Complications After Photodynamic Therapy

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Objective: To evaluate the incidence of complications of photodynamic therapy (PDT) with verteporfin in subfoveal choroidal neovascularizations secondary to age-related macular degeneration and pathologic myopia.

Methods: In this retrospective interventional case series, the occurrence of complications after PDT in a clinical setting was analyzed. Consecutive medical records of patients with age-related macular degeneration and pathologic myopia treated with PDT were reviewed for complications. Complications included treatment-related systemic adverse events, injection site effects, and ocular adverse events.

Results: We included 273 patients (198 with age-related macular degeneration and 75 with pathologic myopia) in the study. A total of 485 photodynamic treatment sessions were performed. Infusion-related back or chest pain was reported by 6 patients (2.2%; 95% confidence interval [CI], 0.8%-4.7%). Injection site effects, extravasation, and photosensitivity reactions were not observed. Dyspnea and flushing during infusion were observed in 2 patients (0.7%; 95% CI, 0.09%-2.6%). Body pain, shortness of breath, and elevated blood pressure were noted in 13 patients (4.8%; 95% CI, 2.6%-8.0%). General pruritus was described by 6 patients (2.2%; 95% CI, 0.8%-4.7%), starting 4 hours after the infusion of verteporfin, and resolved within 72 hours after PDT. A total of 8 patients (2.9%; 95% CI, 1.3%-5.7%) reported an acute severe visual acuity decrease of at least 4 Early Treatment Diabetic Retinopathy Study lines occurring within 7 days of treatment.

Conclusions: Complications associated with PDT are uncommon, but there were limitations of retrospective studies for identifying safety problems. Complications like acute severe visual events may occur in about 3% of patients. We believe that this risk is outweighed by the benefits of PDT on visual function in most patients.

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Photodynamic therapy (PDT) with verteporfin reduces the risk of moderate and severe vision loss in patients with subfoveal choroidal neovascularizations (CNVs) due to age-related macular degeneration (AMD) and pathologic myopia (PM). Given the results of the verteporfin therapy trials, the recognition of the lesion components, the estimation of their proportions, and the size of the lesion are important criteria for the appropriate selection of eyes for treatment with PDT.

In this study, we analyzed the rate of complications after PDT in a retrospective clinical setting. Photodynamic therapy is a selective drug-based treatment for CNV due to AMD and PM that has a proved long-term safety profile. Verteporfin is a drug shown to be relatively safe. Safety data were described in the 2-year phase 3 Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) studies. In total, the incidence of treatment-related serious adverse events was 3.8% for verteporfin-treated patients compared with 1.4% for placebo recipients. No treatment-related deaths occurred in any of the clinical trials. The total rate of withdrawal from the ocular studies due to adverse events (regardless of the association with treatment) was low: 3.4% for the verteporfin-treated patients compared with 0.6% for placebo recipients. Clinically significant ocular events were defined, as in the TAP and VIP study protocols, as serious adverse events, and included an acute severe visual acuity decrease, defined as a decrease of at least 4 Early Treatment Diabetic Retinopathy Study (ETDRS) lines of visual acuity occurring within 7 days of treatment, arteriolar or venular nonperfusion, retinal capillary nonperfusion of at least 1 Macular Photocoagulation Study (MPS) disc area, or an extensive vitreous hemorrhage of at
least 4 MPS disc areas. These events occurred in 3.5% of the PDT-treated patients and 1.7% of the placebo recipients. Transient visual disturbances were noted in 29.8% of the verteporfin-treated patients and 12.8% of the placebo group. Mild or moderate injection site events were the only important treatment-related systemic adverse events. Infusion-related back pain was reported by verteporfin-treated patients at an incidence of 2.2%. Most of the cases occurred in patients with AMD. Photosensitivity reactions were also reported in 2.2% of verteporfin-treated patients.

**METHODS**

A retrospective study was undertaken to analyze the frequency of complications after PDT. All data accumulation conformed with all country laws, and the study was performed in adherence with the tenets of the Declaration of Helsinki. Inclusion criteria were subfoveal CNV due to AMD or PM, treated with PDT. In all patients, PDT with verteporfin was performed after written informed consent was obtained. At each visit, patients underwent a complete eye examination, including a detailed medical and ocular history. Examinations included ETDRS visual acuity, binocular ophthalmoscopy, fluorescein angiography with a scanning laser ophthalmoscope (Heidelberg retina angiograph; Heidelberg Engineering GmbH, Heidelberg, Germany), and color fundus photography. All the examinations were performed at baseline and 1 week, 3 months, and 6 months after initial PDT. Thereafter, patients were followed up at 6-month intervals. If patients noted some systemic adverse events and/or some ocular adverse events affecting the treated eye, they were asked to come immediately to a control visit. Patients were asked with a questionnaire about all treatment-related systemic adverse events (abdominal pain, allergic reactions, back or chest pain, cardiovascular symptoms [atrial fibrillation, transient elevated blood pressure, peripheral vascular disorder, and syncope], digestive abnormalities, nervous disorder, respiratory disorder [cough, dyspnea, pharyngitis, or pneumonial], skin disorder), injection site reactions, photosensitivity reactions, and ocular adverse events. Clinically significant ocular events were defined, similar to the TAP and VIP study protocols, as serious adverse events, and included an acute severe visual acuity decrease, defined as a decrease of at least 4 ETDRS lines of visual acuity occurring within 7 days of treatment, arteriolar or venular nonperfusion, retinal capillary nonperfusion of at least 1 MPS disc area, and an extensive vitreous hemorrhage of at least 4 MPS disc areas. In addition, we noted visual disturbances or scotomas. Because vision loss is part of the natural history of CNV-related conditions, vision loss was recorded as an adverse event only when spontaneously reported by the patient within 7 days after treatment and suspected to be different from the usual pattern of natural progression of the disease. All patients with ocular adverse events underwent an angiographic examination to assess arteriolar, venular, or retinal capillary nonperfusion.

Descriptive statistics are provided for all baseline demographic and clinical characteristics of interest. The frequency of complications was calculated, and 95% confidence intervals (CIs) were estimated.

**RESULTS**

We included 273 patients (114 men and 159 women) with subfoveal CNV due to AMD or PM. All 273 patients had a minimal follow-up of 12 months. During the mean ± SD follow-up of 22.5 ± 5.7 months, we performed 485 PDT sessions. In detail, 75 patients, aged 24 to 82 years (mean ± SD, 63 ± 11 years), had subfoveal CNV secondary to AMD. In these patients, myopia ranged from −9.0 to −22.0 diopters (mean ± SD, −15.0 ± 4 diopters). The initial visual acuity ranged from 20/200 to 20/60 (median, 20/80). The remaining 198 patients, aged 50 to 92 years (median ± SD, 69 ± 12 years), had subfoveal CNV secondary to AMD. The initial visual acuity ranged from 20/200 to 20/60 (median, 20/80).

Adverse events, such as injection site reactions, extravasation of verteporfin, and photosensitivity reactions, were not observed in our series. Infusion-related pain was reported by 6 patients (2.2%; 95% CI, 0.8%–4.7%), all of whom were treated for CNV secondary to AMD. Infusion-related back pain was reported in 5 patients (1.8%; 95% CI, 0.6%–4.2%). One patient (0.4%; 95% CI, 0.01%–2.0%) described retrosternal chest pain during the infusion period. All patients reported this as mild (n = 2) or moderate (n = 4) pain that resolved by ending or discontinuing the infusion with verteporfin. Four of these patients received repeated PDT, one of whom reported no back or chest pain during treatment. Thirteen patients with AMD (4.8%; 95% CI, 2.6%–8.0%) experienced right-sided body pain, with shortness of breath and an elevated blood pressure. One of these patients also described a rash for a few hours after treatment. Such symptoms were not noted in patients with PM. In addition, 2 patients with AMD (0.7%; 95% CI, 0.09%–2.6%) complained of dyspnea and flushing during the first minutes of the infusion. The infusion was discontinued, and the dyspnea resolved within 20 minutes of treatment with corticosteroids. Two patients (0.7%; 95% CI, 0.09%–2.6%) (1 with AMD and 1 with PM) noted mild to moderate nausea during the verteporfin infusion. The nausea resolved within 6 hours after PDT. General pruritus was described by 6 patients (2.2%; 95% CI, 0.8%–4.7%) (4 with AMD and 2 with PM), starting 4 hours after the infusion of verteporfin. Symptoms resolved within 72 hours after PDT. Two patients with AMD (0.7%; 95% CI, 0.09%–2.6%) reported syncope, which was seen 9 and 24 hours after PDT. The same patients noted a mild to moderate headache during the verteporfin infusion. A detailed clinical examination of these patients revealed no abnormalities. Patients recovered uneventfully. Nervous disorders, like hypoaesthesia, paresthesia, and dizziness, were noted by 5 patients (1.8%; 95% CI, 0.6%–4.2%) (4 with AMD and 1 with PM), starting 1 hour after the infusion of verteporfin. Symptoms resolved within 48 hours after PDT.

Eight patients (2.9%; 95% CI, 1.3%–5.7%) (7 with AMD and 1 with PM) reported an acute severe visual acuity decrease of at least 4 ETDRS lines occurring within 7 days of treatment. In most of these eyes (n = 7), the visual acuity decrease was related to extensive intraretinal and subretinal hemorrhages of at least 4 MPS disc areas. The visual acuity decrease persisted in 2 patients (0.7%; 95% CI, 0.09%–2.6%) for longer than 3 months after the initial decrease, whereas 6 patients recovered to their baseline visual acuity after spontaneous resolution of the hemorrhages or after treatment with alteplase (recombinant tissue-type plasminogen activator) (Activase; Genen-
tech Inc, San Francisco, Calif) and gas injection.1,2 The patient with AMD with the persistent severe visual acuity decrease showed extensive pigment epithelial atrophy after the resorption of the subretinal hemorrhages. We observed no ophthalmoscopic or angiographic abnormalities in the patient with PM who experienced a persistent severe visual acuity decrease.

Retinal arteriolar or venular capillary nonperfusion of at least 1 MPS disc area or an extensive vitreous hemorrhage was not observed. A transient visual disturbance during the first 3 days after treatment was noted by 76 patients (27.8%; 95% CI, 22.6%-33.6%), 46 of whom had AMD. These events tended to occur early after treatment, and patients often reported haziness, blurriness, and flashing light. These visual disturbances resolved spontaneously within a few days to a few weeks.

### COMMENT

Our findings show that PDT is well tolerated in a clinical setting in patients with CNVs secondary to AMD and PM. Most observed adverse events in our series were mild or moderate and transient. No new safety issues were identified in patients with PM. There was no evidence of increased or cumulative toxic effects with each subsequent treatment of verteporfin.

Infusion-related back or chest pain or body pain during the verteporfin infusion was reported in our study only by patients with AMD. We noted infusion-related back or chest pain in 6 patients (2.2%). Most patients reported this as mild to moderate pain that resolved by ending or discontinuing the infusion with verteporfin. When patients were rechallenged with infusion, outcomes were mixed and there were several instances when no pain was reported. In the TAP and VIP studies, infusion-related back pain was reported by verteporfin-treated patients at an incidence of 2.2%. Most of the cases occurred in patients with AMD, with only 1 case being reported in the PM arm of the VIP trial.1 The mechanism of infusion-related pain is not clear. It has not been associated with any evidence of hemolysis, allergic reaction, or renal toxic effects, and usually resolves by the end of the infusion.

The activation of the alternative complement pathway and the production of anaphylatoxins may lead to the body pain phenomenon (which included back, chest, and right-sided pain) and to symptoms like flushing, rash, dyspnea, and elevated blood pressure. This hypothesis of complement activation is supported by small studies that suggested that neutrophil margination was a possible mechanism for verteporfin infusion–related pain.9,10 In the TAP and VIP trials,1,2 injection site events decreased from 11.9% in the first year to less than 3% in the second year. This may reflect the adoption of more careful procedures by the study centers following increased awareness of these events from the 1-year results. Similarly, there was a lower incidence of injection site events in the VIP trial.1,2 The low incidence reflects the experience gained by the clinicians in the administration technique and the increased awareness of this adverse event during training. In our study, we noted no injection site events. We believe injection site events can be minimized if recommended procedures are followed and patients are monitored carefully throughout the 10-minute infusion.

Photosensitivity reactions were reported in 2.2% of patients treated with PDT in the TAP and VIP trials.1,2 These were generally mild to moderate transient reactions, and usually developed from direct exposure to sunlight within 3 days of treatment. Photosensitivity reactions rarely occurred in the VIP trial despite the shorter light protection period of 24 hours compared with the 48 hours used in the TAP investigation. This strongly suggests that the reduction in photosensitivity reactions is related to better education and compliance by the patients, and not to the length of the light protection period. If recommended procedures are followed closely and the patient is monitored carefully throughout the infusion, injection site events can be minimized, particularly those involving extravasation. This is demonstrated by the fact that we have not observed any photosensitivity reactions among our series of patients undergoing PDT.

Cardiovascular symptoms considered to be related to PDT (atrial fibrillation, transient elevated blood pressure, and peripheral vascular disorder) were noted in 4.8% of our verteporfin-treated patients. One of these patients also described a rash for a few hours. All patients were older than 65 years and had a history of systemic hypertension. In addition, 0.7% of our patients complained of respiratory symptoms like dyspnea. The infusion was discontinued and the dyspnea resolved within 20 minutes of treatment with corticosteroids. The activation of the alternative complement pathway may lead to symptoms like flushing, rash, dyspnea, and elevated blood pressure. General pruritus was described by 2.2% of our patients, starting 4 hours after the infusion of verteporfin. Similar symptoms were observed in the TAP and VIP studies. Symptoms like general pruritus are known as allergic symptoms, which are related to agents like pollen, concomitant medications, and fluorescein. The pruritus observed in our study was temporally related to the fluorescein angiography and the PDT, but is also attributed to other factors. On the other hand, verteporfin for injecting is a lipid-based formula, and it has been suggested that liposomes may activate the alternative complement pathway and the production of anaphylatoxins.9,11,12

Two (0.7%) of our patients reported syncope within 48 hours after the PDT session. The same patients noted a mild to moderate headache during the verteporfin infusion. The detailed medical workup revealed no underlying cause. We have no proof that the syncope was related to the treatment with verteporfin, but the mild to moderate headache during the verteporfin infusion and the unremarkable medical workup may point to the PDT session as the underlying cause of the syncope.

A total of 2.9% of our patients reported an acute severe visual acuity decrease of at least 4 ETDRS lines occurring within 7 days of treatment. In most eyes (n=7, all with AMD), the visual decrease was related to extensive intraretinal and subretinal hemorrhages. The visual acuity decrease persisted in 0.7% of the patients. One patient with the persistent severe visual acuity decrease showed extensive pigment epithelial atrophy after the resorption of the subretinal hemorrhages. We observed no
ophthalmoscopic or angiographic abnormalities in the patient with PM who experienced a persistent severe visual acuity decrease. Similar rates of acute severe visual acuity decreases were observed in the TAP and VIP studies. Because a vision decrease is part of the natural history of CNV-related conditions, these events may have been unrelated to the PDT session. However, all patients included in our study had predominantly classic CNV. Because extensive intraretinal and subretinal hemorrhages are not common complications of predominantly classic CNV, we speculate that the hemorrhages were caused by a vascular alteration after PDT. One reason may be an extensive structural disintegration and an extensive loss of vascular continuity after the splitting of the basal lamina in atherosclerotic channels after PDT. The angiographic workup in the patients with acute visual loss revealed no retinal arteriolar or venular or capillary nonperfusion. The patient with PM who experienced acute visual loss showed no ophthalmoscopic or angiographic abnormalities related to the PDT session. Because the rate of this complication is quite low, we believe that the benefit of PDT outweighs the risk of severe vision decrease after PDT with verteporfin.

A transient visual disturbance within 3 days after treatment was noted in 27.8% of our patients. These events tended to occur early after treatment and resolved spontaneously within a few days to a few weeks. Patients with CNV secondary to AMD had a much higher incidence of visual disturbance compared with patients with PM (60.5% vs 39.5%). These symptoms may have been due to changes of retinal or choroidal blood flow. These effects may be more pronounced in older patients (aged >60 years) with a sclerotic vascular system than in younger patients. In the TAP and VIP studies, transient visual disturbances were noted in 30% of the verteporfin-treated patients and in 12.8% of the placebo group.

In summary, complications after PDT in CNVs secondary to AMD and PM are uncommon, but there were limitations of retrospective studies for identifying safety problems. Complications like acute severe visual events may occur in about 3% of patients. We believe that this risk is far outweighed by the benefits of PDT on visual function in most patients; in particular, extravasation and photosensitivity reactions may be avoided if treatment guidelines are followed closely.

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REFERENCES