MEETING NOTES FROM THE 45TH ANNUAL ARDS MEETING

In our continued coverage of the 45th annual meeting of the Aspen Retinal Detachment Society (ARDS), Retina Today *is pleased to offer an overview of the presentations delivered by Ivana Kim, MD, and Charles C. Wykoff, MD, PhD.*

In Surgical Interventions for Choroidal Melanoma*, Daniel Learned, MD, provides an informative summary of Dr. Kim's lecture on the growing need for vitrectomy in patients with choroidal melanoma. During her presentation, Dr. Kim addressed the increasing need for intraocular surgery in this patient population and noted that patients with vitreous hemorrhage following treatment of melanoma can experience significant improvement of vision as a result of surgery.*

Similarly, in the ENDURANCE Extension Study Following VISTA*, Thanos Papakostas, MD, covers Dr. Wykoff's discussion on the efficacy and safety of PRN aflibercept in patients with clinically relevant diabetic macular edema (DME). During his lecture, Dr. Wykoff noted that the results of the phase 4 ENDURANCE extension study maintained the outcomes achieved during the phase 3 VISTA DME trial by continuing close observation and using targeted treatment.*

—Timothy G. Murray, MD, MBA

Surgical Interventions for Choroidal Melanoma

The role of vitreoretinal surgery in tumor management.
By Daniel Learned, MD

"Vitreoretinal surgical techniques are playing a growing role in management of patients with choroidal melanoma."—Ivana Kim, MD

Ivana Kim, MD, gave an informative presentation on the growing indications for vitrectomy in patients with choroidal melanoma. Dr. Kim stated that there are two main reasons for surgical intervention in these patients: (1) for molecular prognostication purposes, and (2) to improve vision following complications of radiation, including exudative detachment or vitreous hemorrhage. Other more controversial indications include primary management of the tumor, including endoresection or silicone oil tamponade.

PROGNOSTIC SURGICAL INTERVENTIONS

Biopsy of choroidal melanoma allows DNA or RNA analysis of the tumor, which provides prognostic information. At present, knowing the molecular profile of a tumor does not change the treatment plan, but it does provide the patient with information on the risk of metastasis. It can guide surveillance protocols for patients and determine whether the patient qualifies for clinical trials investigating adjuvant therapy to decrease the risk of metastasis. Dr. Kim described the two main approaches for fine needle aspiration biopsy: transscleral and transvitreal.

A transsceral approach can aid in biopsy of anterior tumors, but transvitreal is probably the more common approach. The transvitreal approach can be performed using indirect ophthalmoscopy and a 20-D lens, but, according to Dr. Kim, most surgeons use a microscope-based technique. There are variations on the microscope-based approach. Some surgeons do a complete three-port vitrectomy with adjuvant laser, while most "are minimalistic," she said, creating only two ports—one for the light, one for the needle—and doing no vitrectomy. Each is an accepted method to obtain a fine needle biopsy.

PRIMARY MANAGEMENT OF TUMOR

Endoresection is a surgical technique that has waxed and waned in recent decades, Dr. Kim said. Reported complications include retinal detachment, tumor recurrence, and death.

Controversy remains as to whether resection should be done without adjuvant radiation therapy. Dr. Kim explained that the risk of death is not specifically related to metastasis, but, rather, to the possibility of an air embolism during surgery.[1] The air emoblism has been speculated to occur when air enters the large, exposed choroidal vasculature during resection.

Dr. Kim reviewed recent publications on endosection and brachytherapy from different groups.[2,3] Ultimately, neither showed improvement in vision with resection compared with brachytherapy. There was more recurrence, however, and a higher rate of retinal detachment with endoresection than has been reported with radiotherapy. In Dr. Kim's opinion, with no proven benefit to vision and higher rates of local recurrence, "which, traditionally, has been a risk factor for metastatic disease," radiotherapy is preferable to endoresection when available. When not available, however, endoresection may be a reasonable option.

Dr. Kim also reviewed the use of silicone oil tamponade in the setting of plaque radiotherapy. The idea behind this is that oil attenuates radiation, so it may limit the scatter of radiation to other parts to the eye. Tara McCannel, MD, PhD, found that patients with large tumors treated with a 23 mm plaque trended toward improved visual outcomes at 28 months.[4] Dr. McCannel also noted less macular edema and fewer

WATCH IT NOW

Surgery in Patients With Choroidal Melanoma

By Ivana Kim, MD, and Timothy G. Murray, MD, MBA

Ivana Kim, MD, reviews her lecture on the surgical management of patients with choroidal melanoma. Dr. Kim discusses both primary management of patients and postradiation management of complications that threaten vision, such as vitreous hemorrhage and persistent exudative retinal detachment.

WATCH IT NOW

Long-term Anti-VEGF Therapy for DME

By Charles C. Wykoff, MD, PhD, and Timothy G. Murray, MD, MBA

Charles Wykoff, MD, PhD, discusses his presentation on long-term anti-VEGF therapy for DME. Based on data from VISTA study participants whose treatment extended into the fourth year after randomization, Dr. Wykoff reviews injection frequency, the effect of focal laser, and the relationship between reductions in treatment frequency and worsening of retinopathy severity.

abnormal macular findings. In smaller tumors, however, there was no statistically significant improvement in vision when oil was used.

SURGERY FOR POSTRADIOTHERAPY CONDITIONS

Two postradiotherapy conditions that can cause decreased vision and require subsequent surgery are vitreous hemorrhage and exudative detachment.

In a retrospective review of 836 patients who received proton beam radiotherapy at Massachusetts Eye and Ear Infirmary between 2008 and 2014, less than 2% of patients underwent secondary surgery. The average time from treatment with radiation to second surgery was 3 years (unpublished data).

Dr. Kim said patients in the study with vitreous hemorrhage had more significant improvement of vision overall; however, she emphasized that these hemorrhages "are not your standard 'let's clear the blood and we are done'" hemorrhages. These eyes are at higher risk for rhegmatogenous detachment, rebleeding, or development of other complications of radiation retinopathy. As such, they should be followed closely. The surgical approach in the study included vitrectomy with laser over the tumor and areas of ischemic retina. Dr. Kim stated that she would have a low threshold to consider injection of bevacizumab (Avastin, Genentech) at the end of the surgery.

Of eight patients in the study with exudative detachments, two had improved vision, six had attached retinas at last follow-up, and one required enucleation. The vision outcomes for those who received earlier intervention were better, Dr. Kim said. Because of this, she said, her approach is now more aggressive in patients who present with baseline retinal detachment associated with melanoma.

"We consider pharmacologic therapy very soon or immediately after radiation. If there is worsening after radiation or no resolution after 3 to 6 months and there's evidence of tumor regression, we would consider early vitrectomy at that time," she said. Some series suggest that triamcinolone injection at the

time of plaque removal[5] or bevacizumab injection in patients with baseline retinal detachments[6] may be beneficial in improving or reducing postradiation complications.

SUMMARY

Comfort with intraocular surgery in patients with choroidal melanoma is increasing. Surgical indications include molecular prognostication, treatment, and visual rehabilitation following radiation or tumor-related complications. Patients with vitreous hemorrhage after previous treatment of melanoma can have significant improvement in vision as a result of surgery. Exudative detachments related to choroidal melanoma carry a poor visual prognosis and should be treated first medically and then surgically if no improvement is achieved.

1. Rice JC, Liebenberg L, Scholtz RP, Torr G. Fatal air embolism during endoresection of choroidal melanoma. *Retin Cases Brief Rep.* 2014;8(2):127-129.
2. Konstantinidis L, Groenewald C, Coupland SE, Damato B. Long-term outcome of primary endoresection of choroidal melanoma. *Br J Ophthalmol.* 2014;98:82-85.
3. Caminal JM, Mejia K, Masuet-Aumatell C, et al. Endoresection versus iodine-125 plaque brachytherapy for the treatment of choroidal melanoma.. *Am J Ophthalmol.* 2013;156(2):334-342.
4. McCannel T A, McCannel C A. Iodine 125 brachytherapy with vitrectomy and silicone oil in the treatment of uveal melanoma: 1-to-1 matched case-control series. *Int J Radiat Oncol Biol Phys.* 2014;89(2):347-352.
5. Parrozzani R, Pilotto E, Dario A et al. Intravitreal triamcinolone vs intravitreal bevacizumab in the treatment of exudative retinal detachment secondary to posterior uveal melanoma. *Am J Ophthalmol.* 2013;155:127-133.
6. Mantel I, Schalenbourg A, Bergin C, et al. Prophylactic use of bevacizumab to avoid anterior segment neovascularization following proton therapy for uveal melanoma. *Am J Ophthalmol*. 2014;158(4):693-701.

ENDURANCE Extension Study Followed VISTA Patients in Year 4 of Treatment

Charles Wykoff, MD, PhD, reviewed the phase 4 ENDURANCE study results.

By Thanos Papakostas, MD

Charles C. Wykoff, MD, PhD, is director of research at Retina Consultants of Houston and serves as the elected deputy chair of ophthalmology for the Blanton Eye Institute, Houston Methodist Hospital. He is a leader in clinical trials and is a co-author on more than 80 publications in peer-reviewed journals. His research interests encompass angiogenesis and retinal vascular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), and venous occlusive diseases.

Dr. Wykoff discussed the results of the phase 4, multicenter, open-label ENDURANCE study, an extension study following patients who were treated in VISTA. Specifically, this study assessed whether the efficacy and safety achieved with 2 mg intravitreal aflibercept (Eylea, Regeneron) injection for DME during the phase 3 VISTA DME trial was maintained with individualized, as-needed treatment in the extension study.

TREATMENT BURDEN

Dr. Wykoff presented an example of a patient who received multiple injections over 2 to 3 years, with a resulting improvement in visual acuity from 20/80 to 20/32. He made the point that, despite this good visual outcome, frequent visits and injections impose a burden on both the patient and the health care system.

He also summarized the numbers of injections given in landmark DME trials such as the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T, Protocol I, and the open label extension study following RISE and RIDE. He noted that the retreatment algorithms in the second halves of these trials resulted in differences in the long-term need for injections.

DESIGN OF THE STUDY

ENDURANCE was a postmarket study designed to assess the need for aflibercept treatment in the VISTA study population, essentially in the fourth year of treatment. All patients from VISTA at four clinical trial sites were offered the opportunity to enroll in ENDURANCE, and 67% of eligible patients chose to do so.

During ENDURANCE, patients were treated as needed (PRN) with 2 mg aflibercept in the presence of clinically relevant DME. Visit intervals were prescribed according to protocol, and, if specific criteria were met, macular laser was applied in an attempt to decrease treatment burden. The primary endpoint was the number of aflibercept injections administered. Secondary endpoints included visual acuity and retinal thickness as measured by optical coherence tomography (OCT).

Clinically relevant DME was defined as DME limiting visual function per the treating investigator. During ENDURANCE, patients were initially seen every month, and, if no aflibercept was given over three visits, the interval was increased to 8 weeks. If no aflibercept was given at three more visits, the interval was further increased to 12 weeks.

ENDURANCE patients were about 3 years older than they had been at enrollment in VISTA, and they had gained a mean 10 letters of visual acuity and lost approximately 190 µm of central retinal thickness since baseline, consistent with results observed during the VISTA phase 3 trial. During ENDURANCE, 10% of patients discontinued the trial during the first year and 4% of scheduled visits were missed.

OUTCOMES

Visual acuity outcomes achieved during VISTA were maintained during the 1 year of the ENDURANCE study. Mean visual acuity fluctuated by less than 1.5 letters at any time point measured. Outcomes during ENDURANCE were not dependent on the arms into which patients were originally randomized in VISTA, and they were not dependent on the need for retreatment during ENDURANCE.

During ENDURANCE, most patients demonstrated stable visual acuity, fluctuating by less than 5 letters at any given time point. About 15% of patients showed substantial gain in visual acuity and 15% showed substantial loss at some point. Most of these substantive changes were due to cataract extraction or progression. The anatomic gains achieved were also stable and maintained

during ENDURANCE, fluctuating by less than approximately 30 µm at any time point measured.

How many aflibercept injections did it take to maintain the gains achieved during VISTA? In ENDURANCE, 30% of patients did not receive any additional aflibercept and 70% received at least one injection. Mean injection frequency was 4.5 over the course of the fourth year after randomization into VISTA.

At the end of 1 year in ENDURANCE, 52% of patients had a visit interval of 8 to 12 weeks, and about half of patients were undergoing monthly visits. During ENDURANCE, 62% of patients met eligibility criteria for macular laser after a mean of 19.5 weeks, and, of those, 68% received a mean of 1.7 macular laser sessions. The annualized aflibercept injection frequency was 8.2 before macular laser and 7.8 after macular laser, a mean difference of injection frequency of 0.4—probably not clinically relevant and certainly not statistically relevant in this small sample. Approximately 12% of patients demonstrated progression of diabetic retinopathy, and 7% demonstrated new vitreous hemorrhages.

LIMITATIONS

The most important limitation of the ENDURANCE study was its small sample size, with only 60 patients. The study had a very structured follow-up. There was no opportunity for further extension of treatment interval, there was no opportunity to switch anti-VEGF agents, and there was no opportunity for adding or switching to a steroid.

SUMMARY

Dr. Wykoff noted that the visual and anatomic gains achieved during phase 3 DME trials of both aflibercept and ranibizumab (Lucentis, Genentech) have been maintained in extension studies, with individualized dosing in both circumstances. Approximately 25% to 30% of patients may not require any additional dosing in that fourth year, specifically for DME. Perhaps most important, about a third of patients will experience obvious worsening of DR severity when injection frequency is decreased substantially. ■

Daniel Learned, MD

- vitreoretinal fellow, Massachusetts Eye and Ear, Boston, Mass.
- financial disclosure: none acknowledged
- daniel_learned@meei.harvard.edu

Thanos Papakostas, MD

- assistant professor of ophthalmology, Weill Cornell Medical College, New York, N.Y.
- financial disclosure: none acknowledged
- thanosp@me.com