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Photodynamic Therapy with Delayed Light Application for the Treatment of Bilateral Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration

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Purpose: To determine if photodynamic therapy (PDT) with delayed light application at 17 minutes after the start of infusion was effective in the second eyes of patients with bilateral subfoveal classic choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Methods: The records of 20 patients with bilateral subfoveal classic CNV secondary to AMD who were treated with bilateral PDT in the same session were reviewed. Treatment for the second eye of patients was begun 120 seconds after termination of treatment for the first eye. This time interval was necessary for applying the contact lens and entering the new laser parameters, and it was kept constant in all cases. Best-corrected visual acuity (BCVA), ophthalmologic examinations, fluorescein and indocyanine angiograms were used to evaluate the results of PDT. Follow-up time ranged from 6 to 12 months with a mean of 8.7 (±2.1) months.

Results: Mean (±SD) treatment sessions were 1.7 (±0.6) in first eyes and 1.7 (±0.5) in second eyes. Among first eyes, BCVA improved in 7 of the 20 eyes (35%); stabilized in 7 eyes (35%); and worsened in 6 eyes (30%). Among second eyes, BCVA improved in 5 of the 20 eyes (25%); stabilized in 8 eyes (40%); and worsened in 7 eyes (35%).

Conclusions: In most cases, bilateral PDT in the same session achieved cessation of fluorescein leakage from CNV without loss of vision or growth of CNV in the second eyes of patients with bilateral subfoveal classic CNV secondary to AMD. Further studies with a larger number of patients and longer follow-up are necessary to confirm whether bilateral PDT in the same session is beneficial for bilateral subfoveal classic CNV related to AMD. **Jpn J Ophthalmol 2003;47:595–598**

Key Words: Age-related macular degeneration, bilateral choroidal neovascularization, photodynamic therapy, verteporfin.

Introduction

Choroidal neovascularization (CNV) is responsible for 80–90% of cases of severe, irreversible central vision loss in patients with age-related macular degeneration (AMD).[1,2] The neovascular form of AMD (also termed wet, exudative, disciform or serous AMD), which is characterized by CNV, occurs in only approximately 20% of AMD patients, but it is the leading cause of blindness among people in the western world over 50 years of age.[1,2]

Patients with CNV secondary to AMD in 1 eye are at high risk of severe vision loss in the fellow eye, which, when it occurs, will result in a significant adverse impact on the patient's quality of life. About 50% of patients with bilateral CNV are legally blind within 5 years, compared with 12% of patients with unilateral CNV.[3]

Laser photocoagulation and photodynamic therapy (PDT) represent two therapeutic options for the management of neovascular AMD that have been proven effective in randomized clinical studies.[4,5] Laser photocoagulation has been used for several years and provides visual benefit in a small number of patients; only 13–26% of neovascular AMD patients presenting with extrafoveal, juxtafoveal, or small and well-demarcated subfoveal lesions meet laser treatment eligibility criteria.[4] Persistent

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or recurrent CNV usually within 2 years of treatment has been reported in approximately 50% of patients treated.[6] In addition, significant and immediate vision loss has been found to occur after photocoagulation as a result of indiscriminate damage to the retina overlying the treated area.[4] PDT with verteporfin represents an advance in the treatment of neovascular AMD. Results from clinical investigations demonstrate that PDT with verteporfin can effectively and safely reduce the risk of vision loss in AMD patients with predominantly classic subfoveal lesions, and in many patients with occult CNV, without causing permanent damage to the overlying neurosensory retina.[7]

In this study, we tried to determine if verteporfin therapy with delayed light application at 17 minutes after the start of infusion was effective in the second eyes of patients with bilateral subfoveal classic CNV secondary to AMD.

Materials and Methods

We reviewed the records of 20 patients with bilateral subfoveal classic CNV secondary to AMD who were treated with bilateral PDT in the same session with verteporfin. Each patient signed a written consent statement after receiving a full verbal and written explanation of the therapy, including the potential benefits and risks of treatment. Major inclusion criteria for participants included evidence of bilateral subfoveal classic CNV secondary to AMD, lesion size $\leq$9 Macular Photocoagulation Study (MPS) disc areas and greatest linear dimension $\leq$5400 μm, and best-corrected visual acuity (BCVA) of 20/200 or more in both eyes. In a patient qualifying for treatment, the eye with better visual acuity and/or smaller lesion size was accepted as the first eye. Patients having prior ocular surgery or a specific condition such as glaucoma, dense cataract, or another form of retinal disease were excluded. Standardized protocol refraction was performed and the visual acuity of each eye was determined with Snellen charts. A complete ocular examination was performed including slit-lamp examination, non-contact lens biomicroscopy of the fundus, and color and monochromatic fundus photography using a standard fundus camera. Fundus fluorescein and indocyanine green angiograms were carried out simultaneously on a Heidelberg Scanning Laser Ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany).

The spot size was determined by measuring the greatest linear dimension of the entire lesion and adding an additional 1000 μm to this value, to provide at least a 500 μm border at all edges. Verteporfin (Visudyne; Novartis Ophthalmic AG, Hettlinger, Switzerland) was reconstituted with sterile water and diluted with 5% dextrose to achieve a drug dose of 6 mg/m^2 body surface area and a total infusion volume of 30 mL. The solution was infused intravenously at a rate of 3 mL/min over 10 minutes. Fifteen minutes after the start of dye infusion, 689 nm light was delivered to the first eye by an ocular photoactivation diode and laser link slit-lamp microscope (Coherent, Palo Alto, CA, USA) as described in previous studies.[5] The delivered irradiation was kept constant at 50 J/cm^2 within 83 seconds. The second eyes were treated 120 seconds after termination of treatment for the first eyes. This time interval was necessary for applying the contact lens and entering the new laser parameters, and it was kept constant in all cases.

Follow-up examinations were scheduled at 1 month and at 3 months after the treatment, and every 3 months thereafter. All patients were followed-up for at least 6 months. At the follow-up, the CNV evaluation was done according to a grading system developed to assess the presence or absence of leakage from the CNV components. The extent of fluorescein leakage was graded as follows: (1) progression (leakage from the CNV beyond the area of the lesion noted at baseline), (2) moderate leakage (area of CNV occupying $>$50% of the area of CNV noted at baseline and no progression), (3) minimal leakage (leakage from the CNV occupying $<$50% of the area of CNV noted at baseline), and (4) absence of leakage (no CNV within the area of the lesion at baseline). Retreatments were considered when minimal leakage, moderate leakage, or progression was observed at the 3-month follow-up.

Results

Twenty patients with bilateral subfoveal CNV secondary to AMD who were treated with bilateral PDT in the same session were enrolled. Their ages ranged from 58 to 77 years with a mean ($\pm$SD) age of 68.0 ($\pm$6.2). Follow-up time ranged from 6 to 12 months with a mean of 8.7 ($\pm$2.1) months. BCVA at screening ranged from 20/200 to 20/50 in the first eyes and from 20/200 to 20/63 in the second eyes. Among first eyes, 8 (40%) eyes were treated once, 10 (50%) eyes were treated twice and 2 (10%) eyes were treated 3 times. Among second eyes, 7 (35%) eyes were treated once, 12 (60%) eyes were treated twice, and 1 (5%) eye was treated three times. Retreatments were carried out 12 weeks after the last treatment with the same protocol. Mean ($\pm$SD) treatment sessions were 1.7 ($\pm$0.6) in first eyes, 1.7 ($\pm$0.5) in second eyes. There was no loss to follow-up of any of these patients during the trial.

Among first eyes, BCVA improved in 7 of the 20 eyes (35%), stabilized in 7 eyes (35%), and worsened in 6

eyes (30%). Among second eyes, BCVA improved in 5 of the 20 eyes (25%), stabilized in 8 eyes (40%), and worsened in 7 eyes (35%). Photodynamic therapy with verteporfin did not cause any systemic complications. No skin photosensitivity reactions were reported after an initial treatment or multiple course of therapy. No PDT-related ocular complications were reported. Table 1 gives age, sex, and follow-up of the study population and the outcome of first and second eyes.

Discussion

PDT with verteprofin is a two-step process involving the intravenous administration of a nontoxic photosensitizer and its subsequent activation by a specific wavelength of light using a nonthermal diode laser device.[8] Efficacy and selectivity of PDT depend upon numerous factors. These include the amount of photosensitizer injected, the formulation in which it is administered, and the duration of infusion; the absorption wavelength, the extinction coefficient, and the target area of the photosensitizer; the light source, the timing of light delivery, and the amount of light delivered; and the treatment procedure.[9] Based on a study of a number of photosensitizers with different chemical structures, Haimovici et al[10] reported that the localization of the photosensitizer in the structure of the rabbit eye is strongly structure- and time-dependent. Hence, for a given sensitizing agent, the time interval between drug administration and light treatment plays an important role. When low doses of photosensitizer are used, significant selective localization of the photosensitizer in the neovasculature is obtained within short time intervals after administration.[9] Furthermore, the selectivity of PDT in general depends upon where the light is directed, how deep the light penetrates through tissues and where the photosensitizer is concentrated.[9] Since photosensitizers are cleared at different rates from different tissues, careful timing of the light exposure within the period when the photosensitizer is at a maximal concentration in the target tissue can increase the selectivity of PDT.[11]

Before clinical studies in patients with AMD could be initiated, the optimal dose of verteporfin, the light dose and the timing of irradiation were determined in the primate model of experimentally induced CNV.[12–14] In the primate model of experimental study, the optimal dose of verteporfin was 0.375 mg/kg (approximately 6 mg/m^2) and the optimal time for irradiation using light at a wavelength of 692 nm was 20–50 minutes after commencing the intravenous injection of verteporfin.[13,14] Irradiation performed too early (ie, within 5 minutes of verteporfin injection) caused some damage to retinal and larger choroidal vessels.[13,14] The PDT effect was less intensive if irradiation was performed at 10 minutes instead of 15 minutes after verteporfin infusion, although verteporfin

Table 1. Age, Sex, and Follow-up of Study Population and Outcomes for First and Second Eyes

Patient no.	Age	Sex	Follow-up (mo)	VA initial (first eye)	VA last (first eye)	PDT number (first eye)	VA Initial (second eye)	VA last (second eye)	PDT number (second eye)
1	58	Male	9	20/200	20/200	2	20/200	20/200	2
2	64	Male	9	20/160	20/160	1	20/200	20/200	1
3	72	Female	12	20/200	20/100	2	20/200	20/200	2
4	70	Female	6	20/100	20/80	1	20/200	20/200	1
5	69	Female	9	20/80	20/80	2	20/125	20/160	1
6	75	Male	12	20/63	20/50	3	20/80	20/200	2
7	77	Female	12	20/125	20/160	2	20/200	20/160	2
8	60	Female	9	20/100	20/200	1	20/100	20/200	2
9	63	Male	9	20/160	20/160	2	20/200	20/160	2
10	59	Female	12	20/100	20/50	3	20/200	20/200	2
11	75	Female	9	20/100	20/125	1	20/125	20/63	2
12	73	Female	9	20/50	20/50	2	20/160	20/200	3
13	67	Male	6	20/100	20/80	1	20/200	20/100	1
14	65	Male	6	20/100	20/200	1	20/100	20/200	1
15	75	Male	9	20/50	20/32	2	20/100	20/100	2
16	72	Female	6	20/63	20/63	1	20/100	20/180	1
17	65	Male	6	20/80	20/100	2	20/125	20/200	1
18	58	Male	9	20/80	20/125	1	20/200	20/200	2
19	74	Female	6	20/80	20/63	2	20/200	20/200	2
20	70	Female	9	20/50	20/50	2	20/63	20/200	2

VA: visual acuity, PDT: photodynamic therapy.

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plasma levels were higher at the earlier time point (ie, 10 minutes). This result suggests that uptake by the endothelial cells was not optimal at 10 minutes after verteporfin infusion. The optimal time for irradiation therefore depends on endothelial cell uptake and indeed may vary between species.[15] Irradiation soon after intravenous application of the sensitizer leads to an enhanced vascular effect, and in the setting of CNV treatments, to a loss of the retino-choroidal selectivity with dramatic occlusive effects within the retinal vasculature.[16]

To evaluate the short-term safety and maximal tolerated dose of verteporfin, multicenter phase I and II nonrandomized clinical trials were initiated in patients with subfoveal CNV.[15–17] Based on these studies, the effective single treatment providing the best visual outcome consisted of a verteporfin dose of 6 mg/m^2 infused intravenously over 10 minutes and a light intensity dose of 50 J/cm^2 delivered over a period of approximately 83 seconds. The optimal time for irradiation (at 690 nm, light intensity 600 mW/cm^2) was 15 minutes after the start of verteporfin infusion. This treatment procedure is being used in several phase III randomized clinical trials and in clinical application also.[15]

In our study, the second eyes of patients were irradiated 17 minutes after the start of verteporfin infusion. A 2-minute delay was necessary for applying the contact lens to the second eye and entering the new laser parameters, and it was kept constant in all cases. Among the first eyes, BCVA improved in 7 of the 20 eyes (35%), stabilized in 7 eyes (35%), and worsened in 6 eyes (30%). Among second eyes, BCVA improved in 5 of the 20 eyes (25%), stabilized in 8 eyes (40%), and worsened in 7 eyes (35%). Both groups had almost the same retreatment rates during follow-up.

Although the number of patients observed in our study was small and the follow-up period was relatively short, the preliminary results are promising. In most cases, bilateral PDT in the same session achieved cessation of fluorescein leakage from CNV without loss of vision or growth of CNV in the second eyes of patients with bilateral subfoveal classic CNV secondary to AMD. Further studies with a larger number of patients and longer follow-up are necessary to confirm whether bilateral PDT in the same session is beneficial for bilateral subfoveal CNV related to AMD.

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