Treating Uveal Melanoma: Past, Present, and Future

Genomic analysis can help to personalize treatment and lead to better outcomes.

BY AARON S. GOLD, OD; VICTOR M. VILLEGAS, MD; ANDREA WILDNER, CRA; JENNIFER THOMSON, CRA; FIONA J. EHLIES, BSc, CDOS; AND TIMOTHY G. MURRAY, MD, MBA, FACS

Uveal melanoma is the most common primary malignant intraocular tumor in adults, with an estimated incidence in the United States of approximately six cases per 1 million people.1 Before the use of plaque radiotherapy, enucleation was the standard treatment for these tumors. Fortunately, radioactive iodine-125 (125I) brachytherapy has been shown to be an effective treatment alternative for small and medium-sized melanomas.2 This globe-preserving treatment is equally effective as enucleation in local tumor control and in the prevention of metastasis among patients with small and medium-sized choroidal melanomas; however, patients may experience sight-threatening complications of brachytherapy such as radiation retinopathy, radiation papillopathy, cataract, and neovascular glaucoma.2,4,5

Other globe-preserving treatments, such as laser tumor ablation, have been used in the past in an attempt to avoid the vision-threatening side effects of radiation. Unfortunately, tumor recurrence rates after laser ablation range between 15% and 64%.6 Why some lesions appear to be more resistant to laser ablation than others may now be better understood thanks to the recently developed ability to assess the genetic makeup of uveal melanoma. The use of genomic analysis, along with personalized medicine, may soon reshape the treatment of small uveal melanoma.

PERSONALIZED MEDICINE

Personalized medicine, or precision medicine, is a relatively new term used to describe treatments targeted to the needs of individual patients on the basis of genetic, biomarker-based, phenotypic, or psychosocial characteristics that distinguish one patient from others with similar clinical presentations.7 The goal of personalized medicine is to minimize unnecessary side effects by tailoring the treatment to the individual patient.

An example of this outside of ophthalmology is the use of gene therapy to provide stable, therapeutic levels of specific clotting factors in individuals with hemophilia.7,8 This approach has been used previously in ophthalmology as well. Gene therapy, administered via recombinant adeno-associated virus, has been used to treat patients with a specific form of Leber congenital amaurosis.9

Within the realm of ocular oncology, however, the role of genetic analysis for uveal melanoma has been limited to determining the aggressiveness of the tumor following local treatment. Although treatments for uveal melanoma have evolved, this is the first time we can incorporate genomic analysis of these tumors into treatment to minimize visual side effects.

THE PAST: EVOLUTION OF UVEAL MELANOMA TREATMENT

Medium-Sized and Large Tumors

Until 1978, patients diagnosed with uveal malignant melanoma were routinely enucleated; however,
Zimmerman et al suggested that enucleation may accelerate the dissemination of malignant cells into systemic circulation and accelerate death by metastatic disease.\textsuperscript{10} Pre-enucleation irradiation was proposed to minimize the possibility of tumor metastasis at the time of enucleation. This evolved into the development of the multicenter Collaborative Ocular Melanoma Study (COMS), a set of clinical trials in Northern America with the primary objective of comparing enucleation versus radiation in patients with uveal melanoma and evaluating survival outcomes in these patients.\textsuperscript{11} The study consisted of separate trials for large (> 10 mm apical height and > 16 mm diameter) and medium-sized (2.5-10 mm apical height and < 16 mm diameter) melanoma. More than 1000 patients were enrolled in each trial.

The clinical trial of large melanoma compared enucleation alone with enucleation preceded by external beam radiation therapy. With a 5-year survival rate of 57% in the enucleation arm and 62% in the enucleation with preoperative radiation arm, the study concluded that statistically, pre-enucleation external-beam radiation to the orbit for large choroidal melanoma did not improve survival when compared with enucleation alone.\textsuperscript{12} The study of medium-sized melanoma compared enucleation and 125I brachytherapy for treatment of melanoma. With a 5-year survival rate of 81% in the enucleation arm and 82% in the brachytherapy arm, and a 10-year survival rate of 65% in both treatment arms, the study concluded that 125I brachytherapy was equally effective as enucleation alone in the prevention of metastasis.\textsuperscript{13} Based on this finding, brachytherapy has been the preferred treatment modality for medium-sized melanoma for 30 years.

**Small Tumors**

Unlike large and medium-sized melanoma, the treatment modality for small melanoma has been less definitive. Because mortality associated with small melanoma has been reported to be relatively low, serial observation until evidence of tumor growth has been a well-accepted practice in ocular oncology. A study by Gass found no increased mortality caused by the observation of small tumors for evidence of growth prior to treatment.\textsuperscript{13} However, other studies have shown a 6% to 10% risk of metastasis for small melanoma, even with treatment.\textsuperscript{14–16} Additionally, Finger has suggested it is reasonable to assume that waiting for documentation of small malignant melanoma growth may marginally increase a patient’s risk for metastases.\textsuperscript{17} Still, why some tumors metastasize and others do not was not well understood until genetic analysis of melanoma became available.

**THE PRESENT: MOLECULAR GENOMICS**

Genetic testing can now help to determine the aggressiveness of a tumor and the likelihood of its metastasis prior to local treatment.\textsuperscript{18} The distinction of two classes of molecular genetic signatures for uveal melanoma was first reported by Onken et al in 2004, using gene expression profiling of messenger RNA.\textsuperscript{19} Reverse transcriptase was used to revert messenger RNA to DNA, which was then analyzed via polymerase chain reaction to devise a microassay for tumor classification.

The results of gene expression profile (GEP) analysis can be used to classify uveal melanoma as having a low (class 1a or 1b) or high (class 2) risk of metastasis.\textsuperscript{19} GEP has been shown to exceed clinical and histologic prognosticators in its ability to predict uveal melanoma metastasis and mortality.\textsuperscript{20} Although thicker tumors, epithelioid cell pathology, and older patient age are significantly related to class 2 tumors, no definitive clinical marker for differentiating between class 1 and class 2 tumors has been found.\textsuperscript{21}

For traditional globe-conserving treatment of uveal melanoma, genetic material has typically been obtained through transscleral fine-needle aspiration biopsy at the time of plaque brachytherapy.\textsuperscript{22,23} More recently, fine-needle aspiration biopsy via a transvitreal route has been reported.\textsuperscript{24,25}

GEP has been shown to be useful in determining risk of metastasis for patients who have already been diagnosed with uveal melanoma via clinical evaluation and ancillary testing. This type of genomic analysis may also aid in diagnosis of atypical lesions under 2.5 mm that cannot be easily identified as a small melanoma versus a large atypical nevus. Distinguishing between these two entities clinically can be challenging and often results in observation for evidence of tumor growth prior to initiating treatment. GEP gives the ocular oncologist the opportunity to treat uveal melanoma earlier, before tumor cells can metastasize.

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The following case reports are examples of how GEP may assist in tumor management.

**Case Report 1**
A 43-year-old white woman presented to our office for evaluation of a choroidal mass in her right eye (OD). On examination, BCVA was 20/80 OD and 20/15 in the left eye (OS). Fundus examination OD revealed a pigmented choroidal mass with subretinal fluid (Figure 1). Ultrasonography showed mass thickness of 2.3 mm. Spectral-domain optical coherence tomography (SD-OCT) revealed that the exudative retinal detachment extended into the macula. Rather than proceeding directly to brachytherapy, we chose to treat the lesion with laser ablation and transvitreal fine-needle aspiration biopsy for GEP. The genetic results showed that this tumor possessed a GEP class 1a signature. With this information, we elected to monitor the lesion. The tumor has now been stable on clinical examination and ultrasonography for 18 months, and visual acuity has shown improvement to 20/30.

**Case Report 2**
A 61-year-old white woman presented to our office for follow-up examination of an atypical pigmented choroidal lesion that was stable in size on serial review for more than 3 years. Although the lesion has remained only 1.0 mm thick on ultrasonography, SD-OCT shows persistent subretinal fluid (Figure 2). We have treated the lesion with repeated anti-VEGF therapy. The patient also had a worsening cataract with visual acuity of 20/60. We performed combined anterior/posterior surgery in an attempt to improve visual acuity and stabilize vascular activity in the fundus. Two weeks later, the patient underwent phacoemulsification with intraocular lens implantation, pars plana vitrectomy (PPV), membrane peel, and laser ablation over the tumor (sparing the foveola). Additionally, transvitreal fine-needle aspiration biopsy for GEP was performed. Although the patient’s visual acuity improved to 20/50 on her week 1 postoperative visit, GEP later revealed a class 2 signature for the tumor. Because of this, we proceed with brachytherapy to ensure neutralization of the lesion.

**THE FUTURE: GEP AND PERSONALIZED MEDICINE**
For small atypical lesions, we currently perform PPV, transvitreal fine-needle aspiration biopsy for GEP...
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(Figures 3 and 4), and membrane peel with endolaser over the tumor.

For small malignant melanoma, laser ablation alone may be definitive when coupled with low-risk GEP characteristics. GEP results now allow us to further personalize treatment, if necessary, whereby tumors with GEP signatures of class 2 subsequently undergo 125I brachytherapy with a cumulative dose of 85 Gy to the tumor apex, and GEP class 1 tumors are monitored without the need for radiation therapy.

We have performed more than 100 treatments using this protocol for patients with lesions up to 2.5 mm thick with focal exudative detachments. Thus far, 95% of patients have displayed GEP signatures of class 1 (73% class 1a and 22% 1b). Surprisingly, 4% of these small lesions have shown a class 2 GEP signature. Only 1% of the tumors failed to amplify for GEP. Complications such as retinal detachments have occurred in less than 3% of patients.

We believe that retinal detachment risks are related to transvitreal fine-needle aspiration biopsy technique. Furthermore, lesions with higher GEP classification appear to have a higher likelihood of retinal detachment. Injection of intravitreal steroids at the time of endolaser treatment and may also lower the risk of epiretinal membrane formation and subsequent retinal detachment.

The incidence of uveal melanoma recurrence is less than 1% thus far with this treatment protocol. No patients have shown evidence of metastatic disease.

Although these are preliminary results, they suggest that GEP can play an important role in uveal melanoma treatment. This new form of personalized medicine appears to simultaneously neutralize low-risk tumors, quickly identify high-risk tumors, and subsequently limit the number of patients who would likely experience radiation-associated side effects in the future, thus limiting long-term intraocular radiation management.