Enabling Personalized Medicine in the Management of Uveal Melanoma

The value of a repository for tumor biopsy specimens after gene expression profiling.

BY THOMAS M. AABERG JR, MD

Uveal melanoma is the most common ocular cancer and the second most common form of melanoma, with an incidence rate of approximately 4.3 new cases per million individuals per year in the United States.[1] Uveal melanoma is unusual in that it is one of the few cancers that is clinically diagnosed. Given that the majority of uveal melanoma patients qualify for eye-sparing treatment of the primary tumor, this means that there is rarely any tumor tissue that is archived by local pathology. Additionally, although fewer than 4% of patients present with metastatic disease because of micrometastases at the time of diagnosis, nearly 50% of patients will develop metastatic disease, primarily in the liver, for which there is no currently approved treatment.[1-4] Among those patients who have a high risk of metastatic disease based upon gene expression profile (GEP) of the primary tumor at the time of initial diagnosis, more than 80% will be at risk for development of metastases within 5 years and will have an average survival of 9 months from time of progression.[5,6]

There is an urgent need for effective therapies for metastatic uveal melanoma. Thus, a significant number of novel therapies and new combinations of existing drugs are currently being tested in early-stage clinical trials (Table 1). Many of these studies require patients to have a high risk of tumor metastasis based on selected diagnostic tests, a trend expected to expand in the future. In addition, many current, and likely future, clinical trials include additional biomarker analyses at baseline and after treatment to facilitate accurate evaluation of targeted therapy approaches.

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It has been well established over the past 20 years that a number of key chromosomal alterations are associated with the more aggressive forms of uveal melanoma. For example, loss of chromosome 3 carries a higher risk of primary tumor metastasis.[7] Unfortunately, intratumoral heterogeneity for monosomy 3 often occurs.[8-10] Given that monosomy 3 in as little as 6% of tumor cells reflects increased risk of distant disease,[11] the impact of heterogeneity makes accurate prognosis of metastasis difficult. Additionally, chromosomal detection methods, such as in situ fluorescent hybridization for monosomy 3, have significant tumor tissue requirements, and this has resulted in as much as a 50% technical failure rate in fine-needle biopsy specimens.[12-14] In addition to chromosome 3 changes, other cytogenetic changes, such as alterations of chromosomes 6p and 8q, are associated with an increased risk of metastasis.[15] Other findings, such as the mutually exclusive mutations in GNAQ (47%) or GNA11 (44%) in large uveal melanoma tumors have also been reported.[6] These mutations are associated with chronic activation of the mitogen-activated protein kinase

TABLE 1. SELECTED CLINICAL TRIALS CURRENTLY ENROLLING HIGH-RISK UM PATIENTS.[22]

Treatment	Mechanism of Action	Comparator	Phase	Study Design	Clinical Trial Registry Number
AEB071	Protein kinase C inhibitor	None	1	Dose escalation to MTD. 28-day cycles. Safety and efficacy at MTD.	NCT01430416
Bevacizumab/ Temozolomide	Anti-angiogenic monoclonal Ab/ cytotoxin	None	2	Bevacizumab on days 8 and 22. Temozolomide on days 1-7. 28 day cycles up to 6X. Bevacizumab maintenance for patients with SD. RR. SD. PFS. Duration of response. Safety.	NCT01217398
Carbozantinib	Multi-tyrosine kinase inhibitor	Temozolomide or Dacarbazine	2	Randomized. Carbozantinib QD on days 1-28. Temozolomide on days 1-5. Dacarbazine on day 1. 28 day cycles. PFS. Survival. RR. Safety.	NCT01835145
Everolimus/ Pasireotide	mTOR inhibitor/ somatostatin analogue	None	2	Everolimus QD. Pasireotide on day 1. 28-day cycles. CR. PR. SD. Safety.	NCT01252251
Ipilimumab	Cytotoxic T-lymphocyte antigen-4 (CTLA-4)-blocking antibody	None	1 / 2	Ipilimumab on day 1 up to 4X. 21-day cycles. Possible maintenance dosing every 12 weeks. MTD. PFS. Survival. Metastasis free survival.	NCT01585194
Ipilimumab	Cytotoxic T-lymphocyte antigen-4 (CTLA-4)-blocking antibody	None	0	Ipilimumab on day 29, repeated every 3 weeks for up to 4X. Radiation on day 1. Safety. RR. PFS. Survival.	NCT01730157
MEK162/ AEB071	MEK kinase inhibitor/Protein kinase C inhibitor	MEK162	1b	MEK162 BID. AEB071 BID. Dose escalation. MTD. 28 day cycles. RR. PFS.	NCT01801358
Sorafenib	Multi-kinase inhibitor	Placebo	2	Randomized, blinded. Sorafenib BID or placebo until disease progression. CR. PR. PFS. Survival. Safety.	NCT01377025
Vorinostat	Histone deacetylase inhibitor	None	2	Vorinostat BID 3 days weekly for 4 weeks. 28 day cycles. CR. PR. PFS. Safety.	NCT01587352

Abbreviations: Ab, antibody; BID, twice daily; CR, complete response; MTD, maximum tolerated dose; PFS, progression-free survival; PR, partial response; QD, once daily; RR, response rate; SD, stable disease.

(MAPK) signal transduction pathway. However, these mutations have not been associated with the risk of metastasis. More recently, GEP has advanced to the diagnostic forefront of the uveal melanoma field.[3,5] GEP takes a snapshot of the tumor environment that can be used as a baseline to track post-treatment changes or monitor tumor status over time. Because tumor heterogeneity does not have a strong impact upon the clinical accuracy of the GEP test, there is a very low technical failure rate of only 3% to 4% in both research and clinical settings. Results from multicenter prospective and retrospective studies have shown that GEP is superior at predicting metastasis in uveal melanoma patients compared with clinical, pathologic, or chromosomal approaches.[3,5,7]

GENE EXPRESSION PROFILING

The GEP test discussed in this article (commercially known as the DecisionDx-UM GEP test; Castle Biosciences) is a standalone platform that requires no additional pathologic staging information for maximal prognostic accuracy.[3,16-19] The expression levels of 12 tumor-associated genes and 3 control genes are measured in uveal melanoma samples obtained by fine-needle aspiration biopsy (FNAB), formalin-fixed paraffin embedded (FFPE) post-enucleation specimens, or resected tumor tissue. This GEP test stratifies tumors into 2 classes with an additional subgroup in the lower risk class. Patients in Class 1A have a 2% probability of tumor metastasis over the 5 years following initial testing. Class 1B and Class 2 tumors are associated with a 21% and 72% probability of tumor metastasis over the subsequent 5 years. Clinically, patients in Class 1B have a 3-year metastasis free survival rate of 93%, vs 50% for patients in Class 2. In a prospective study by the Collaborative Ocular Oncology Group (COOG), there was, as expected, a significant association between the classification of tumor specimens as Class 2 by GEP and monosomy 3.[5] However, 21% of tumors were discordant for GEP and chromosome 3 status. In this subset, the GEP results demonstrated superior prognostic accuracy for future metastasis, resulting in the GEP test being superior to, and independent of, chromosome 3 status. In addition, chromosome 3 status did not provide prognostic information independent of the GEP result.

The GEP test has had a significant impact on patients' clinical management.[20,21] In the first study, a blinded survey of ocular oncologists found that GEP data affected the follow-up surveillance strategy selected.[20] Eighty-nine percent of the clinicians who assessed the genetic biology of the tumor ordered a GEP test for uveal melanoma biopsy tissue, 49% performed cytology, and 20% had a chromosomal analysis performed. Seventy-four percent used the test results to determine the frequency of metastatic disease surveillance. In addition, 23% of clinicians offered information on clinical trials to high-risk patients. The second report was a systematic review of all patients from an insurance database.[21] Seventy-four percent of clinicians took clinical action as a result of GEP test results. Almost all patients (96%) with Class 1 uveal melanoma underwent low-intensity surveillance, whereas 95% of patients with Class 2 uveal melanoma underwent high-intensity surveillance. Also, approximately half (52%) of patients with Class 2 uveal melanoma were referred to medical oncology for possible clinical trial enrollment vs only 3% of patients with Class 1 uveal melanoma. Thus, the GEP results allowed low-risk patients to avoid considerable medical costs and inconvenience, while giving high-risk patients the best information available for making informed treatment decisions. As a result of these clinical uses, the GEP test has been widely adopted as the standard of care in the management of uveal melanoma.[3]

MANAGEMENT OF METASTASIS: THE FUTURE IS CLOSE

The US National Institutes of Health clinical trials database lists more than 40 active clinical trials for uveal melanoma patients that are testing treatments for metastatic disease and for delaying the development of metastatic disease—so-called adjuvant therapy trials.[22] A high risk for metastatic disease is an almost universal requirement for these studies, and many require that high risk be determined by GEP testing or cytogenetic analysis. The promise of these new clinical approaches was recently demonstrated.[23] Uveal melanoma patients with GNAQ/GNA11 tumor mutations that cause chronic hyperactivation of the MAPK signal transduction pathway responded to treatment with the MEK1/2 inhibitor selumetinib. Data from an interim analysis revealed a median progression-free survival in the selumetinib group (n=27) of 16 weeks and an 11% regression rate, vs 4 weeks in the temozolomide group with no tumor regressions (n=28). An overview of some adjuvant clinical trials currently enrolling high-risk uveal melanoma patients is shown in Table 1.[22]

TUMOR REPOSITORY: ENABLING TOMORROW'S PERSONALIZED MEDICINE ADVANCES TODAY

Because uveal melanoma is a clinical diagnosis and eye-sparing procedures constitute the major form of management of primary uveal melanoma, there is usually no tumor tissue to store for future genetic studies.[17,24] Yet advances in uveal melanoma genetics and targeted therapy trials are fueling the need to preserve tissue for

future mutational analyses. Archived tissue would allow physicians to assess the biology of patients' tumors to 1) assist in achieving accurate patient inclusion in clinical trials, 2) identify patients that may be at risk for related diseases, and 3) offer security to family members who are concerned with familial disease development.[25,26] There is a gap, however, between these needs and today's reality. Although some academic centers have tissue repositories or banks, these repositories have been universally set up for research purposes, and the banked tissue is not available for the benefit of that individual patient at a later date, such as enrollment into a clinical trial that requires high risk confirmation or mutational status as an enrollment criterion.

Given that the GEP test is standard of care at more than 100 ocular oncology centers today, Castle Biosciences has funded the Castle Clinical Sample Repository to address this unmet patient need, allowing patients to store additional tumor tissue samples free of charge for up to 5 years following initial testing in the DecisionDx-UM GEP assay. The tumor tissues deposited in the Castle Clinical Sample Repository will remain under the control of each individual patient. A patient may choose to have the tissue analyzed for enrollment in a future clinical trial or an inherited mutational analysis (eg, BAP1), or offer it up for research purposes of his or her own choosing. Central to the repository's mission is the fact that the patient will authorize the use of his or her own tumor sample. The process for sample storage is straightforward: A signed storage authorization form outlines the patient's right to release frozen biopsy material from the repository for research (or any other) purpose, but only with written authorization. Patients also retain the right to have their samples destroyed at any time. At present, the stored tumor sample will be collected via a second biopsy at the time of the initial surgical procedure to obtain tissue for GEP analysis. With the results from the GEP test of the initial biopsy in hand, and tissue availability for future testing, patients and physicians will be better prepared for managing ongoing treatment decisions.

CONCLUSIONS

The dynamic combination of the rapidly advancing field of personalized medicine, ongoing developments in targeted cancer therapy, the fact that uveal melanoma is often a clinical diagnosis and there is rarely any traditional pathology tissue, and a motivated patient community is fueling the need for a repository for uveal melanoma tumor tissue. The hope is that this initiative will enable acceleration of promising treatment regimens, just as the GEP test has enabled appropriate care to be implemented for patients at low vs high risk of primary tumor metastasis. ■

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