Photodynamic therapy using verteporfin in circumscribed choroidal haemangioma

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Aim: To investigate the safety and efficacy of photodynamic therapy with verteporfin in patients with choroidal haemangioma.

Methods: A non-randomised, prospective clinical investigation of 19 patients with symptomatic circumscribed choroidal haemangioma was performed. Unsuccessful pretreatment (external beam irradiation, laser photocoagulation) was performed in four patients. Patients were included when (1) subretinal exudation involving the fovea, (2) a decrease in visual function, and (3) additional symptoms (for example, metamorphopsia) were present. Photodynamic therapy (PDT) was performed with verteporfin at a concentration of 6 mg/m² body surface area and a light dose of 100 J/cm² at 692 nm.

Results: The mean follow up time was 10.6 months (2–24 months). The mean number of treatment sessions was 2.15 (range 1–5). Visual acuity improved by at least one line in 73.3%, by at least two lines in 42.1%, was stable in 21.1%, and decreased by one line in 5.2% of the patients. Exudation was completely resolved in 94.8% of the cases. Regression of tumour height was documented in all 19 tumours. Patients receiving any pretreatment before PDT, a visual acuity of 0.1 and less, a history of more than 30 months, and no significant response after the first PDT session, did not show any significant improvement. Cox regression analysis revealed that the number of PDT treatment sessions was inversely associated with the improvement in visual acuity of at least two lines. No recurrences and no local or systemic side effects were observed during the follow up time.

Conclusion: PDT using verteporfin is a safe and effective therapy for the treatment of symptomatic choroidal haemangioma even in tumours located beneath the fovea.

Benign choroidal haemangioma may threaten the eye and impair visual function when exudative activity is present.¹ Numerous treatments (that is, scatter photocoagulation,² brachytherapy,³ low dose external beam irradiation,^{4,5} proton beam irradiation,^{6,7} transpupillary thermotherapy,^{8–12} and hyperthermia¹³) are available. However, in the long term approximately 50% of the patients will have a visual acuity of 20/200 or worse particularly due to chronic macular oedema.² Photodynamic therapy (PDT) with verteporfin has been shown to be effective in the treatment of choroidal neovascularisation in age related macular degeneration, myopia, presumed ocular histoplasmosis syndrome, and idiopathic causes.^{14–16} Selective occlusion of the choroidal neovascularisation can be achieved, while the neurosensory retinal layers and Bruch's membrane are almost unaffected, leaving retinal function constant.¹⁷ PDT should therefore represent almost an ideal treatment for a subretinal vascularised and exudative lesion such as choroidal haemangioma.

Recently, two reports demonstrated that choroidal haemangioma could be successfully treated by PDT with verteporfin.^{18,19} In the present study, we report on our preliminary experience with this method in a small series of 19 patients with circumscribed choroidal haemangioma.

PATIENTS AND METHODS

One eye of each of 19 patients was included in this prospective, non-randomised clinical study at the university eye hospital in Essen, Germany. The diagnosis of circumscribed choroidal haemangioma was made based on the findings of ophthalmoscopy, colour fundus photography, fluorescein angiography, and ophthalmic ultrasound. Fluorescein angiography was performed using a fundus camera (Zeiss, Jena, Germany) on a digital system (Pawłowski, Jena,

Germany). Pictures at a 30° angle were taken before dye injection, after 10 seconds to 3 minutes, and at 10 minutes following administration of 10 ml sodium fluorescein solution.

Choroidal haemangiomas were classified depending on their distance from the fovea: group 1, within one disc diameter around the geometric centre of the fovea; group 2, more than one and less than two disc diameters around the fovea; group 3, more than two disc diameters around the fovea. Unsuccessful treatment was previously performed on four patients: two of them were treated with low dose ocular irradiation, the third underwent several sessions of laser photocoagulation, and the fourth patient was treated with both laser photocoagulation and afterwards with low dose ocular irradiation.

Patients were included when at least the first three (a–c) of the following conditions caused by the choroidal haemangioma were present: (a) symptoms (decrease in visual function, metamorphopsia), (b) decrease in visual acuity, (c) subretinal exudation involving the fovea, (d) exudative retinal detachment, (e) failure of a previous treatment. Exclusion criteria were active hepatitis, significant liver disease, porphyria, other porphyrin sensitivity, intraocular surgery within the past 2 months, any significant ocular disease (age related macular degeneration, diabetes mellitus, vascular retinal diseases, retinal arterial and venous occlusive diseases, glaucoma) that could compromise vision in the treatment eye, incompatibility and allergic reactions against fluorescein, and gravidity.

Each patient signed a written informed consent statement before joining the study.^{15,16} Best corrected visual acuity (Landolt single optotypes at a distance of 5 metres according to DIN 58220), slit lamp examination, intraocular pressure measurements, ophthalmoscopy, ophthalmic ultrasound (B-scan and standardised A-scan), and fluorescein angiography were performed within 1 week before the first treatment and

Table 1 Patients, tumour characteristics, and course of therapy after PDT in 19 choroidal haemangiomas

Patient No	Age (years)	Sex	Duration of symptoms (months)	Tumour location*	Pretreatment†	VA before PDT‡	VA at end point‡	Tumour height before (mm)	Tumour height at end point (mm)	No of PDT sessions
1	61	M	120	1	no	0.03	0.06	3.5	2.4	1
2	51	M	58	1	no	0.05	0.03	2.6	1.7	1
3	73	M	4	3	no	0.4	0.7	4.3	3.9	4
4	50	M	9	1	no	0.63	1.0	1.6	0.0	2
5	54	M	23	3	no	0.12	0.2	1.3	1.1	2
6	42	M	40	1	LDI + LC	0.1	0.1	NA§	NA§	1
7	45	M	2	2	no	0.63	0.8	2.3	0.0	3
8	33	M	71	1	no	0.05	0.05	2.8	2.1	3
9	34	M	2	2	no	0.4	1.0	3.0	1.0	2
10	59	F	72	3	LDI	0.03	0.03	2.7	2.3	3
11	45	F	6	1	no	0.32	0.63	2.4	0.1	2
12	40	M	72	1	LC	0.02	0.02	2.4	1.2	3
13	63	M	30	1	no	0.12	0.16	3.2	3.0	5
14	74	F	29	1	no	0.63	0.8	1.9	0.0	1
15	36	F	16	3	no	0.25	0.5	2.3	1.3	1
16	27	M	5	3	no	0.8	1.0	1.9	1.4	1
17	57	F	36	3	LDI	0.005	0.05	4.2	1.7	5
18	48	M	2	3	no	0.2	1.0	4.8	2.0	2
19	77	F	2	2	no	0.5	0.9	2.8	0.0	1

*As measured by colour fundus photos and angiography. 1 = central margin within 1 disk diameter (DD) from the fovea, 2 = between 1 and 2 DD from the fovea, and 3 = more than 2 DD away from the fovea.

†LDI = low dose irradiation, LC = laser coagulation.

‡VA = visual acuity, Landolt single optotypes at a distance of 5 metres according to DIN 58220.

§NA = not available.

at follow up visits (months 1 and 3 after the first treatment, and afterwards at 3 month intervals). One patient denied any further examinations 3 months after the first treatment (patient No 2, Table 1).

The patients received verteporfin (Visudyne; Novartis Ophthalmics, Hettlingen, Switzerland) intravenously at a drug dose of 6 mg/m² body surface area over 2 minutes as a bolus injection. The laser beam was applied 5 minutes after stopping the infusion. PDT was conducted using a diode laser emitting light at 689 nm for photosensitisation (Visulas II, Zeiss, Jena, Germany); 100 J/cm² were delivered at an irradiance of 600 mW/cm² over 166 seconds. According to observations from other experimental studies, the rationale for the shorter infusion time, compared with that used for other applications of verteporfin, was to increase the efficacy and concentration of the drug within the tumour²⁰ and to increase the photodynamic effect on larger vessels due to an increased light dose.²⁰ The size of the treatment spot was calculated based on the greatest linear dimension of the choroidal haemangioma. No additional safety margins were added. Several spots were applied, if the dimension of the tumour exceeded the maximal spot size (Mainster wide field contact lens) to completely cover the area of the choroidal haemangioma. An overlap of the spot sizes was avoided. The optic disc was strictly excluded by the application of the laser beam.

Retreatment was performed when subretinal exudation was documented by ophthalmoscopy and fluorescein angiography within 3 months following the last treatment. It was

restricted in size to the remaining prominent and exudative portion of the choroidal haemangioma. Treatment was stopped when the exudation was completely resolved and symptoms were almost reversible. In order to minimise the number of retreatments, a residual persistence of tumour mass without any symptoms was not an indication for retreatment.

Using the spss 10.0 software the associations between the various parameters were compared (Spearman test). The influence of various parameters on improvement of visual acuity after PDT was assessed (Cox regression analysis). We calculated hazard ratios (RR) with 95% confidence intervals (95% CI). All p values are presented two sided without adjustment for multiple testing.

RESULTS

The mean age of the 19 patients was 51 years (range 27–77 years). Subretinal exudation and symptoms were present before therapy with a mean duration of 31.5 months (range 2–120 months). The mean follow up time was 10.6 months (range 2–24 months). Treatment of PDT was well tolerated in all patients without any side effects. The mean number of PDT sessions applied was 2.15 (range 1–5). The characteristics are shown in Table 1.

Figure 1 Visual acuity before and at last examination after PDT.

Figure 2 Final visual outcome at the final follow up of the patients depends on the duration of symptoms before the first PDT treatment.

Figure 3 Fundus photography, and fluorescein angiography of a choroidal haemangioma in a 48 year old patient. The duration of symptoms was 8 weeks before the first PDT. The visual acuity increased from 0.2–1.0 while the tumour size decreased from 4.8–2.0 mm. Ophthalmoscopic appearance (A), and fluorescein angiography (B, C) before the first PDT. Ophthalmoscopic appearance (D), and fluorescein angiography (E, F) 12 months after the first, and 9 months after the second PDT.

Visual acuity

Figure 1 summarises the visual acuity of the patients before and on the final follow up: 14 patients (73.7%) experienced an improvement, while four patients (21.1%) were stable and one patient (5.2%) showed a marginal decrease in visual acuity. In seven cases (36.8%) the visual acuity was 0.1 (20/200) or below before the first PDT treatment. These patients showed only slight if any improvements during therapy. Only one of the pretreated patients revealed a substantial improvement in visual acuity, while the remaining three experienced no change although exudation was reduced. One patient who had symptoms for 58 months had a slight decrease in visual acuity on the first follow up from 0.05 to 0.03. He denied any further follow up examinations. The remaining two patients with no significant response had experienced symptoms for at least 71 months.

An increase in visual acuity of at least two lines was found in eight patients (42.1%). The duration of symptoms within this subgroup ranged between 2–36 months. An improvement in visual acuity (at least two lines) was statistically significant correlated with a short history of symptoms ($p = 0.007$).

Figure 2 depicts the relation between final visual acuity and the duration of symptoms: it shows that final visual function is at least in part determined by the duration of the symptoms before the first treatment was started. Final visual acuity was below 0.2 (20/100) when the symptoms were present for 30 months or more. However, despite a persistence of symptoms for 30 months, one patient achieved a final visual acuity of 0.63.

Ophthalmoscopic and fluorescein angiographic findings

Following therapy, a continuous decrease in exudation in all patients was observed. Exudation was completely resolved in 18 patients (94.8%), while residual exudation involving the fovea was observed in one patient (5.2%). Following PDT focal atrophy of the retinal pigment epithelium and atrophy of the choroid was observed (Figs 3–5). Fluorescein angiography revealed a continuous rarefaction of the tumour vascularisation caused by an increase in hypofluorescent areas over the

choroidal haemangioma during the early phases and a decrease in hyperfluorescence during the late phases of the fluorescein angiogram. The areas of hypofluorescence during the early phases enlarged slightly with increasing numbers of retreatment. Figures 3–5 depict typical examples before and after treatment.

Ophthalmic ultrasound

Figure 6 demonstrates the difference in tumour height before and after treatment. A decrease in tumour height was documented in all eyes at the end of the therapy. Mean height of the tumours was 2.63 mm (range 1.3–4.8 mm) before the first PDT treatment and 1.33 mm (range 0–3.9 mm) at the final follow up. The extension of tumour shrinkage was positively correlated with an improvement in visual acuity ($p = 0.01$).

Predictive factors of visual improvement

Analysis was performed for patients who experienced an improvement of at least two lines after PDT. Patient No 17 (Table 1) was excluded because the initial visual acuity was less than 0.02. The results of the Cox regression analysis are summarised in Table 2 which shows that the number of PDT treatments was a predictive factor (inverse) for a benefit in visual acuity. The difference in tumour height before and after therapy ($p = 0.06$) was tentatively predictive but was not statistically significant (<0.05). The duration of symptoms before the first PDT ($p = 0.13$) failed statistical significance. Owing to the short follow up time and the small number of cases, the interpretation of the results of the Cox regression analysis is limited.

DISCUSSION

This study presents the largest prospective study reported to date of circumscribed haemangiomas treated with PDT. In accordance with previous investigations, no side effects of PDT with verteporfin were observed.^{14–16 18 19} In all but one patient, exudation was completely resolved. Visual acuity improved in 73.7% of the cases. An improvement in visual acuity of at least

Figure 4 Fundus photography, and fluorescein angiography of a choroidal haemangioma in a 45 year old patient. The duration of symptoms was 6 months before the first PDT. The visual acuity increased from 0.32 before the first PDT to 0.63 at the final follow up, while tumour height decreased from 2.4–0.2 mm. Ophthalmoscopic appearance (A), and fluorescein angiography (B, C) before the first PDT. A continuous decrease in exudation was observed at 4 weeks (D) and at 3 months following the first PDT (E), while reactive changes of the retinal pigment epithelium were observed. Ophthalmoscopic appearance (F), and fluorescein angiography (G, H) 11 months after the first PDT.

two lines was found in 42.1% of the patients and was significantly correlated with a short history of symptoms. This observation was not reproducible in the Cox regression analysis, probably because of the relatively short follow up time and the small number of cases. However, two patients who experienced such an improvement, reported the onset of symptoms occurred 16 and 36 months before treatment, respectively. In both patients, the central tumour margin was more than two disc diameters away from the fovea, which might have had a positive influence upon visual acuity. Patients with an initial visual acuity of 0.1 (20/200) or worse, a duration of symptoms of more than 30 months, and those pretreated with another therapy showed no functional improvement, even if PDT was applied repeatedly and exudation was resolved. These conditions describe tumours for which PDT probably is not a beneficial treatment.

Two case reports^{18, 19} regarding PDT and choroidal haemangioma have been published. The visual acuity improved in these five patients, the tumour height decreased, and subretinal fluid was resolved. Surprisingly, Madreperla¹⁸ observed this effect after a single session of PDT using only 50 J/cm² compared to 100 J/cm² applied by Barbazetto and Schmidt-Erfurth,¹⁹ as well as in this study. The cases in Madreperla's

study had small tumours, a short history of symptoms, and only a moderate reduction in visual acuity before therapy,¹⁸ which may have been beneficial for the final outcome.

Three tumours involved the fovea.^{18, 19} In our study, the fovea was treated in nine cases and no treatment associated side effects, particularly on the retina, were observed. In contrast with argon scatter coagulation or transpupillary thermotherapy^{2, 8} selective treatment of choroidal haemangiomas using PDT may preserve foveal function.

In the present study, PDT was repeated at intervals of 3 months in many of the tumours because subretinal fluid and symptoms were persistent. The presence of tumour vessels (fluorescein angiography) or tumour mass (sonography) was not the main criterion for further treatment. Barbazetto and Schmidt-Erfurth¹⁹ reported on retreatments in a case with a subfoveal choroidal haemangioma (four sessions of PDT at intervals of 1 month) because of a persistence of the tumour height. Improvements in visual acuity following retreatments in the presence of completely flattened subfoveal tumours may be rare since most of these eyes are amblyopic. Our findings suggest that retreatments may be necessary only until exudation has been completely resolved.

Figure 5 Fundus photography, and fluorescein angiography of a choroidal haemangioma in a 39 year old patient. The patient was pretreated with argon laser photocoagulation (three times). The duration of symptoms before the first PDT was 72 months. Ophthalmoscopic appearance (A), and fluorescein angiography (B, C) before the first PDT. Ophthalmoscopic appearance (D), and fluorescein angiography (mid-phase (E), late phase (F)) at 12 months after the first PDT and at 3 months after the third PDT. Subretinal fluid resolved and the tumour height decreased while the visual acuity remained unchanged during the follow up period.

Figure 6 Tumour height before and after PDT at the final follow up.

According to our data the most predictive factor for a significant increase in visual acuity by at least two lines was the number of treatment sessions. The number of treatments was correlated negatively with an increase in visual acuity. Our study suggests that retreatment of residual haemangioma is no longer necessary when subretinal exudation has been completely resolved. This finding may help to minimise the number of treatment sessions.

Compared with other forms of treatment, PDT has important advantages. Like argon laser scatter coagulation or transpupillary thermotherapy, PDT is a safe, rapid, and easily performed, outpatient procedure, independent of the patient's age, and is available in almost every department for retinal diseases. In accordance with previous reports¹⁸⁻¹⁹ our study shows that PDT is suitable for the treatment of subfoveal choroidal haemangiomas. This has been a limitation of both laser scatter coagulation²¹ and transpupillary thermotherapy.⁸ Radiation therapy is effective in the treatment of choroidal haemangiomas.^{2-7, 22} In contrast with PDT, brachytherapy and proton beam therapy require an operative procedure, and are usually only available in specialised centres. Low dose external

beam irradiation is a non-invasive therapeutic modality with minimal side effects even in subfoveal tumours. In the long term (mean follow up time of 5.3 years), resolution of subretinal fluid was achieved in 63.8% of cases and visual acuity was stable or improved in 77.8%.⁴ Radiation induced retinopathy or optic disc neuropathy by the high fractionated low dose irradiation are not a concern since the total of approximately 20 Gy is far below the estimated dose of 30–40 Gy needed for inducing retinal dysfunction.²³ To date no case of a secondary tumour induced by a low dose irradiation of a choroidal haemangioma is known. Based on an average of 2.1 treatment sessions the costs of PDT are similar to those for external beam irradiation in our department. Our results may help to reduce the costs of PDT, because the number of treatment sessions was a predictive factor for the visual outcome.

The present data show that PDT with verteporfin is a safe and effective treatment for symptomatic choroidal haemangioma.

Clearly, a limitation of our study is the short follow up time and the small number of patients compared with other reported studies: recurrences of subretinal fluid and a decrease in visual acuity after several treatments have been observed anywhere from several months to 10 years after therapy.²⁻²¹ Focal atrophy of the retinal pigment epithelium was not followed by a decrease in visual acuity in the present study, particularly in subfoveal lesions. A longer follow up time will be necessary to exclude such a decrease and recurrent subretinal fluid, and to compare the number of retreatments and the outcome of PDT with other treatment methods. However, the preliminary data justify the use of PDT as a first line therapy in symptomatic circumscribed choroidal haemangiomas.

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Table 2 Univariate Cox proportional hazard regression analysis for improvement of visual acuity of at least two lines

Parameter	RR (relative risk)	95% CI	p Value*
Age (continuous)	1.00	0.94 to 1.06	0.98
Sex male Ref: female	0.57	0.13 to 2.56	0.46
Duration of symptoms (months) (continuous)	0.93	0.85 to 1.01	0.09
Pretreatment Yes Ref: no	0.03	0.0 to 28.68	0.31
Location† group 1 Ref: group 2 and 3	0.52	0.10 to 2.68	0.43
No of PDT sessions (continuous)	0.2	0.05 to 0.87	0.03
Visual acuity before PDT (continuous)	1.01	0.98 to 1.04	0.35
Tumour height before PDT (mm) (continuous)	0.96	0.43 to 2.17	0.92
Tumour shrinkage (mm) (continuous)	2.52	0.96 to 6.61	0.06

*All p values are two sided.

†As measured by colour fundus photos and angiography. 1 = central margin within 1 disc diameter (DD) from the fovea, 2 = between 1 and 2 DD from the fovea, and 3 = more than 2 DD away from the fovea.

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