Radiation Therapy for Age-related Macular Degeneration

An assessment of the latest technology and its safety.

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Choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) leads to vision loss due to disruption of the retinal pigment epithelium and damage to the photoreceptor layer.[1] Although anti-vascular endothelial growth factor (anti-VEGF) agents effectively inhibit the growth and permeability of new blood vessels, they must be frequently injected over an indefinite period of time. Treatment of CNV with laser photocoagulation can also be successful, but only 10% to 15% of patients with the disease have extrafoveal lesions deemed appropriate for the treatment.[2] Furthermore, laser photocoagulation causes direct retinal destruction.[3] Radiation therapy recently has resurged as a potential treatment option for retinal diseases. In light of this approach taken by some medical device companies, we briefly review the forms of radiation therapy currently employed and the potential ocular complications of radiation therapy.

Radiation is believed to have a broad spectrum of action, as it damages proliferating and established endothelial cells, fibroblasts, and other inflammatory cells, all of which are involved in the pathology of wet AMD.[5] When ionizing radiation passes through the nucleus of the cell, it induces double-strand DNA breaks. If the breaks are improperly repaired, they can lead to an exchange-type chromosome aberration and form a dicentric chromosome (a chromosome with two or more centromeres). Dicentric chromosome frequency is a sensitive index of the amount of radiation that passes through the nucleus of the cell. Research has shown that the harmful effects of ionizing radiation result from its ability to induce double-strand breaks in the DNA within the nucleus of the cell.[5] For example, it has been estimated that approximately 2,000 ionization events occur directly in the nuclear DNA following exposure to 1 Gy of low linear-energy–transfer radiation. Studies of human lymphocytes show that abnormal dicentric chromosomes form in a dose-dependent manner over a twentyfold dose range (0.25-5.0 Gy) of photon radiation. The result of forming these dicentric chromosomes is that cells cannot successfully divide.

Low-dose beta radiation has been shown to shrink ocular tumors. It affects subfoveal CNV by inhibiting angiogenesis, diminishing inflammatory reactions, and inhibiting fibrosis.[6]

Historically, external beam radiation has been studied for the treatment of wet AMD. However, it has found limited success, with some studies noting a ben-

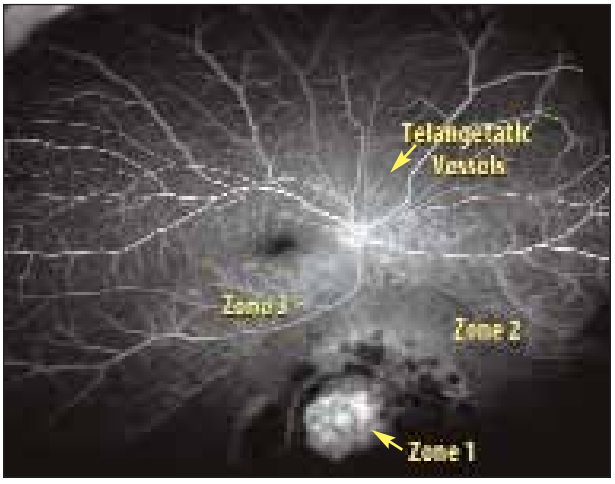

Figure 1. Optos widefield fluorescein angiogram in the early venous phase demonstrating circumferential zones of affect from the radioactive plaque. Zone 1 overlies the plaque and contains destroyed melanoma and neurosensory retina. Zone 2 is the hypofluorescent area immediately adjacent to the plaque containing the ablated choriocapillaris and overlying retina. Zone 3 contains the area of radiation retinopathy, commencing at the inferior arcade and essentially bisecting the patient's macula. Evident is the decreasing amount of retinopathy as you move circumferentially away from the plaque. Subtle telangetatic vessels superior to the optic nerve are marked with an *.

Figure 2. Optos widefield fluorescein angiogram in the late venous phase reiterating the zones of affect from the brachytherapy. The continuum of change is evident, from retinal necrosis overlying the plaque to adjacent areas of ischemia to radiation retinopathy.

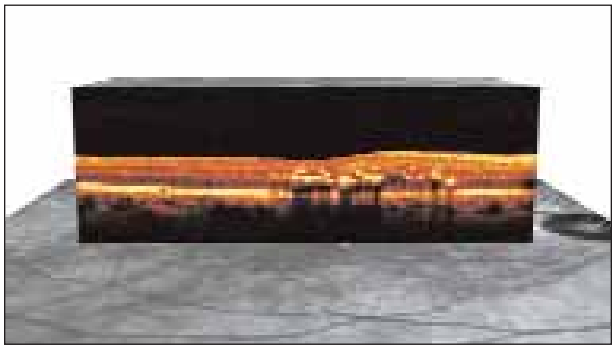

Figure 3. Heidelberg SD-OCT demonstrating retinal edema, inflammation, and exudation in the area of the fovea.

efit while others found none.[7]

Radiation therapy for the treatment of neovascular AMD is currently being investigated using two new approaches: epimacular brachytherapy with strontium-90 (NeoVista, Inc., Fremont, CA), and x-ray therapy with the IRay system (Oraya Therapeutics, Newark, CA).

NeoVista, Inc., has developed a strontium-90 applicator that allows targeted delivery of a single dose of 24 Gy beta ionizing radiation after vitrectomy.[8] This technology has been developed to minimize damage to the retina or surrounding tissue while delivering a therapeutic dose to the CNV lesion. Strontium-90 has a rapid fall-off in radiation, approximately 10% for every 0.1 mm away from the source. The IRay System is designed to deliver a highly localized dose of low-energy x-Ray radiation noninvasively to the macula using a robotic positioning system, a targeting algorithm, and a device for eye stabilization.[9]

UNDERSTANDING BETA RADIATION

Animal studies demonstrate that low-dose radiation targeted to specific sites results in no adverse effects on adjacent tissues.[10] Beneficial effects of radiation for CNV have been reported since the 1990s.[11] Low-dose radiation leads to morphologic and DNA changes in vascular endothelium, including apoptosis.[12,13]

Fractionated irradiation in cumulative doses up to 30 Gy has been shown to be safe, posing no threat to the retina or optic nerve.[14] Use of nonfractionated external beam radiation has been reported to result in radiation retinopathy, cataract, edema, and conjunctivitis.[15]

The epimacular brachytherapy with strontium-90 currently being studied for the treatment of wet AMD

TABLE 1.*

Tissue	Effect	Dose for clinically observable damage	Dose delivered by epimacular brachytherapy
Cornea	Edema	30-50 Gy	.00039 GY
Conjunctiva	Conjunctivitis	55-75 Gy	.00040 Gy
Lens	Cataract	2 Gy	.00056 Gy
Retina	Radiation retinopathy	35-55 Gy	24 Gy
Optic nerve	Optic neuropathy	> 55 Gy	2.4 Gy

Adapted from Finger et al. Am J Ophthalmol. 1999;127:170-177.

is delivered in one dose of 24 Gy over a 2- to 4-minute time frame.[16] The scientific rationale for dosing and timing has been previously described in the oncology setting.[17] This targeted dose of 24 Gy directed at the active component of a subfoveal lesion is the equivalent of 2.4 Gy effective dosing in the optic nerve and 0.00056 Gy in the lens.

This type of epimacular radiation therapy is being examined in a number of clinical trials, one of which is CABERNET. CABERNET is a randomized, controlled, multicenter, phase 3 study comparing the results of beta radiation given in conjunction with two doses of the anti-VEGF drug ranibizumab (Lucentis, Genentech) as compared to multiple injections of ranibizumab alone. The purpose is to investigate the safety and efficacy of a single session of epimacular brachytherapy (combined with ranibizumab loading doses) compared with ranibizumab monotherapy.

Unlike external beam radiation, the epimacular brachytherapy system ensures delivery of a therapeutic dose of beta radiation to the wet AMD lesion and avoids any deleterious radiation exposure to other ocular structures such as the optic nerve and the lens. CABERNET involves 450 patients at 40 sites worldwide and has recently finished enrollment.

More importantly, this technology is also being explored to evaluate its safety and efficacy in patients that require persistent, frequent therapy with anti-VEGF agents in a pilot trial called MERITAGE. Recent preliminary results[18] suggest that epimacular brachytherapy may decrease the burden of treating neovascular AMD significantly.

X-RAY THERAPY

X-rays and gamma rays are high-energy photons and are emitted by events outside the nucleus. The wavelengths of gamma rays and x-rays overlap[19] and can penetrate multiple layers of tissues. The Oraya device delivers collimated x-ray beams to deliver 24 Gy to the macula. Early investigations have analyzed the result on nontarget tissue such as the lens and optic nerve.[19] Three doses of 8 Gy each were delivered via three different converging beams. Oraya has begun studying the efficacy of this system outside the United States.

RADIATION RETINOPATHY

External beam radiation has been in use for more than a decade as a wet AMD treatment.[20] The typical energy delivered in this type of radiation is between 80 and 200 MeV (million electron volts). The incidence of complications from radiation therapy is well documented and directly related to the location of the treatment and the distance from the treatment location.

The most clinically significant of these complications is radiation retinopathy. With proton beam therapy, radiation levels remain uniform until the energy is

reduced. Radiation retinopathy is thought to occur after proton beam therapy is used because a larger area of the retina is irradiated during the procedure; it has been reported when the delivered dose is as little as 14 Gy.[21]

CLINICAL CASE WITH RADIATION

We present a clinical case that serves as a useful illustration of the range of effects of radiation in the eye. As clinicians gain greater familiarity with how radiation affects various tissues in the eye, they should gain greater comfort with and be better equipped to potentially employ this approach to treatment.

One of the authors (MDB) recently managed a melanoma patient who was treated with brachytherapy. Fluorescein angiography of the eye was performed, confirming that radiation from the plaque destroyed the tumor. In this case, the retina and choroid overlying the plaque were treated aggressively with 184 Gy at the apex in order to ensure complete tumor destruction. Figure 1 shows a zone present directly overlying the plaque, in which the retina and overlying neurosensory retina were completely destroyed because the dose of radiation was targeted for tumor destruction. Adjacent to this zone was a zone of collateral damage that decreased radially away from the radiation epicenter; radiation retinopathy commenced at the patient's inferior arcade and extended up to and essentially bisected the patient's macula. The end result of therapy was a continuum of clinical changes, from retinal necrosis to ischemia to radiation retinopathy. Above this area, the superior half of patient's macula demonstrated only a small degree of radiation-induced vascular change. The area of retina superior to this remained normal.

This case illustrates how radiation-induced damage decreases with increasing distance from the source of radiation. A number of factors influence the development of radiation retinopathy, such as total radiation dosage, fraction size, concomitant chemotherapy, and preexisting vascular disorders. New approaches to radiation therapy for wet AMD that seek to minimize the side effects encountered from the delivery of a radiation dose in the eye appear promising at this stage.

Table 1 illustrates the relation between dose of radiation and the threshold to cause clinically observable damage to ocular structures. ■

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