Proton Beam Irradiation for Neovascular Age-Related Macular Degeneration

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Objective: To evaluate safety and visual outcomes after proton therapy for subfoveal neovascular age-related macular degeneration (AMD).

Design: Randomized dose-ranging clinical trial.

Participants: One hundred sixty-six patients with angiographic evidence of classic choroidal neovascularization resulting from AMD and best-corrected visual acuity of 20/320 or better.

Methods: Patients were assigned randomly (1:1) to receive 16-cobalt gray equivalent (CGE) or 24-CGE proton radiation in 2 equal fractions. Visual acuity was measured using standardized protocol refraction. Complete ophthalmological examinations, color fundus photography, and fluorescein angiography were performed before and 3, 6, 12, 18, and 24 months after treatment.

Main Outcome Measure: Proportion of eyes losing 3 or more lines of vision from baseline. Kaplan–Meier statistics were used to compare cumulative rates of vision loss between the 2 treatment groups.

Results: At 12 months after treatment, 36 eyes (42%) and 27 eyes (35%) lost 3 or more lines of vision in the 16-CGE and 24-CGE groups, respectively. Rates increased to 62% in the 16-CGE group and 53% in the 24-CGE group by 24 months after treatment ($P = 0.40$). Radiation complications developed in 15.7% of patients receiving 16 CGE and 14.8% of patients receiving 24 CGE.

Conclusions: No significant differences in rates of visual loss were found between the 2 dose groups. Proton radiation may be useful as an adjuvant therapy or as an alternative for patients who decline or are not appropriate for approved therapies. *Ophthalmology 2006;113:2012–2019 © 2006 by the American Academy of Ophthalmology.*

Anti–vascular endothelial growth factor therapy with pegaptanib (Macugen, Eyetech Pharmaceuticals, New York, NY) and photodynamic therapy (PDT) using verteporfin currently are the preferred treatments for patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1–4] Although patients treated with PDT experience less visual loss than patients who receive no treatment, the beneficial effects of PDT depend on lesion characteristics,[1,3,5] with lesion size being the strongest predictor of treatment benefit.[5] With room for improvement in our therapy for neovascular AMD, alternatives such as radiation are being investigated. Radiation may be effective through several mechanisms, including inhibition of proliferating endothelial cells, angiogenic cytokine-producing inflammatory cells, and cell types involved in scar formation, including the retinal pigment epithelium. Radiation has the added benefit of fewer treatments, which can present a significant advantage for the elderly.

In preclinical studies, these angiogenic inhibitory effects have been demonstrated using radiation doses of 16 Gy or less,[6] and significant radiation retinopathy has not been observed in patients treated with low doses of radiation (≤25 Gy) for orbital, paranasal, and nasopharyngeal tumors.[7]

These findings have stimulated interest in evaluating radiation as a treatment method for CNV secondary to AMD. Initial data by Chakravarthy et al[8] reported an inhibitory effect of radiation therapy on CNV. A number of additional studies have demonstrated possible benefit,[8–13] whereas data from several other studies suggest no treatment effect.[14–16] Interpretation of these conflicting results is difficult because of one or a combination of the following factors: variable doses and fractionation schemes, small sample sizes, differences in patient risk factors and prognostic factors, lack of long-term follow-up, and nonrandomized designs.

Originally received: July 12, 2005.
Accepted: May 26, 2006. Manuscript no. 2005-636.

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Presented in part at: Retina Society Annual Meeting, December 1999, Wailea, Hawaii.

Supported by the Massachusetts Eye and Ear Infirmary Retina Research and Melanoma Research Funds, Boston, Massachusetts; T. F. C. Frost Trust, London, United Kingdom; and Cripplegate and Dowsett Educational Fund, London, United Kingdom.

The authors have no conflicts of interest related to the article.

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ISSN 0161-6420/06/$–see front matter
doi:10.1016/j.ophtha.2006.05.036

Two randomized controlled trials using 24 Gy of 6-mV photons in 4 fractions, as well as 8 and 16 Gy of 6-mV photons in 4 fractions, also demonstrated a treatment benefit for distance visual acuity at 1 year and 18 months, respectively.[17,18] The observed benefit, however, was absent for reading ability, and CNV size increased during follow-up.[18] Another small randomized study of radiation treatment (single fraction 750 cGy using 6-mV photons) versus observation for patients with subfoveal neovascular AMD demonstrated marginally more favorable visual outcomes for the treatment.[19] Conversely, data from several other randomized trials demonstrated no benefit.[20–24] The Radiation Therapy for Age-Related Macular Degeneration Study showed that 16 Gy applied in 8 fractions provided no visual acuity or contrast sensitivity benefit at 1 year.[20,21] Hart et al[22] used 12 Gy in 6 fractions and Marcus et al[23] used 14 Gy in 7 fractions; both trials showed no difference in distance visual acuity, near visual acuity, or CNV progression as assessed by fluorescein angiography. A recent multicenter, randomized trial of external beam irradiation comparing 20 Gy in 5 equal fractions with sham radiotherapy also found no visual acuity benefit at 1 year.[24]

Charged particle radiation has been used infrequently to treat patients with CNV.[13,25,26] Preliminary beneficial effects of proton beam irradiation were observed in a nonrandomized study using a single fraction of 8 cobalt gray equivalents (CGEs).[13] (A CGE is the proton dose in grays times a relative biological effectiveness factor of 1.1.) Flaxel et al[26] treated 46 patients with 8 or 14 CGE of protons in a single fraction. The lower dose seemed to be ineffectual, but at 12 months after treatment, 75% of eyes treated with the higher dose showed improved visual acuity and 90% showed no leakage. Although radiation retinopathy developed in almost half the patients treated at the higher dose, serious vision loss attributable to radiation was observed in only 1 patient at 15 months after therapy.[26]

We conducted a randomized clinical trial to evaluate safety and visual outcomes after 16 CGE versus 24 CGE of proton therapy in collaboration with the Proton Therapy Research Group at the Massachusetts General Hospital. Based on our previous experience with metastatic tumor treatment,[27] we chose to deliver our doses in 2 equal fractions. Furthermore, in contrast to many other forms of external beam radiation that have been used to treat CNV, the physical properties of protons allow the delivery of more than 90% of the radiation dose to the target tissue, therefore minimizing radiation exposure to other tissues.[28–30]

Patients and Methods

The study protocol was approved by the Institutional Review Board of the Massachusetts Eye and Ear Infirmary. Informed consent was obtained from all patients before eligibility screening.

Study Design

This was a randomized, unmasked trial of 2 radiation doses for patients with subfoveal CNV secondary to AMD treated between October 1995 and February 2000. Patients were assigned to receive a total dose of 16 or 24 CGE proton therapy fractionated in 2 equal doses over a 2- to 3-day period. Enrollment of PDT-eligible patients was stopped after the 1-year results of the first multicenter, randomized placebo-controlled clinical trial of PDT recommended verteporfin therapy for the treatment of patients with predominantly classic subfoveal CNV resulting from AMD.[1] Patients with predominantly classic CNV were offered proton beam irradiation if the lesion did not fit the eligibility criteria for PDT treatment.

Patient Selection

All patients aged 50 years or more with primary or recurrent (after prior thermal laser therapy) classic subfoveal CNV (occult CNV also could be present) identified by fluorescein angiography and with best-corrected visual acuity of 20/320 or better in the study eye were eligible for the study. The ability to give informed consent and to return for follow-up visits for 2 years were also criteria for enrollment. Patients who had a minimum of 1 follow-up examination were eligible for inclusion in the final data analysis. Patients with CNV secondary to non-AMD causes, vision-compromising diseases other than AMD, and occult-only CNV were excluded. Eligibility was confirmed by completion of an eligibility review form. The eligibility review form was submitted to a study coordinator who randomly assigned (1:1) each patient to receive a total dose of 16 or 24 CGE. The dose assignment then was recorded on the ophthalmologist's treatment planning page, which included fundus drawings and measurements of the lesion, and was sent to the Harvard Cyclotron for completion of the treatment plan approximately 3 days before initiation of radiation therapy.

Proton Therapy

Before radiation, axial lengths were measured and a treatment mask and bite block were fabricated.[31] Treatment parameters were generated by the ophthalmologist using the fluorescein angiogram results obtained at baseline. The size of the lesion was estimated using superior, inferior, temporal, and nasal measurements from the fovea.[30] The area of neovascularization, with a margin of 2 mm to 90% dose, was treated using a light field technique. This method of alignment of the beam with a target eliminates the need for surgical localization and has been used successfully to treat ciliary body melanomas, choroidal metastases, and benign vascular tumors such as retinal angiomas and choroidal hemangiomas.[27,32] A narrow light beam coaxial with the central axis of the proton beam is shone through the aperture and is projected onto the globe. The patient's head and eye are positioned so that the borders of the light beam are matched to anatomic landmarks on the surface of the globe. The entry port represented by the edge of the light beam is at the limbus, which serves as an unambiguous landmark for alignment. This placement spares the lens from irradiation, thus minimizing the risk of radiation-related cataracts. (See Fig 1 for illustration of successful closure of CNV after proton therapy.)

Study Procedures

All patients underwent visual acuity testing using the Early Treatment Diabetic Retinopathy Study charts and a standardized protocol. Best-corrected visual acuity testing, color fundus photography, fluorescein angiography, and a complete ophthalmological examination at baseline were performed to determine eligibility. Patients returned for safety and clinical assessments 3, 6, 12, 18, and 24 months after treatment. At each of these visits, patients underwent best-corrected visual acuity measurement, fluorescein angiography assessment, and an ophthalmological examination; all visual acuity measurements and photography were performed by certified, masked personnel using established study protocols.