic distribution of haematoporphyrin derivative in normal and tumour tissue of the mouse. *Cancer Res* 1981; 41: 4606.
- Packer A, Tse D, Hayreh SS, et al. Haematoporphyrin photoradiation therapy for iris neovascularisation. *Arch Ophthalmol* 1984; 102: 1193–7.
- Selman SH, Kreimer-Birnbaum MK, Klaunig JE, et al. Blood flow in transplantable bladder tumours treated with haematoporphyrin derivative and light. *Cancer Res* 1984; 44: 1924–7.
- Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumour. *Cancer Res* 1976; 36: 2326–9.
- Oosterhuis JA. Haematoporphyrin derivative photoradiation of malignant melanoma in the anterior chamber of the rabbit. In: Oosterhuis JA, ed. *Ophthalmic tumours*. Dordrecht: Junk, 1985.
- Gosbell A, Barry W, Favilla I. Computer-aided volume measurement of choroidal melanomas. *Aust NZ J Ophthalmol* 1987; 15: 349–57.
- Gosbell A, Barry W, Favilla I, Turner I. Computer-aided area measurement of ocular images. *Aust NZ J Ophthalmol* 1987; 15: 341–8.
- Kessel D. In vivo fluorescence of tumours after treatment with derivatives of haematoporphyrin. *Photochem Photobiol* 1986; 44: 107–8.
- Proffio AE, Wuld LR, Sarnaik J. In: Kessel D, ed. *Methods in porphyrin sensitization*. New York: Plenum, 1985: 35–41.
- Kaye AH, Morstyn G, Brownbill D. Adjuvant high dose photoradiation therapy in the treatment of cerebral glioma: a phase I–II study. *J Neurosurg* 1987; 67: 500–5.
- Kaye AH, Hill JS. A review of photoradiation therapy in the management of central nervous system tumours. *Aust NZ J Surg* 1988; 58: 767–80.
- Gragoudas ES, Goitein M, Verhey L, et al. Proton beam irradiation of uveal melanomas: results of 51/2-year study. *Arch Ophthalmol* 1982; 100: 928–34.
- Henderson BW, Dougherty TJ, Malone PB. Studies on the mechanism of tumour destruction by photoradiation therapy. In: Doiron DR, Gomer CJ, eds. *Porphyrin localization and treatment of tumours*. New York: Liss, 1984: 601–12.