

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Update in Uveal Melanoma



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### H&O What is uveal melanoma?

**JH** Uveal melanoma can occur in any of the 3 structures that comprise the uveal tract: the iris, the ciliary body, and the choroid. Melanomas of the ciliary body and the choroid are often considered together and referred to as posterior uveal melanomas. These melanomas overlap anatomically, are treated similarly, and have a much poorer prognosis than iris melanomas. They account for approximately 95% of uveal melanomas. In the United States, there are about 2,000 new cases of uveal melanoma each year. Approximately 40% of these patients have a high-risk molecular signature, meaning that they will probably develop metastatic disease if they live long enough. The metastatic disease often remains in a microscopic, latent state for years, and older patients may die of another cause before they develop detectable metastases. Histology varies, with spindle cells representing a good prognosis and epithelioid cells representing a poor prognosis. The presence of these cells forms a continuum, with most patients having a mix of spindle and epithelioid cells; discrete histologic subtypes are not seen.

### H&O How is uveal melanoma diagnosed?

**JH** The diagnosis of uveal melanoma can almost always be made based on a clinical examination and noninvasive modalities, such as ultrasound. Fine needle biopsy is occasionally required for diagnosis in atypical cases, but it is not commonly needed for diagnosis. However, the use of fine needle biopsy prior to the treatment of the primary tumor is now commonplace throughout the world because of the need for accurate prognostication,

which allows us to customize our metastatic surveillance schedule for each patient, depending on whether they are at low or high risk for metastasis. By monitoring those at high risk more frequently, we can detect their metastatic disease earlier, at a time when treatments can be more effective. In the near future, several clinical trials will be opening that will enroll these high-risk patients for the evaluation of adjuvant therapy prior to detection of overt metastatic disease. Fine needle biopsy can be safely performed by an experienced surgeon with a short learning curve. Physicians who are unfamiliar with this procedure should learn it from an experienced surgeon.

### H&O How is uveal melanoma treated?

**JH** The treatment of primary uveal melanoma depends on the size and location of the tumor. Approximately 90% of patients with posterior uveal melanomas will be treated with some type of radiation therapy. In the United States, this treatment almost always involves a form of brachytherapy using I-125, in which a radioactive device called a *plaque* is sewn to the outside of the eye, left in place for several days, and then removed. There are a few centers that use proton beam radiation instead of plaque radiotherapy for this indication. Approximately 10% of patients will require enucleation, which is indicated if the tumor is very large or invading ocular structures.

Outside the United States, there are some differences in treatment preferences. For example, stereotactic radiotherapy and surgical resection of the tumor are performed in some European centers, but these techniques are less popular in the United States.

## H&O What is known about metastasis in uveal melanoma?

**JH** Uveal melanoma has a somewhat different spectrum of metastasis than cutaneous melanoma, for reasons that are not fully understood. For example, uveal melanomas very rarely spread to the regional lymph nodes. Rather, they almost always spread hematogenously, and approximately 90–95% of the time, the metastasis is first detected in the liver. Other sites of metastasis include the lungs and, less frequently, subcutaneous nodules. Only in advanced metastatic disease do we typically see patients develop metastasis in the viscera, bone, lymph nodes, and brain.

## H&O What was the goal of your recent study on HDAC inhibitors and uveal melanoma?

**JH** Metastatic melanoma, from any primary site, is very difficult to treat. Treatment is even more difficult with uveal melanoma as compared with cutaneous melanoma. Although there are several different options for targeted therapy in cutaneous melanoma, no targeted therapies have been shown to be beneficial in a state of overt metastatic disease in uveal melanoma. We try to identify patients with metastasis early, and we tend to treat them with localized hepatic perfusion chemotherapy, such as chemoembolization. However, this approach has had limited success. It appears that when tumors metastasize, they shed microscopic amounts of tumor cells or tumor seeds into the liver and perhaps other locations. These seeds may remain dormant for years, and then, for unknown reasons, they start to grow and progress very rapidly. Without treatment, patients usually succumb to the disease within months.

Our ultimate goal is to prolong survival. Upon diagnosis, we try to identify patients who likely have undetectable micrometastatic disease. We aim to treat these patients in an adjuvant setting, before the metastatic disease becomes overtly manifest and aggressive, to try to maintain or prolong the time that the micrometastatic seeds remain in a dormant state. We were able to meet the first part of that goal several years ago, by developing a 15-gene expression profile that identifies the tumor as either class 1 or class 2, based on a fine needle biopsy of the primary tumor. Only about 5% of patients with a class 1 tumor will develop metastasis within 5 years, compared to approximately 80% for those with a class 2 tumor. We recently published the results of a multicenter, prospective study that validated the accuracy of the 15-gene assay and its superiority over other alternatives. The test has been licensed to a facility certified by the Clinical Laboratory Improvement Act/College of American Pathologists for routine clinical use, and it is being used by approximately 80 centers around the world.

The goal of the current study, published in *Clinical Cancer Research*, was to identify potential classes of existing compounds that might function in an adjuvant setting to maintain dormant micrometastatic tumor cells in their dormant state. We knew that one feature of class 2 tumor cells was that they had become undifferentiated and behaved more like stem cells, so we hypothesized that pharmacologic manipulation of the class 2 cells to make them more differentiated may cause them to remain dormant for a longer period of time. Thus, we used gene expression profiling and bioinformatic analysis to compare class 2 uveal melanoma cells to normal uveal melanocytes in order to identify a set of genes that are associated with differentiation, with the aim of identifying classes of existing compounds that might drive the class 2 uveal melanoma cells into a more differentiated state. Using these bioinformatic approaches, the compounds that were most highly predicted to cause this change were the histone deacetylase (HDAC) inhibitors.

At the same time, we had been looking for several years for a gene mutation that might be closely linked to the class 2 gene expression profile. Using exome capture and deep sequencing, we identified a gene on chromosome 3—*BAP1*—that is mutated almost exclusively in the class 2 uveal melanomas. The evidence currently suggests that this mutation is a rate-limiting step in the development of the class 2, metastatic phenotype. When we depleted *BAP1* from class 1 uveal melanoma cells, they became undifferentiated and more like stem cells, similar to the phenotype of class 2 tumor cells. *BAP1* is an enzyme that removes ubiquitin molecules from histone H2A and in this way influences the expression of a set of genes that may be involved in maintaining melanocyte differentiation. *BAP1* is opposed by a known oncogene, *BMI1*, that has the opposite function of adding ubiquitin molecules to histone H2A. Fortuitously, other scientists discovered that *BMI1* could be blocked by HDAC inhibitors.

So we had 2 different lines of evidence suggesting that HDAC inhibitors might be a reasonable place to start in the selection of agents for adjuvant therapy. These compounds meet many of the criteria that we have been looking for in an adjuvant therapy. They are readily available, have been in clinical use for many years (such as the well-known anti-seizure drug valproic acid), have relatively mild side effect profiles, and most can be taken orally. Plus, there is theoretical reason to believe that agents that induce dormancy, rather than kill tumor cells, may create less selective pressure within the tumor to evolve clones of resistant tumor cells.

In the current study, we progressed through a series of biochemical, cell culture, and preclinical animal experiments. We studied 3 different HDAC inhibitors—valproic acid, panobinostat, and suberoylanilide hydroxamic acid (SAHA)—and observed very similar

results. All 3 compounds caused class 2 uveal melanoma cells to become highly differentiated, to stop growing, and to lose other aggressive features. In the final part of the study, we implanted small tumor seeds in mice and then administered valproic acid, which significantly retarded the growth of these seeds.

### **H&O** What are the clinical implications of your study?

**JH** Researchers at several centers around the United States are preparing to initiate clinical trials with HDAC inhibitors in uveal melanoma in the near future. Initially, the trials will likely be conducted in patients with detectable, but very early, metastatic disease. If efficacy is found, treatment will be examined in a truly adjuvant setting, in which the drug will be initiated at the time of the primary eye tumor diagnosis.

Although HDAC inhibitors appear to be a reasonable place to start, they are likely not the final answer.

As we understand more about the function of the BAP1 protein, we expect to gain even better ideas of how to use targeted compounds to treat class 2 uveal melanomas. My laboratory and many others are now working to understand exactly what BAP1 is doing biologically, and to recognize the pathologic consequences that result when BAP1 is lost. We can then use various approaches to identify new classes of compounds that may be of therapeutic benefit.

### **Suggested Readings**

Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*. 2010;330:1410-1413.

Landreville S, Agapova OA, Matatall KA, et al. Histone deacetylase inhibitors induce growth arrest and differentiation in uveal melanoma. *Clin Cancer Res*. 2012;18:408-416.

Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group Report Number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology*. 2012 Apr 20. [Epub ahead of print]