Photodynamic therapy with verteporfin for juxtafoveal choroidal neovascularization secondary to pathologic myopia—1-year results of a prospective series

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Abstract

Purpose To study the efficacy of photodynamic therapy (PDT) with verteporfin in the treatment of juxtafoveal choroidal neovascularization (CNV) secondary to pathologic myopia.

Methods Prospective, open label, two-centre, noncomparative, interventional case series. Consecutive patients with juxtafoveal CNV associated with pathologic myopia were recruited and treated with a standard regimen of PDT with verteporfin. Patients were being followed up every 3-monthly and retreatment was considered when there was evidence of angiographic leakage. Outcome measures included changes in the mean best-corrected visual acuity (BCVA) at the 1-year follow-up when compared with the baseline, the proportion of patients who had stable (within 1 line) and improved visions.

Results A total of 11 eyes from 11 patients with juxtafoveal CNV secondary to pathologic myopia were recruited and all completed the 1-year follow-up. The mean age at presentation was 44.8 years. The refractive error ranged from -6.0 to -15.0 D ($\pm$ SD was -9.55 ± 3.04 D). The logMAR BCVA improved from 0.57 to 0.39 at the 1-year follow-up (Wilcoxon signed-ranks test, $P = 0.027$). The mean improvement was 1.8 lines. Five eyes (45.4%) had BCVA improved by ≥ 3 lines. None of the treated patients had visual loss of

≥ 1 line. The mean number of treatments over the 12-month study period was 2.3 sessions.

Conclusions The results are encouraging, especially on considering the low retreatment rate, stable or improved BCVA in all treated eyes, and consistently good safety profile. Juxtafoveal myopic CNV may be an expanded indication for PDT with verteporfin.

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Introduction

Choroidal neovascularization (CNV) at the macula may cause severe and permanent loss of vision.¹ It can be associated with a number of diseases and pathologic myopia belongs to one of them. Pathologic myopia is the second most common cause of CNV, after age-related macular degeneration.² The problem has caused significant socioeconomic setbacks in many countries as it commonly affects younger population or workforce.³ The scenario is worse in the Asian population as the prevalence of high myopia in the adult is as high as 9%, which is 4–5 times more than that of American or European population.^{4–6} Around 4–11% of highly myopic eyes may finally develop CNV at the macula.⁷

In a retrospective study of 50 eyes with predominately juxtafoveal myopic CNV managed by observation alone, 31 eyes (62%) suffered moderate-to-severe visual loss (three-lines deterioration or more) after 5 years, further increasing to 76% upon 10 years of follow-up.⁸ Juxtafoveal CNVs should not be deemed less visually alarming than their subfoveal counterparts because vision can be jeopardized by foveal extension of the CNV or secondary foveal involvement by haemorrhage or subretinal fluid.⁸ Hotchkiss and Fine⁹ noted that 14 of 27 eyes (51.9%) with myopic CNV developed visual loss of two Snellen lines or more after 2 years. The prognosis was guarded among the juxtafoveal group as only one out of five (20%) could maintain a vision of 20/40 or better.⁹

The optimal management for juxtafoveal CNV secondary to pathologic myopia remains elusive. Direct argon green laser photocoagulation has been studied by Ruiz-Moreno and Montero¹⁰ in 23 eyes from 21 patients with juxtafoveal CNV; the initial improvement in visual acuity was lost after 24 months as a result of laser scar creeping and foveal extension over time. The similar time-dependent annihilation of treatment benefit was shown by Secretan *et al*⁸ in the laser treatment arm for juxtafoveal myopic CNV as there was no statistically significant difference between direct laser-treated and untreated eyes after 5 years. Roles of submacular surgery, macular translocation surgery, and indocyanine green (ICG)-enhanced photothrombosis of the ingrowth site of lesion in managing juxtafoveal CNV were limited by demanding techniques, invasiveness of the procedure, or associated tissue destructions during the procedures.^{11–14}

Photodynamic therapy (PDT) has been demonstrated to be a safe treatment in preserving vision in pathologic myopia patients suffering from subfoveal CNV.^{15,16} Clinical value of PDT in treating juxtafoveal CNV is not known but has been suggested to be 'possibly indicated'.¹ PDT dissipates less amount of laser energy to surrounding neurosensory retina and retinal pigment epithelium and, theoretically, it causes an involution of the CNV, with less tissue destruction, and scar expansion.^{15–18} Recently, Cohen *et al*¹⁹ reported a success of PDT on three cases of juxtafoveal myopic CNV.

The aim of this study is to investigate the treatment outcomes, change in visual acuities, and number of treatments required, with respect to angiographic responses on juxtafoveal myopic CNV, by using PDT with verteporfin.

Materials and methods

This was a prospective, consecutive, interventional study involving two centres and aimed at investigating the safety and efficacy of PDT with verteporfin for

juxtafoveal CNV of pathologic myopia. The protocol was reviewed and approved by the Ethics Committee of the Chinese University of Hong Kong.

Patient selection

Patients were recruited from two tertiary ophthalmic centres in Hong Kong, Hong Kong Eye Hospital and Prince of Wales Hospital, and the enrolment started in February 2000. Informed consents were obtained from all eligible participants.

Inclusion criteria of the study included: (i) pathologic myopia defining as high myopia with spherical equivalent ≤ -6.0 D or axial length ≥ 26.5 mm; (ii) aged 18 years or older; (iii) CNV at the juxtafoveal area; area of CNV $\geq 50\%$ of the area of the total lesion; (iv) greatest linear dimension (GLD) of the entire lesion must not exceed 5400 μm ; (v) best-corrected visual acuity (BCVA) of at least 20/200 or better; (vi) active CNV on clinical examination and angiography.

Exclusion criteria included: (i) other clinical features suggesting that the CNV may be secondary to other causes other than pathologic myopia (such as large drusen, geographical atrophy, chorioretinal scar); (ii) any systemic contraindications for verteporfin or angiographic dyes; (iii) patients who had received previous treatment such as focal laser before enrolment; (iv) tears of the RPE; or (v) other maculopathy or significant concurrent ocular diseases in the study eye that has compromised or could compromise vision in the study eye such as diabetic maculopathy or retinal vascular occlusion; (vi) pregnancy.

Ophthalmologic examination, colour fundus photography, fluorescein angiography (FA)

All participants received a comprehensive ocular examination including dilated fundus and macular examinations with a contact lens or a 90-diopter lens, followed by colour fundus photography, digital FA at baseline and at every 3-month interval visits. FA was performed in a standard manner using digital fundus camera (Zeiss FF3/4 with OIS Winstation 1024, MediVision Inc, CA, USA). The following features had been recorded—any leakage and degree of leakage from CNV. The sizes of the lesion were measured as Macular Photocoagulation Study disc area (MPSDA) and they were arbitrarily divided into $\leq 1/2$, $> 1/2$ to ≤ 1 , and then number of MPSDA. The exact location with respect to the foveolar avascular zone, compositions of lesion including proportion of classic and occult, proportion of blood, retinal pigment epithelium hyperplasia, and serous detachment of retinal pigment epithelium, retinal abnormalities in pathologic myopia such as lacquer

cracks or chorioretinal scar were also recorded. BCVA was measured with a standard Snellen chart by a single optometrist. To quantify the differences in vision, all Snellen visual acuity were converted to logarithm of the minimum angle of resolution (logMAR) visual acuity.²⁰

Photodynamic therapy

PDT with verteporfin was given according to the VIP study in an outpatient setting. The laser spot size was chosen by adding 1000 μm to the measured GLD. A standard verteporfin (Visudyne, Novartis AG, Bülach, Switzerland) infusion followed by laser application at 689 nm (Coherent Inc., CA, USA) was given.

Follow-up, retreatment and end point

Follow-up examinations were performed every 3 months with BCVA, fundus examination, fundus photography, and FA. The extents of fluorescein leakage from the CNV were assessed. Retreatment would be considered on follow-up if there was persistent or new leakage in FA. Retreatment was given in the same method as the initial treatment described previously. Treatment end point was achieved when there was complete absence of angiographic leakage in FA.

Outcome measurements

The primary outcomes were the proportion of eyes that have improved (one or more lines), stable, or decreased (one or more lines) vision at the end of 1-year. The mean and median changes in visual acuities at the 12-month examinations would be measured.

Secondary outcome parameters included proportion of eyes with final vision of 20/40 or better and the proportion of eyes that had lost three or more lines. Other

important parameters included the number of treatments required during the study period. Any ocular or systemic adverse events due to PDT were also tabulated.

Statistical analysis

Demographic characteristics of the patients were summarized by descriptive statistics using statistical software (SPSS version 10.1.0, SPSS Inc., Chicago, IL, USA). Each 0.1 logMAR unit represents one line of visual acuity. Improvement in BCVA was defined as any improvement by one or more lines, and worsening in BCVA was defined by a decrease in one or more lines. The change in proportion of eyes with BCVA of 20/40 or better before and after PDT was analysed using the Fisher's exact test. Nonparametric analyses for continuous variables between various groups were compared using Wilcoxon signed-ranks test.

Results

Characteristics of patients (Table 1)

From February 2000, 11 eyes from 11 patients with juxtafoveal CNV secondary to pathologic myopia had been recruited, and completed 1-year follow-up. There were nine (81.8%) female and two (18.2%) male patients and all were Chinese. Left eye was involved in three patients and there were eight right-eye lesions. No bilateral involvement was noted. The mean $\pm$ standard deviation (SD) age at presentation was 44.8 ± 15.4 years, ranging from 19 to 67. The refractive error ranged from -6.0 to -15.0 D, and the mean $\pm$ SD was -9.55 ± 3.04 D.

Visual outcomes at 1-year follow-up (Table 1)

On initial presentation, the mean $\pm$ SD logMAR BCVA was 0.57 ± 0.30 . The initial Snellen BCVA ranged from

Table 1 Patient demographics at baseline and functional changes with photodynamic therapy

Patient number	Sex	Age (years)	Study Eye	Spherical equivalent	Size of CNV (disc area)	Baseline BCVA	BCVA at 3 months	BCVA at 6 months	BCVA at 9 months	BCVA at 12 months	Change in logMAR lines	Number of treatment
1	M	19	L	-7.00	$\leq 1/2$	20/30	20/15	20/15	20/15	20/15	+3.0	1.00
2	F	59	R	-10.00	$\leq 1/2$	20/200	20/100	20/200	20/200	20/200	0	3.00
3	F	57	R	-8.00	$\leq 1/2$	20/70	20/30	20/30	20/30	20/30	+3.6	1.00
4	F	67	R	-6.50	$> 1/2 - \leq 1$	20/200	20/100	20/200	20/200	20/200	0	3.00
5	F	30	L	-8.50	$\leq 1/2$	20/30	20/25	20/25	20/25	20/25	+0.8	1.00
6	F	58	R	-15.00	$\leq 1/2$	20/70	20/70	20/70	20/70	20/70	0	1.00
7	F	52	R	-13.00	$> 1/2 - \leq 1$	20/100	20/70	20/50	20/50	20/50	+3.0	2.00
8	F	39	R	-7.00	$\leq 1/2$	20/100	20/200	20/200	20/200	20/100	0	4.00
9	F	28	L	-6.00	$\leq 1/2$	20/30	20/40	20/30	20/30	20/30	0	4.00
10	F	48	R	-12.00	$\leq 1/2$	20/100	20/30	20/30	20/30	20/25	+6.0	1.00
11	M	36	R	-12.00	$\leq 1/2$	20/70	20/70	20/40	20/35	20/30	+3.6	4.00

Figure 1 Changes in mean logMAR BCVA with time in patients receiving photodynamic therapy for juxtafoveal myopic choroidal neovascularization.

Figure 2 Scattered plot of the BCVA before and after photodynamic therapy at 1-year.

20/30 to 20/200 with a mean of 20/60. At 1-year follow-up, the mean $\pm$ SD logMAR BCVA was 0.39 ± 0.37 . The Snellen BCVA ranged from 20/15 to 20/200 with a mean of 20/37. There was a mean improvement by 1.8 lines. The change in the mean logMAR BCVA at 12 months was statistically significant (Wilcoxon signed-ranks test, $P = 0.027$). Most of the visual improvement occurred within the first 3 months after the initial PDT (Figure 1). The changes in BCVA of each individual case at 12 months were displayed in the scatter plot (Figure 2). The median Snellen BCVA at presentation was 20/70

(logMAR 0.54) and at 1-year follow-up was 20/30 (logMAR 0.18). The visual improvement was 3.6 lines.

Five eyes (45.4%) had BCVA improved by one or more lines and all of them indeed had a moderate gain in vision (improved by three or more lines). Six (54.5%) eyes had stable vision and none of the treated patient had visual loss of one line or more. At baseline, three eyes (27.3%) of patients had initial BCVA of 20/40 or better. At the 12-month follow-up, six (54.5%) eyes had BCVA of 20/40 or better. This, however, was not statistically significant because of a small sample size (Fisher's exact test, $P = 0.193$).

Number of PDT treatments

A total of 25 treatment sessions had been given to 11 eyes during 12-month with a mean of 2.3. treatments. Five (41.7%) eyes received only one single PDT session during the 12 month study period (Figure 3). Retreatment was performed for cases with persistent, recurrent or new angiographic leakage in FA. One (8.3%) eye requiring two PDT sessions, with two (16.7%) eyes requiring three, and three (25.0%) eyes requiring four sessions of PDT.

Adverse events and complications

Three had limited, localized haemorrhage from the CNV after the first session of PDT, which were resolved spontaneously without jeopardizing the vision and subsequent treatments. Potential but serious complications such as severe acute loss of vision and rip or tear in retinal pigment epithelium did not occur in our series. None of the patients suffered from any discomfort or complications that arose either from infusion or laser application including low back pain, catheter-induced complications, or photosensitivity.

Discussion

Subfoveal CNV with pathologic myopia is a major cause of visual disability in developed countries, especially in the Asian population that has high prevalence of high myopia.⁴ The natural course and the best modality of treatments for juxtafoveal CNV are, however, less certain because of limited data available in the literatures.¹

Ruiz-Moreno and Montero¹⁰ demonstrated that argon green laser photocoagulation could improve BCVA in myopic juxtafoveal CNV initially in a group of 23 eyes from 21 patients with a poor baseline BCVA of 18/200 (80/200–2/200). The improvement fades with time, and is no longer significant after the third year. Similarly, Secretan *et al*⁸ observed the absence of statistically significant difference between direct laser-treated and untreated eyes after 5 years on patients with myopic

Figure 3 Case 1, left eye. (a) Fundus photography of the patient at presentation showing typical myopia retinopathy with tessellated pattern and temporal peripapillary crescent. A tiny subretinal haemorrhage involving fovea associated with an elevated macular mass was seen. (b, c) A juxtafoveal choroidal neovascularization with early hyperfluorescence and late profuse angiographic leakage could be seen in the fluorescein angiography. (d) At 3 months after photodynamic therapy, the blood reabsorbed and the lesion looked inactive. (e, f) Fluorescein angiography demonstrated a smaller eccentric fibrotic scar encroached by a ring of hyperplastic retinal pigment epithelium. There was no significant angiographic leakage in both early and late phases. Similar fundus and angiographic features sustained to the 1-year-follow-up.

juxtafoveal CNV. In the series of Jalkh *et al*²¹, 19 eyes with extrafoveal CNV associated with myopia had been treated with photocoagulation, visual acuity worsened in 68% of eyes, remained stable in 21%, and improved in 11%. All except two eyes showed progressive enlargement of the atrophic photocoagulation scar associated with worsening in visual acuities.

In a study of 22 eyes with microperimetry by using scanning laser ophthalmoscope, 16 eyes (72.7%) had laser scar expansion as early as a few months after direct laser photocoagulation. The laser scar expansion ratio was much greater in the myopic group (109.2%) than in the AMD group (28.7%). Laser scars after direct photocoagulation for juxtafoveal CNV may expand and involve the fovea, causing secondary retinal dysfunction in a long-term follow-up.²²

Subretinal dissection of myopic subfoveal CNV has met disappointing results due to postoperative atrophic scar formation and scotoma in 89% of cases.¹¹ Tsujikawa *et al*²³ have reported severe damage of choriocapillaris, retinal pigment epithelium, and neurosensory retina on the extraction pathway of CNV. Interpretation of subretinal surgery on juxtafoveal CNV was difficult because of the limited number of operated cases.²⁴ Macular translocation surgery in relocating the centre of fovea to a site with healthier retinal pigment epithelium may explain observed visual improvement in some reported case series.^{11,13} However, genuine clinical efficacy of macular translocation surgeries for myopic CNV is largely uncertain owing to lack of randomized controlled studies, steep learning curve, and potential postoperative complications including recurrence of

CNV, retinal detachment, glaucoma, and cataract.²⁴ ICG-enhanced laser photothrombosis of neovascular complex feeder vessels is still an evolving new technique after Costa *et al*.⁹ Nevertheless, its proclaimed clinical efficacy may be curtailed by the presence of confounding factors.

PDT has been suggested to be an option of treatment based on the evidence extrapolated from Verteporfin in Photodynamic Therapy Study (VIP), studies on subfoveal CNV secondary to pathologic myopia.^{15,16} Unlike other surgical or laser methods, PDT itself has been standardized and is easily reproducible. PDT theoretically dissipates less amount of laser thermal energy to the surrounding neurosensory retina with minimal scar formation.^{15–18} It is recognized to be a noninvasive method with a high level of safety on human eyes. Cohen *et al*¹⁹ recently demonstrated successful lesion involution and visual improvement after PDT in a case report.

In our prospective series, there were 11 eyes from 11 patients with juxtafoveal CNV secondary to pathologic myopia. The mean age of onset was 44.8 ± 15.4 years, which was comparable to the verteporfin-treated group in the VIP study but was much younger than that in the study of age-related macular degeneration.^{15,25} In this series, the mean logMAR BCVA improved from 0.57 to 0.39 and the improvement is statistical significant (Wilcoxon signed-ranks test, $P = 0.027$). The mean BCVA improved most rapidly in the first 3 months after treatment and the improvement could be sustained to the 12-month follow-up (Figure 1). There was a mean 1.8 lines of improvement in BCVA at 12 months from the baseline. At the 12-month follow-up, 54.5% could keep a

relatively good vision of 20/40, which was much higher than 27.3% at the baseline. The difference, however, did not reach statistical significance because of small sample size. None of the patients in our series had a final BCVA worse than 20/200 after PDT or a drop in vision of one line or more. The findings seem to be more favourable than the natural history of the disease without receiving any intervention.^{8,9,21}

Retreatment is common in PDT and the number of treatments required within the 12 months of follow-up is an important clinical parameter to be measured in calculating the cost effectiveness of the treatment. In our study, the mean number of treatment in the first year was 2.3 treatments. This is lower than the mean of 3.4 treatments for AMD or pathologic myopia and 2.9 treatments for ocular histoplasmosis syndrome.^{15,25,26} Five (41.7%) of 11 patients in our series required only a single treatment in achieving a complete cessation of angiographic leakage without any evidence of recurrence in subsequent follow-up.

Our series has its own limitations including a short follow-up period of only 1 year, a small sample size and no comparative control group. Moreover, they are all Chinese patients, and different ethnicity might have different natural course or clinical response to treatment. The preliminary results are encouraging especially on considering the low retreatment rate, stable or improved BCVA in all treated eyes, more than half having final vision of 20/40 or better and consistently good safety profile.

Based on our findings, juxtafoveal myopic CNV may be an expanded indication for PDT with verteporfin. A randomized controlled trial of larger sample size and longer follow-up are warranted to assess its long-term safety and efficacy.

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