Thoughts Concerning Anti-VEGF Treatment for Radiation Retinopathy and Radiation Optic Neuropathy

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During the 2012 American Academy of Ophthalmology’s (AAO) Retina Subspecialty Day, there was a panel, “Tumor Management: Radiation, Retinopathy and Masquerade,” moderated by Evangelos Cragoudas, MD. I was a panelist along with Jerry Shields, MD; David Abramson, MD; Brenda Gallie, MD; and Arun Singh, MD. A case of radiation optic neuropathy (RON) with radiation maculopathy (RM) was shown, and I was asked my opinion concerning management. As is my practice, I responded that I typically wait for the first signs of a patient’s radiation vasculopathy (eg, edema, exudate, cotton wool spots, hemorrhage) to discuss the use of anti-VEGF intervention. As part of informed consent, I tell them that few patients escape an episode of untreated RON or RM with useful vision. Although we all have seen selected cases of spontaneous resolution of radiation vasculopathy and “burnout” over time, the final vision outcomes are typically poor.1-3

In 1997, I first published cases in which intravitreal anti-VEGF injections were found to successfully decrease vascular transudation associated with RM and RON.4,5 Since that time we have published several clinical case series showing similar findings with vision preservation.6-9 Now there are many worldwide reports that radiation-induced macular retinal vessel transudation can be controlled with periodic intravitreal anti-VEGF medication.10-13

Unfortunately, at the AAO I also learned that in some countries only 2 to 3 monthly anti-VEGF injections are approved for each patient. Even in the United States some patients suffer from living “just too far” away for compliance. This is analogous to giving just 1 or 2 shots of insulin for treatment of a lifetime of diabetes. Such approaches are inadequate and doomed to failure. It is my opinion that most intraocular radiation vasculopathy will be successfully suppressed only with consistent periodic intravitreal anti-VEGF therapy.

WHEN SHOULD WE STOP THERAPY?

Unfortunately, we have witnessed a few cases in which patients significantly delayed their follow-up anti-VEGF treatment and developed off-treatment recurrent optic disc and/or macular edema. Though these cases typically respond a second time after restarting intravitreal anti-VEGF therapy, measurable damage occurred in the interim. These cases cement my conviction concerning the efficacy and need for continuous anti-VEGF treatment for radiation vasculopathy.

As a result of long-term experience, I typically counsel patients that periodic intravitreal anti-VEGF treatment for intraocular radiation vasculopathy is analogous to insulin treatment for diabetes. It merely suppresses a progressive disease. The more consistent we are with treatment, the more likely vision will be preserved.

WHAT ANTI-VEGF DOSE IS BEST?

Anti-VEGF strength also appears to make a difference. Analyses of our pilot data was presented at the 2012 American Society of Retinal Specialists and Retina Society meetings. In the Genentech and investigator-sponsored
study, 2.0 mg ranibizumab was used to treat cases that were not suppressed by standard dose therapy. This series included both post-plaque and post-external beam radiation therapy (EBRT) patients. We found that in patients who were not responding to standard-dose anti-VEGF therapy, their radiation maculopathy responded to 2.0 mg ranibizumab. Because more anti-VEGF worked better, there must be more VEGF in these irradiated eyes.

**WHY MIGHT THERE BE MORE VEGF IN THESE EYES?**

First, choroidal melanomas have been noted to produce VEGF. Second, radiation is known to induce a progressive obliterative vasculopathy with secondary VEGF-producing ischemia. Therefore, it is reasonable to assume that, compared with exudative macular degeneration, eyes irradiated for cancer contain higher levels of VEGF. This includes both those with intraocular tumors and eyes treated with EBRT for metastatic, orbital and sinus tumors.

**WHAT DOES ALL THIS TEACH US?**

Published studies that show radiation dose to the macula can be used to predict the incidence of radiation maculopathy. Therefore, it is reasonable to assume there is a need to decrease the radiation dose used to treat tumors in the eye. Decreased radiation dose (and dose rates) will lead to less, or more treatable, intraocular radiation vasculopathy.

**HOW CAN WE DECREASE THE RADIATION DOSE?**

Several of my ophthalmic oncology colleagues do not share my experiences and views about anti-VEGF therapy. Therefore, I have tried to look for an objective reason why their results might differ. Basic radiation therapy teachings tell us that the higher the dose and the faster the dose rate the greater the complication rates. So let us compare commonly used radiation treatments and make some simple recommendations.

**RUTHENIUM-106 PLAQUE THERAPY**

In Europe, the most commonly used plaques contain ruthenium-106 (Ru-106). Ru-106 plaques emit beta radiation, particles that typically travel 5 to 6 mm into the eye and have a very high base-to-apex dose gradient. For example, in treatment of a 5-mm high tumor, the base (sclera, choroid, and retina) dose can be 3 to 4 times that seen using an equivalent apex dose of iodine-125 (I-125). In addition, when a Ru-106 plaque is placed near the macula, that macular retina will receive much more and faster irradiation compared with either I-125 or palladium-103 (Pd-103) seeded plaques. Because dose and dose-rate matter, the higher Ru-106 radiation dose will produce a more severe retinopathy or optic neuropathy that is less likely to respond to anti-VEGF medications.

**EXTERNAL BEAM RADIATION THERAPY**

Proton beam therapy doses are typically numerically similar to prescription doses used in the choroidal melanoma apex during I-125 and Pd-103 plaque therapy. However, these 2 treatments are actually like radiation apples and oranges. Consider that plaque brachytherapy is delivered slowly (typically over 5 to 7 days), whereas protons are given in several daily or alternate-day sessions of less than 15 minutes each. These high-dose-rate sessions are not radiobiologically equivalent to slow-dose brachytherapy. It is generally accepted that the faster you give a radiation dose the more the long-term side effects. Treatment plans should reflect a balance between a dose fast enough to kill the tumor but slow enough to preserve normal tissues.

This also applies to standard photon-based EBRT for choroidal metastasis, orbital and sinus tumors. At The New York Eye Cancer Center we currently recommend EBRT dose rates of 180-200 cGy per day as well as treating to the lower range of acceptable total treatment doses. In this way, we are preparing the patient to avoid or delay intraocular radiation vasculopathy or make it less severe and more treatable.

An analogy can be taken from the heat radiation (flame) of a candle. If you take the heat energy all at once (high-dose rate) by putting your finger on the flame and leaving it there, you will burn the skin on your finger. But if you absorb the same amount of heat energy over time (by moving your finger back and forth through the flame for a longer time) it will just become warmed. The former burn is more difficult to treat. Similarly, high-dose-rate radiation is less likely to respond to periodic intravitreal anti-VEGF therapy.

**I-125 AND PD-103 PLAQUE THERAPY**

In the United States, most eye cancer specialists use low-energy I-125 or Pd-103 plaque therapy. However, I have found that low-energy plaque therapy is delivered in several ways. Though the first series and the Collaborative Ocular Melanoma Study suggested a 5 to 7 day continuous treatment, some centers are decreasing the course of treatment to 3 days (a higher dose rate). As mentioned, this shorter treatment interval should increase late normal tissue side effects.

Another problem is a legacy of Collaborative Ocular Melanoma Study (COMS) dose planning. Here, the COMS required a minimum dose of 85 Gy to 5 intraocular
millimeters. That is, for a 2.5 mm high tumor one was required to treat to a minimum 5 mm height. Thus, the COMS dose plan increased the dose and dose rate to those smaller tumors while increasing the dose (and dose rate) to normal ocular structures (e.g., the fovea and optic nerve). It is no wonder that the COMS reported the worst visual acuity results of any plaque study. It is reasonable to assume that any center using that legacy COMS dosing strategy will increase both the incidence and severity of RM and optic neuropathy as well as hindering patient response to anti-VEGF therapy. In 2003, the American Brachytherapy Society eliminated the minimum 5 mm COMS requirement.19

OUR CURRENT STRATEGIES

At The New York Eye Cancer Center we perform pre-surgical mathematical modeling to compare the intraocular dose distribution of either I-125 or Pd-103 plaque therapy for each patient. For an equivalent tumor dose; we choose the source that will relatively spare the macula, optic nerve, or, if suprathreshold, the lowest organ dose. In comparison to I-125, most patients are better off with the Pd-103 radionuclide.18,20 We do not use Ru-106 plaques for several reasons beyond the scope of this article. Similarly, for our standard EBRT patients, we discuss our concerns with their treating radiation oncologist. We urge a limit of 180 to 200 cGy daily dose rates and the lowest acceptable total doses. We explain that the eye is relatively sensitive to irradiation.

In treatment of selected posterior choroidal melanomas that are at high risk for RM or RON, I first offer laser demarcation to suppress the ischemic drive likely contributing to elevated intraocular VEGF.21 Laser delivered in 1 or 2 sessions may avoid the need for periodic intravitreal injections. However, in cases where laser does not work, is not possible, or when the tumor is beneath the fovea, anti-VEGF therapy offers the patient the best chance for vision preservation.

We continue to treat patients with anti-VEGF agents for RM and RON related to treatment of ocular lymphoma, uveal metastasis, and cancers of the lacrimal gland, sinus, and ocular adnexa. Regardless of the source, our current strategy is initial monthly dosing of bevacizumab (1.25 mg/0.05 mL) or ranibizumab (0.5 mg) to determine the degree of the clinical response. Encouraged by early and then persistent suppression of macular edema, hemorrhages, and exudates, we titrate the number of injections (to 6–8, and rarely 12-week intervals) needed to stabilize patients over time. Since 1995, there has been only 1 case in which we have been able to completely discontinue maintenance dosing. In recalcitrant cases, the level of VEGF may be too high for standard intravitreal anti-VEGF agents to overcome. These patients may benefit from a higher dose. Bevacizumab is currently available in higher 2.0 and 2.5 mg doses. However, the increased drug volume has increased transient post-injection vision loss and secondary increased intraocular pressures. We recognize that radiation retinopathy is a progressive disease and that dose escalation strategies may offer our patients additional time to forestall vision loss. To date, intravitreal anti-VEGF therapy has allowed us to preserve useful vision in most of our patients over the past 6 years.