ARDS

ASPEN RETINAL DETACHMENT SOCIETY MEETING COVERAGE: OCULAR ONCOLOGY AND RETINAL GENE THERAPY

Few people would have guessed that the 2020 meeting of the Aspen Retinal Detachment Society (ARDS) would be the final in-person retina meeting of the year. The COVID-19 pandemic was a nascent and misunderstood threat when our first speakers took the stage at the end of February. Indeed, by the time the meeting wrapped up on March 4, the US Centers for Disease Control and Prevention was reporting an average of 12 new cases per day; a month later, it was reporting an average of 26,025 per day.[1]

Those who attended this year's meeting were fortunate enough to hear from an array of speakers who shared their expertise and experience on a range of topics. Every year, the ARDS collaborates with Retina Today *to highlight some of the meeting's top talks.*

This year, we begin with a summary of the Taylor Smith and Victor Curtin lecture, which was awarded to Carol. L. Shields, MD. Dr. Shields is a foundational mind behind our understanding of ocular oncology, and the ARDS selection committee is proud to have her join the ranks of other Curtin-Smith lecture recipients.

In another presentation, Christina Y. Weng, MD, MBA, addressed the topic vaulting retina toward the future: gene therapy. For patients with inherited retinal diseases—many of which are currently untreatable—the promise of gene therapy could be the difference between sight and blindness. Retina holds the distinction of being the first field of medicine to have a gene therapy approved by the US FDA. But we are far from finished with advancing this technology. Retina's hunger for further improvement should be a source of pride for us all.

—Timothy G. Murray, MD, MBA

1. US Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Cases, data, and surveillance. Accessed August 23, 2020. Available at: www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html.

INTRAOCULAR TUMORS: A LOOK INTO THE FUTURE

The Taylor Smith and Victor Curtin Lecture was given by Carol L. Shields, MD, at this year's meeting.

Presentation by Carol Shields, MD
Summarized by
Jonathan F. Russell, MD, PhD

In this year's Victor Curtin and Taylor Smith Lecture, titled "Intraocular Tumors: A Look Into the Future," Carol L. Shields, MD, reviewed recent work she and her colleagues completed and ventured some ideas about where ocular oncology is headed. This article summarizes portions of her presentation.

UVEAL MELANOMA

A recent paper by Shields and colleagues delineated the multimodal imaging findings (OCT, autofluorescence, B-scan) helpful for evaluation of small choroidal melanocytic tumors.1 In a large cohort of choroidal nevi, they identified risk factors for transformation to melanoma. Risk factors included thickness greater than 2 mm on B-scan ultrasonography, subretinal fluid on OCT, symptoms of vision loss (20/50 or worse on Snellen acuity), orange pigment on autofluorescence, hypoechogenicity on B-scan, and diameter greater than 5 mm by fundus photography. Each risk factor has a multimodal imaging correlate. The most important risk factor was thickness greater than 2 mm.[2] Similarly, as the number of risk factors present increases, the risk of transformation from nevus to melanoma within 5 years escalates.

Uveal melanoma is often treated with plaque radiotherapy, which is effective but can cause complications such as radiation retinopathy. Anti-VEGF therapy seems to lessen the visual decline associated with radiation maculopathy, and this was confirmed in a large comparative analysis of patients at 1, 2, 3, and 4 years post-plaque.[3,4,5] In her lecture, Dr. Shields said she typically administers intravitreal bevacizumab (Avastin, Genentech) every 4 months after plaque brachytherapy for uveal melanoma to prevent or minimize radiation maculopathy.[5]

A light-activated nanoparticle therapy (AU-011, Aura Biosciences) is in development for treatment of uveal melanoma. This nanoparticle binds selectively to tumor cells. The nanoparticle is coupled with a photosensitive drug, and application of laser causes immediate necrosis of the tumor. This drug candidate has been tested in a limited number of patients,

with preliminary data suggesting preservation of visual acuity much better than plaque radiotherapy. This nanoparticle can control tumor growth, although slightly less (with current methods) in comparison to plaque brachytherapy. There is associated anterior and posterior segment inflammation, which might imply an immune response that could have an impact for circulating tumor cells. Trials are ongoing.

Regarding the genetics of uveal melanoma, Shields and colleagues found that the risk for metastasis is high if mutations are present on chromosomes 3 and 8, whereas the risk is low if no mutations are found on these chromosomes.[6]

Vichitvejpaisal and colleagues[7] used The Cancer Genome Atlas to classify uveal melanoma based on genetics into four classes, A through D, with classes C and D having higher risk of metastasis at 4 years than A and B. Adjuvant sunitinib (Sutent, Pfizer) can be used to prevent metastasis in patients with class C and D disease; this tyrosine-kinase inhibitor has a moderate effect that appears more pronounced in younger patients.[8]

When uveal melanoma metastasizes, experimental treatments include immune mobilizing monoclonal T-cell receptors against cancer, or ImmTACs (Immunocore). ImmTACs are bispecific molecules that bind to melanoma cells and T-cells to facilitate the T-cell attacking the melanoma. This therapy requires weekly infusions but can be remarkably effective.

A recent paper suggests the involvement of protein kinase C in uveal melanoma metastasis, and treatments targeted at this molecule are in development.[9]

UVEAL METASTASES

In a recent study of more than 1,000 patients with uveal metastasis, nearly two-thirds of patients had a primary cancer site of either breast or lung.[10] Most uveal metastases occur in middle-age or older adults.[11] Children with uveal metastases have worse survival rates than adults. Women with uveal metastases have a better prognosis than men because they have a higher incidence of breast cancer that can be controlled with novel systemic therapies.

Whether the primary cancer is discovered before the uveal metastasis or the uveal metastasis is discovered before the primary cancer, no effect on survival has been noted. Breast cancer is usually discovered before uveal metastasis is noted, whereas uveal metastasis from lung cancer is usually found before the lung cancer itself. When small choroidal metastases are present, photodynamic therapy is effective.[12]

RETINOBLASTOMA

Today, 99% of patients with retinoblastoma (RB) survive, and the globe is salvaged in 95% of patients. Treatment is with chemotherapy, utilizing various modalities including intravenous chemoreduction for bilateral RB, intra-arterial chemotherapy for unilateral RB, intravitreal chemotherapy for active vitreous seeds, and intracameral chemotherapy for active aqueous seeds. Following intravenous chemotherapy, 50% of patients have 20/40 or better VA, and survival is excellent out to 20 years.[13]

Enucleation is performed in about 5% of cases, but it is not curative in all patients. In the United States, at 5 years, despite enucleation, 4% of patients have a metastasis, and death occurs in 2% of patients. In high-income countries such as the United States, the mean age at diagnosis of RB is 14 months, and only 0.3% of patients die from RB metastasis. In contrast, in low-income countries, the mean age at diagnosis is 31 months, extraocular extension is common, and 19% of patients die from RB metastasis.[14]

CONCLUSION

In closing, Dr. Shields said she envisions a future in which ophthalmologists try to prevent the development of uveal melanoma, perhaps through annual examinations and self-exams, use of artificial intelligence strategies, and treatment of borderline lesions rather than waiting for growth. For detection and prevention of RB, she envisions germline testing at birth, preimplantation genetic diagnosis, screening to detect early lesions, and perhaps even the use of gene therapy.

Dr. Shields Summarizes Her Talk

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SUBRETINAL GENE THERAPY

This new technology is filled with promise.


Presentation by
Christina Y. Weng, MD, MBA
Summarized by
Jonathan F. Russell, MD, PhD

At this year's meeting, Christina Y. Weng, MD, MBA, delivered an update on subretinal gene therapy. This article summarizes portions of her presentation.

BASICS OF GENE THERAPY

Gene therapy was first suggested as a potential treatment for human disease in 1972, and the era of ocular gene therapy began with two seminal papers in 1994.[1,2] Twenty-five years later, in 2019, the US FDA reported that it had more than 800 applications for cell and gene therapies, reflecting tremendous growth in the field.

Gene therapy involves introducing genes into host cells to treat human disease. Gene therapy encompasses gene augmentation (for autosomal-recessive loss-of-function inherited retinal diseases such as *RPE65*-associated retinal dystrophy), gene suppression or inactivation (for autosomal-dominant gain-of-function diseases), and use of gene therapy to create a biofactory (for wet age-related macular degeneration [AMD] and other complex disorders).

Current gene therapies use viral vectors to introduce a transgene into host cells. The host cells then produce the protein product of the transgene. Alternative methods that do not require viral vectors are being explored, such as nanoparticles and iontophoresis, but these are in earlier stages of investigation.

SUBRETINAL DELIVERY

Both intravitreal and suprachoroidal approaches to gene delivery are being explored, and there are advantages and disadvantages to each. Subretinal delivery requires vitrectomy, and the gene product is transduced only in the area of the surgically induced bleb.

Intravitreal delivery could potentially induce panretinal gene expression, and it is a safe and familiar procedure. A potential downside, however, is that it may not achieve optimal efficiency of transduction to outer retinal cells. Another potential disadvantage is that the intravitreal approach may result in extraocular biodistribution that could induce an inflammatory response.

The first FDA-approved gene therapy in the United States is voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics). This therapy, approved for treatment of biallelic *RPE65* inherited retinal dystrophy, uses an adeno-associated virus (AAV)-2–based vector that encodes the *RPE65* transgene. In the phase 3 study of the therapy, the primary outcome was not visual acuity but rather change in performance in a multiluminance mobility test at 1 year after gene therapy. This outcome measure was significantly improved in patients who received treatment.[3] Secondary outcomes, which included Goldmann visual fields and full-field stimulus threshold, also improved with treatment.

Other gene therapies in development include NSR-REP1 (Nightstar Therapeutics), an AAV-2–based therapy aimed at treating choroideremia, an X-linked recessive disease. This gene therapy also uses subretinal delivery. In a phase 1/2a trial, the therapy significantly improved BCVA.[4] A phase 3 trial is in progress.

RGX-314 (RegenxBio) is an AAV-8–based vector carrying a gene encoding a monoclonal anti-VEGF antibody. It is placed in the subretinal space in patients with wet AMD. In a phase 1/2a clinical trial, investigators observed a dose-dependent increase in protein expression with RGX-314, and patients who received the highest dose of gene therapy required no rescue therapy for 5 to 6 months after injection. The therapy was well tolerated. A phase 3b trial in patients with wet AMD will begin soon. The company is also exploring suprachoroidal delivery using the same therapy for treatment of wet AMD and diabetic retinopathy.

Dr. Weng Talks Gene Therapy

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SURGICAL PEARLS

Before performing subretinal gene therapy with voretigene, Dr. Weng said, it is essential to confirm the diagnosis with genetic testing. Oral steroids are started 3 days before surgery day and continued for approximately 2 weeks. For those beginning to perform the procedure, an OR practice run may be valuable to ensure that all logistics are in place. This is important because the medication must be compounded and then surgically implanted within a certain time window after compounding.

General anesthesia is preferred in patients receiving voretigene, as most of these patients are children. The surgeon should consider setting up the injection apparatus and priming the syringe at the start of surgery. The apparatus consists of a 41-gauge cannula with a polyamide microtip connected to extension tubing, which is connected to the gene therapy syringe. Two syringes are provided in case there is a problem

with the first. Some surgeons use triamcinolone to ensure that the hyaloid is lifted.

To inject voretigene, the subretinal cannula is gently buried along the superotemporal arcade, taking care to avoid vessels or pathology. Once the retina blanches, injection can begin. Optional techniques include bevelling the 41-gauge cannula tip, creating a pre-bleb with balanced saline solution, or using intraoperative OCT. As the bleb crosses the fovea, the surgeon should consider slowing down the rate of injection. Once the injection is complete, it may be best to stay within the bleb for a few seconds before withdrawing the cannula to avoid reflux. One recent study in a porcine model showed that material can reflux out of subretinal injection blebs.[5]

CONCLUSION

After many years of investigation, gene therapy has entered the realm of reality in retinal therapy. Widespread application is currently limited by the technical expertise required to perform subretinal injections and by the high cost of the medication.[6,7] Some of the pointers in Dr. Weng's presentation may help new users get up to speed on the procedure. ■

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