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Photodynamic therapy as initial treatment for small choroidal melanomas

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ABSTRACT

Purpose: To evaluate Verteporfin photodynamic therapy (PDT) as primary treatment for small, posterior choroidal melanoma.
Design: Retrospective cohort review.
Subjects, participants and controls: Retrospective case note review of 20 patients with small juxtapapillary and juxtafoveal choroidal melanomas treated with PDT at the Liverpool Ocular Oncology Clinic.
Methods: Patient and tumour characteristics, PDT session details, visual acuity and B-scan ultrasonography measurements as well as colour fundus photographs at each examination were collated and analysed.
Main outcome measures: Local tumour control and Best Corrected Visual Acuity (BCVA).
Results: The 20 patients (14 male, 6 female) had a mean age of 61.2 years (range, 40–85) and were treated between 2001 and 2012. Seven tumours were amelanotic, while 13 were pigmented. Of 20 melanomas, 11 (55%) showed complete regression on B-scan ultrasonography and colour photography; five (25%) showed partial regression; four (20%) remained unchanged and two (10%) showed further growth, for which alternative standard treatment was required. Baseline BCVA was 0.1 logMAR (mean; range 0.0–0.6) compared to a post-PDT BCVA of 0.4 logMAR (mean; range −0.2 to 1.7) over a follow-up of 60.0 months (mean; range 25–156 months).
Conclusions: PDT can induce tumour regression in a significant proportion of small, posterior, choroidal melanomas but is less reliable than other forms of therapy. It may have a role in patients with special visual requirements if they accept the increased risk of treatment failure requiring radiotherapy.

1. Introduction

Conservation of vision in eyes with posterior choroidal melanoma is challenging. Plaque radiotherapy of such tumours is technically difficult, with increased risk of local tumour recurrence, radiation retinopathy and optic neuropathy [1]. Transpupillary thermotherapy (TTT), is less effective, particularly with amelanotic tumours, associated with a relatively high rate of local treatment failure [2]. TTT also damages the retina overlying the tumour to cause visual loss if the lesion extends close to the fovea. Photodynamic Therapy (PDT) with haematoporphyrin derivatives, attempted by Foulds and Damato in 1986 [3], causes skin phototoxicity [4], and tumour recurrence because of minimal tissue penetration [5].

PDT with Verteporfin (Visudyne; QLT Ophthalmics, Merlo Park, CA) was used extensively in the treatment of exudative age-related macular degeneration, until it was superseded by anti-VEGF therapy, and has been shown to have an excellent safety record [6,7]. PDT induces a series of biochemical events resulting in the formation of singlet oxygen, which causes direct tumour cell damage, destruction of tumour vasculature and activation of an inflammatory response [8–10]. The predominant mechanism of action is endothelial cell damage leading to thrombus formation and vascular occlusion [11].The destructive effect of PDT is limited to the target tissue leaving neighbouring retinal and choroidal tissues relatively unaffected, in contrast to other treatment modalities [12,13].

PDT with Porfimer sodium has been approved for the treatment of lung and oesophageal cancer, whilst PDT with Temoporfin has been used in head and neck cancers [14]. There have been isolated case reports and small case-series suggesting that Verteporfin PDT may a role in the treatment of choroidal melanoma [1,15–19]. PDT is still considered experimental because of failure of local tumour control and uncertainty about treatment parameters [12,15,17,20]. There is a paucity of clinical long-term results. We assessed long-term visual outcome and tumour control in 20 choroidal melanomas treated with Verteporfin PDT over a 10-year period.

2. Methods

A retrospective case note review was conducted of all patients

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diagnosed with a choroidal melanoma who underwent PDT as the initial treatment between October 2001 and August 2012. Our diagnostic criteria for small choroidal melanoma were based on the Collaborative Ocular Melanoma Study classification [21] and involved identification of well-accepted clinical features (i.e., documented growth, confluent orange pigment, subretinal fluid, low internal acoustic reflectivity on ultrasonography and tumour thickness exceeding 2 mm). PDT was offered to patients with a small choroidal melanoma at the posterior pole in whom radiotherapy with Ruthenium-106 plaque radiotherapy (RPR) or proton beam radiotherapy (PBR) would have been associated with a high risk of significant visual loss. Histopathological confirmation of the diagnosis and determination of chromosome 3 status for prognostication were attempted when the likelihood of obtaining sufficient tumour material outweighed the risks involved (i.e., retinal detachment, vitreous haemorrhage, tumour seeding) [22]. Biopsies were conducted trans-retinally with a 3-port, 25-gauge vitreous cutter without additional vitrectomy, laser or tamponade [23].

All patients were treated at the Liverpool Ocular Oncology Clinic at St Paul's Eye Unit, Royal Liverpool University Hospital. This retrospective study was approved by the Royal Liverpool University Hospital Clinical Governance and Audit department (project number AC02398). Fully-informed consent was obtained in all patients, who understood that this was an experimental treatment, with an increased risk of failure that would necessitate radiotherapy. Pre-treatment assessment included detailed ocular and medical history, logMAR visual acuity measurement, colour fundus photography and B-scan ultrasonography.

Treatment with PDT using Verteporfin (Visudyne; QLT Ophthalmics, Merlo Park, CA) followed the standard protocol used for choroidal neovascularization secondary to age-related macular degeneration. An intravenous infusion of verteporfin (6 mg/m^2) was administered over ten minutes, after which standard PDT was applied with the Zeiss Visulas 690 s laser (Carl Zeiss Meditec AG, Jena, Germany) at a dose of 50 J/cm^2 (wavelength 689 nm) over 83 s, commencing five minutes after the start of the infusion. The spot size was adjusted to cover the entire surface of the tumour, with at least 1 mm of normal choroid around the tumour margins, including optic disc in juxtapapillary lesions. Multiple overlapping spots were applied when the melanoma could not be treated with one laser spot. After 2010 where initial review of our outcomes following treatment with PDT were conducted, all patients received PDT at an increased laser fluence of 100 J/m^2, achieved by doubling the standard exposure time from 83 s to 166s.

Only patients with a follow up of 24 months or greater were included in the analysis. Follow-up routinely consisted of clinical examination, colour fundus photographs and B-scan ultrasonography, with further PDT being administered if a clinical response had occurred and if the patient was willing to undergo further PDT. Patients were routinely reviewed 2–4 months following the initial treatment and then every 3–6 months until chorioretinal scarring and atrophy replaced the melanoma. Further treatment was administered if there was incomplete regression. Additional therapy with Ruthenium-106 brachytherapy or TTT was performed if there was no sign of regression or if recurrence developed. Patients whose melanoma was found to show chromosome 3 loss were offered immediate radiotherapy because of the increased risks of metastasis and, possibly, local tumour recurrence.

Patients were discharged to the referring ophthalmologist only when complete regression was noted or when partial regression without recurrence was seen over multiple follow-up examinations. Referring ophthalmologists were contacted to obtain visual acuity and tumour characteristics for patients who were discharged from our unit.

Tumour response was classified as: complete regression; partial regression with PDT alone; partial regression with PDT and additional therapy; tumour unchanged and definite recurrence. Complete regression was defined as a reduction in size of a melanoma with formation of a flat chorioretinal scar or atrophy based on clinical examination, fundus photography and B-Scan ultrasonography. Partial regression (with or without PDT) was defined as a reduction in size of the melanoma without signs of active disease or recurrence, while definite recurrence was diagnosed when there was evident lateral extension or increased thickness of the tumour on clinical examination, fundus photography and/or B-Scan ultrasonography.

Best-corrected visual acuity (BCVA) was measured with logMAR and Snellen charts, but for statistical analysis, logMAR equivalents were used. Visual acuities of "Counting fingers", "Hand Movements", "Light Perception" and "No Light Perception" were assigned values of 2.0, 2.4, 2.7 and 3.0 logMAR respectively, based on the study of Schulze-Bonsel et al. [24] A change (either gain or loss) in visual acuity was classified by a change of 0.1 logMAR on follow-up. Statistical analysis was performed using the SPSS Statistics package (IBM SPSS, version 22) and statistical significance of ordinal data categories was performed using Pearson Chi-square testing as a test of independence i.e. in order to assess whether categorical observations such as the posterior margin, location or presence of melanosis in each tumour was independent of the outcomes of PDT treatment.

3. Results

22 cases were identified but 2 were excluded; 1 patient had less than 24 months follow up, and another patient was found on biopsy to have Monosomy 3 melanoma and immediately received standardised alternative treatment (further details below). Our cohort consisted of 20 patients, 14 men and 6 women, ranging in age from 40 years to 85 years (mean, 61.2). The tumour was located in the right eye in 14 patients and in the left eye in six. Seven tumours were amelanotic and 13 were pigmented. The maximum tumour diameter ranged from 3.7 mm to 11.8 mm (mean, 7.2) and tumour thickness ranged from 0.8 mm–4.2 mm (mean, 1.7). (See Table 1). Four tumours involved the fovea with six extending to within one disc diameter (DD) of the fovea and one separated from the fovea by 1.5 DD. Six melanomas reached the optic disc, with one being less than one DD from the disc. One tumour involved both optic disc and fovea and one temporal tumour impinged on neither of these structures.

The first patient to have undergone PDT was treated in October 2001, with subsequent patients receiving PDT from 2007 to the close of the study. The mean follow up was 60.0 months (range, 25–156), exceeding two years in 11 patients and five years in 9 patients. Of the 20 tumours treated with PDT, 17 received the standard protocol PDT treatment whilst three received PDT with double the standard exposure time. Eight patients underwent one PDT session; nine patients had a total of two PDT sessions and three patients received three sessions of PDT. Table 2 provides a summary of the data set.

3.1. Tumour response

Tumour regression was complete in 55% (11/20) of tumours and partial in 25% (5/20). Four tumours (20%) showed no change in size; three of these had additional therapy consisting of endoresection (1 patient), PBR (1 patient) and RPR (1 patient). The patient that underwent endoresection showed a disomy-3 melanoma.

Two patients (9%) developed definite local tumour recurrence. Both had undergone two sessions of PDT before persistent tumour growth was noted. One patient, a 49-year-old man with a 11.8 mm × 2.4 mm amelanotic tumour in the right eye, was found to have a large exudative retinal detachment on initial presentation and assessment, which improved after the first PDT session, in addition to regression of the melanoma. After the second session of PDT however, the tumour was found to have increased in thickness so that PBR was performed. Nevertheless, this patient had a gain in visual acuity of 10 letters on latest follow-up to −0.2 logMAR in comparison with 0.0 logMAR at initial presentation 54 months earlier. The second patient with recurrence, an 85-year-old woman with a melanotic tumour in the left eye, initially opted for a period of observation but then underwent RPR