Uveal melanoma has an incidence of 4 to 7 persons per million each year in the United States and causes significant vision loss and mortality. It is the most common primary intraocular malignancy in adults and metastasizes to distant sites in half of all patients. Once metastasis is diagnosed it is typically fatal within 1 year because there are currently no effective treatments. Although clinical and histologic features have helped to determine which tumors tend to behave aggressively, technologic advances over the past decade have greatly expanded our understanding of molecular pathogenesis, and genetic studies more accurately predict metastatic risk. Cytogenetic testing demonstrates that nonrandom aberrations of chromosomes 3, 6, and 8 are common, and loss of 1 copy of chromosome 3 (monosomy 3) is predictive of poor likelihood of survival. Gene expression profiling allows lesions to be classified into 1 of 2 distinct molecular classes. Lesions with a class 1 genetic signature are unlikely to undergo metastasis, whereas those with a class 2 genetic signature have a very high metastatic rate. An inactivating mutation of the gene encoding BRCA1-associated protein 1 (BAP1) on chromosome 3 is strongly implicated in metastatic behavior. The purpose of this article is to review the evidence and utility of molecular genetic testing in uveal melanoma management.

Background

Uveal melanoma has been recognized for more than a century, and significant advances in diagnostic accuracy and local tumour control have occurred. Therapeutic decisions have largely been based on clinical features, such as
vision, tumour size, patient preference, and treatment availability at a given center. Zimmerman et al. hypothesized that enucleation surgery for uveal melanoma might accelerate metastatic death due to dissemination of tumour cells.\(^8\) Manschot and van Strik argued that radiotherapy was a poor choice because melanoma cells were seen histologically in irradiated specimens.\(^9\) Both hypotheses were shown to be incorrect in several publications. A large, randomized, prospective multicenter trial, the Collaborative Ocular Melanoma Study, showed that patients in whom large tumours were treated by enucleation had similar survival rates with or without pre-enucleation radiotherapy.\(^10\)

The second finding was that medium-sized tumours had similar outcomes after enucleation or iodine-125 plaque brachytherapy. Advances in local tumour control have resulted in a shift from enucleation to globe-preserving modalities, even for large tumours.\(^11\) Despite such advances, the prognosis for survival remains unchanged.\(^12\) The Collaborative Ocular Melanoma Study found that 45% of uveal melanoma patients were alive and cancer free 12 years after treatment.\(^2\)

**Clinical and histologic features** Until recently, clinical and histologic prognostic indicators were used to predict tumour-related mortality. Patient age, large tumour size, ciliary body involvement, diffuse configuration, and a number of histologic parameters are associated with the worst prognoses.\(^4,13,14\) Callender first classified uveal melanomas histologically in 1931.\(^15\) This original classification was later modified in 1983.\(^16\) The two predominant cell types are well described: spindle cells have elongated nuclei, scant cytoplasm, and cohesive patterns; epithelioid cells have round or oval nuclei and abundant cytoplasm and are discrete, large, and pleomorphic. A spectrum exists between these two cell types, and many lesions exhibit a mixed cellular population. The epithelioid cell type is strongly associated with higher rates of metastasis and mortality whereas the spindle cell type is associated with a better prognosis. Many other cytopathologic features have also been correlated with patient survival.\(^17-21\) These include mitotic rate, size and variability of nucleoli,\(^17,18\) closed-loop vascular patterns by periodic acid-Schiff staining,\(^19\) and silver-staining regions of nucleolar DNA.\(^20\) Systemic micrometastases may occur years before local ocular treatment is initiated.\(^22,23\) Biomarkers including PC-10 monoclonal antibody, osteopontin, S-100 beta, melanoma-inhibitory activity, and human leukocyte antigens, can detect malignant uveal melanoma cells in the serum, but the data regarding their utility for prediction of metastatic behavior are limited.\(^24-28\) Table 1 summarizes clinical and histologic features that have prognostic significance.

**Immunohistochemistry and cell cycling studies** first elucidated proteins of interest involved in uveal melanoma pathophysiology. Both p53 and Bcl-2 are regulators of apoptosis, or programmed cell death. The former is a well-described tumour suppressor gene and the latter a proto-oncogene. A normal p53 protein regulates DNA repair and halts cell replication when chromosomal damage is detected. If the DNA damage cannot be repaired, it activates apoptosis. Although implicated in many cancers, including cutaneous melanoma, we and others have found that p53 mutations are uncommon in uveal melanoma.\(^29\) The Bcl-2 gene proteins either inhibit apoptosis or promote programmed cell death. This proto-oncogene protects malignant cells from apoptosis and is widely expressed in uveal melanoma.\(^30\)

**Cytogenetics** Aberrations in chromosomes 3, 6, and 8 are consistently found in uveal melanoma.\(^5,31-33\) Nonrandom chromosomal aberrations were initially detected using standard karyotyping and fluorescence in situ hybridization (FISH) and later by spectral karyotyping and comparative genomic hybridization (CGH) techniques. Many studies found that loss of a single copy of chromosome 3, also known as monosomy 3, is detected in about half of uveal melanomas and is highly predictive of metastasis.\(^34-37\) In 1996, Prescher et al. demonstrated that monosomy 3 predicts a 5-year survival rate of less than 50%.\(^5\) Different chromosome 6 aberrations are associated with either a higher or a lower incidence of uveal melanoma metastasis. About 25% of uveal melanomas contain a gain in chromosome 6p (6p gain), which is associated with a better prognosis than monosomy 3 alone, while the same percentage of melanomas contain a loss in chromosome 6q, found more commonly in tumours that metastasize.\(^36,38\) Note that patients with neither monosomy 3 nor 6p gain have lower metastatic rates. An amplification of chromosome 8 fragments (8q gain) in monosomy 3 melanomas is predictive of a poor prognosis.\(^31-33\) This preliminary work provided a basis for more accurate techniques such as microarray gene expression analysis, whereby more than 25 000 genes can be tested simultaneously.

**Gene expression profiling (GEP)** This technique has more predictive accuracy than FISH or CGH for monosomy 3.\(^39,40\) In 2003, Tschentscher et al. performed unsupervised hierarchical cluster analysis of gene expression data for uveal melanomas with monosomy 3 and disomy 3 and revealed two molecular classes, each with a distinct genetic signature (multiple loci were tested simultaneously using a

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**Table 1**—Summary of high-risk clinical and histologic features for uveal melanoma metastasis and disease-related mortality

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Epithelioid cell</td>
</tr>
<tr>
<td>Large tumor basal diameter</td>
<td>High mitotic rate</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>Closed PAS-positive loops</td>
</tr>
<tr>
<td>Ciliary body involvement</td>
<td>Mean diameter of 10 largest nucleoli</td>
</tr>
<tr>
<td>Extracocular extension</td>
<td>Degree of pigmentation</td>
</tr>
<tr>
<td>Diffuse growth pattern</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Ring melanoma</td>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Optic nerve involvement</td>
<td>Tumor necrosis</td>
</tr>
</tbody>
</table>

PAS, periodic acid-Schiff staining.
microarray gene chip with 12 500 probe sets. Onken et al. used hierarchical cluster analysis of gene expression to study 25 patients with primary uveal melanoma using microarrays with 45 000 probe sets and found tumours clustered into two groups, described as class 1 and class 2.

Class 1 lesions were unlikely to undergo metastasis, whereas class 2 lesions predicted a greater rate of metastasis and disease-related mortality. Their subgroup analysis demonstrated that class 1 lesions have better prognoses and are associated with disomy 3 and a gain of chromosome 6p, whereas class 2 lesions predict more likely melanoma-related mortality and are associated with a loss of heterozygosity of chromosome 3. In later work, Onken et al. showed that class 2 lesions show downregulation of genes responsible for neural crest and melanocytic differentiation and upregulation of genes promoting an epithelial-like phenotype. Class 1 tumours have now been segregated into group 1A, which has a 2% 5-year tumour-related mortality rate, and 1B, which has a 21% 5-year tumour-related mortality rate (personal communication with J.W. Harbour). As expected, class 2 lesions have greater chromosomal aneuploidy. About 25% of class 2 lesions have downstream deletion of a chromosome 8p fragment that makes the lesion even more aggressive (class 2B melanoma). Parrella et al. describe a bifurcated tumour progression pathway that leads to one of these two classes. It remains unclear whether class 1 and class 2 tumours arise from unique cell lines or whether class 1 tumours can progress to class 2 tumours. Table 2 summarizes differences between class 1 and class 2 lesions.

### Molecular pathogenesis and genetic basis of disease

Familial forms of uveal melanoma are suspected clinically with bilateral, multifocal, or earlier disease presentation, but they account for less than 1% of all cases. A multitude of gene mutations have been implicated in pathways such as tumour suppression, G protein–coupled signaling, cell adhesion marker expression, and retinoic acid response. Although some predisposing mutations have been detected in uveal melanoma, the association is much weaker than that seen in cutaneous melanoma. Population-based studies of uveal melanoma first suggested a genetic basis for the disease, and we are now finding evidence of autosomal dominant inheritance in families carrying germ line mutations of BAP1. BAP1 mutations have resulted in other malignancies such as mesothelioma in uveal melanoma patients and may constitute a unique "BAP1 cancer syndrome."

### Mutations of BAP1 and G-protein-coupled-receptors

Harbour et al. recently found inactivating somatic and germ line mutations of BAP1 in 84% of metastasizing uveal melanoma lesions. BAP1, encoded by a gene on chromosome 3p21, is important for tumour suppression, and mutations occur relatively late during uveal melanoma progression. BAP1 mutations correlate strongly with the class 2 genetic signature and metastatic behaviour. Several germ line BAP1 mutations have been detected in both familial and nonfamilial uveal melanomas. By contrast, oncogenic mutations of GNAQ, found in half of all primary uveal melanoma lesions, occur early in tumourigenesis and do not correlate with molecular class or metastatic rate. The gene is located on chromosome 9q21 and encodes a signal transduction protein controlled by G protein–coupled receptors. In uveal melanoma patients lacking the GNAQ mutation, more than half of the tumours exhibit a GNA11 mutation. G proteins are cell-surface receptors that activate downstream pathways, including the mitogen-activated protein kinase (MAPK) pathway. Up to 90% of primary uveal melanoma lesions exhibit activation of MAPK. A GNAQ mutation alone is insufficient for malignant transformation, but a concurrent mutation of BAP1 has been shown to result in downstream events that shift the gene expression profile of uveal melanomas from class 1 to class 2. Therapeutic targeting of both GNAQ and BAP1 mutations simultaneously may prove to be an effective strategy.

### Using molecular genetic testing to predict survival

Molecular genetic analysis supersedes clinical and histologic prognosticators for predicting disease-related metastasis and mortality. Table 3 summarizes published reports that have used molecular genetic testing for uveal melanoma prognostication and have correlated high-risk test results with known clinical and histologic prognosticators. Most groups find that 40% to 60% of all uveal melanomas exhibit high-risk molecular features. About half of these patients will suffer melanoma-related metastasis and mortality, predictable by the molecular genetic test alone.

### Molecular genetic testing can be correlated with clinical and histologic features

Monosomy 3 or molecular class 2 lesions are associated with features such as large basal tumour diameter, epithelioid cell type, ciliary body involvement, extraocular spread, mitotic rate, and PAS-positive loops. It is important to be clear, however, that...
Table 3—Summary of uveal melanoma published reports in which molecular genetic testing is correlated with disease-related metastasis and mortality rates or clinical and histologic features

<table>
<thead>
<tr>
<th>Reference</th>
<th>Molecular Test (N)</th>
<th>% Patients with Test Result</th>
<th>Mets Rate</th>
<th>Mets-related Mortality Rate</th>
<th>Correlation of High-Risk Molecular Test with Clinical or Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescher et al. (1996)</td>
<td>*Karyo, CGH (54)</td>
<td>no aberration (44%) monosomy 3 (56%)</td>
<td>0%</td>
<td>0% (at 3 years)</td>
<td>tumour diameter, tumour location</td>
</tr>
<tr>
<td>Scholes et al. (2003)</td>
<td>*MSA (105)</td>
<td>no aberration (43%) monosomy 3 (51%)</td>
<td>57%</td>
<td>54%</td>
<td>cell type, PAS loops</td>
</tr>
<tr>
<td>Onken et al. (2004)</td>
<td>*GEP (25)</td>
<td>class 1 (56%) class 2 (44%)</td>
<td>0% (at 2 years)</td>
<td>51%</td>
<td>cell type</td>
</tr>
<tr>
<td>Kilic et al. (2006)</td>
<td>*Karyo (74)</td>
<td>6p gain (18%) monosomy 3 (42%)</td>
<td>4% (at 7.7 years)</td>
<td>32%</td>
<td>cell type</td>
</tr>
<tr>
<td>Damato et al. (2007)</td>
<td>*FISH (356)</td>
<td>no aberration (42%) both monosomy 3 and 8 gain (27%) monosomy 3 (21%) 8 gain (11%)</td>
<td>PI-LG 0% (at 5 years) PI-HG 66%</td>
<td>0% (med. 3.6 years) 42%</td>
<td>tumour diameter, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>Coupland et al. (2008)</td>
<td>*FISH (420)</td>
<td>no aberration (53%) monosomy 3 (47%)</td>
<td>EOS in 10.4% (med. 3.6 years) EOS in 22.7%</td>
<td>0% (med. 3.6 years) 6%</td>
<td>tumour diameter, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>van Gils et al. (2008)</td>
<td>*FISH (46)</td>
<td>class 1 (50%) class 2 (50%)</td>
<td>14% (at 7 years) 100%</td>
<td>0% (med. 2.5 years) 6%</td>
<td>tumour diameter, CB, EOS, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>McCannel et al. (2010)</td>
<td>*FISH, GEP (31)</td>
<td>6p gain (39%) LOH3 (61%)</td>
<td>0%</td>
<td>0% (med. 2.5 years) 6%</td>
<td>tumour diameter, CB, EOS, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>Onken et al. (2010)</td>
<td>*GEP (28)</td>
<td>class 1 (46%) class 2 (54%)</td>
<td>0% (med. 2.0 years) 73%</td>
<td>0% (med. 2.0 years) 73%</td>
<td>tumour diameter, CB, EOS, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>Shields et al. (2011)</td>
<td>*MSA (500)</td>
<td>no aberration (48%) partial aberration (27%)</td>
<td>2.6% (at 3 years) 5.3%</td>
<td>0% (med. 2.0 years) 73%</td>
<td>tumour diameter, CB, EOS, cell type, closed loops, mitotic rate</td>
</tr>
<tr>
<td>Chappell et al. (In press)</td>
<td>*GEP (222)</td>
<td>monosomy 3 (25%)</td>
<td>24%</td>
<td>9% (at 5 years) 60%</td>
<td>age, mean tumour area, cell type</td>
</tr>
</tbody>
</table>

CB, ciliary body involvement; CGH, comparative genomic hybridization; EOS, extracocular spread; FISH, fluorescent in situ hybridization; GEP, gene expression profiling; karyo, karyotyping; LOH3, loss of heterozygosity for chromosome 3; med., median; Mets, melanoma metastasis; MSA, microsatellite assay for chromosome 3 markers; N, number of patients; PI-LG/HG, predictive index for low-grade/high-grade lesions based on a combination of cytogenetic, clinical, and histologic high-risk features.

*Enucleation specimens were analyzed.
†Fine-needle aspiration biopsy (FNAB) specimens were analyzed.

although monosomy 3 and molecular class 2 signature are strongly associated with one another, they not the same thing. The former is based on a single chromosome marker using cytogenetic techniques and is less predictive of metastatic behavior than the latter, which is based on a complex gene expression profile. Kilic et al. found that monosomy 3 and large basal tumour diameter were most predictive of disease-related mortality when considered together.63 Coupland, Damato and coworkers found extracocular spread to be correlated with large basal tumour diameter, epithelioid cell type, closed loops, high mitotic rate, and monosomy 3.65 They devised a predictive index combining these prognosticators that showed 5-year metastatic death rates of 0% for “low-grade” lesions and 66% for “high-grade” lesions.66 However, 42% of patients in this study exhibited no cytogenetic abnormalities using FISH alone. They found that disease-related deaths occurred in patients without monosomy 3 and concluded that accurate prognostication requires integration of cytogenetic analysis with clinical tumour staging and histologic grading.66 Similarly, both Scholes et al. and Kilic et al. found that largest tumour diameter with monosomy 3 was most predictive of disease-related mortality.34,61 However, the presence of monosomy 3 does not always correlate with large tumour diameter. Some groups have detected monosomy 3 in up to one third of small tumours.62,63,67

In the first GEP study by Onken et al., molecular class correlated with cytologic severity.6 The same group recently demonstrated that class 2 lesions have a higher proliferative rate (higher Ki-67 positivity) compared with class 1 lesions.68 In our recent series of 222 consecutive patients with uveal melanoma, 62% were class 1 lesions, whereas 38% were class 2 lesions.64 We did not find any statistically significant echographic or angiographic parameters that differentiated the two classes. The 5-year probability of melanoma-related mortality was 60% (95% CI: 42% to 79%) for class 2 compared to 9% (95% CI: 3% to 25%) for class 1 tumours. Molecular class was the only variable predictive of disease-specific mortality.

Limitations of molecular testing Although some aspects of the uveal melanoma molecular mechanisms have been identified, there are still many unknown factors. For example, comparative RNA analysis revealed dozens of candidate oncogenes that are differentially expressed in chromosome 3 loss melanomas and chromosome 6p gain melanomas.67 Melanoma cells act within a microenvironment of cytokines, fibroblasts, vascular endothelial cells, and many other molecules that are implicated in permitting and stimulating tumour growth. Proteomic analysis (the protein complement of the genome) adds further complexity to the picture. In uveal melanoma subgroups, it
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reveals differential protein expression such as downregulation of heat-shock protein (HSP)-27 and upregulation of vimentin in monosomy 3 tumours. Several investigators have assessed molecular changes in autologous and allogenic primary and metastatic melanomas to better elucidate the changes that confer the propensity to metastasize. Trolet et al. used array-based CGH to study both primary ocular lesions and corresponding liver metastases and developed a prognostic classifier (defined by a gain of 8q and losses of 3, 8p, and 16q) that led to an 86% classification accuracy. Their study showed that many more aberrations occur in metastatic lesions than are predicted by the two molecular classes alone. Meir et al. used microarray GEP and found hepatic metastatic lesions have a distinct genetic signature compared with their corresponding intraocular lesions. Ongoing studies using microarray gene expression analysis will help to elucidate genes of functional significance at differing stages of tumour spread.

The other main limitation addresses the accuracy and availability of the various molecular genetic tests. Newer techniques, such as array-based CGH (aCGH), microsatellite analysis (MSA), single-nucleotide polymorphism (SNP) analysis, and multiplex ligation-dependent probe amplification (MLPA) are more accurate and reliable than karyotyping, FISH, and older cytogenetic techniques. Most groups now use a multiplexed SNP assay to determine the status of chromosomes 3 and 8p and calculate aneuploidy by using global aCGH. Onken et al. have developed a polymerase chain reaction–based multigene expression test for GEP on fine-needle aspirates. Damato et al. validated MLPA, which they prefer to FISH for several reasons, including the ability to simultaneously test 31 genomic sequences on chromosomes 1, 3, 6, and 8; the ability to discriminate sequences differing by a single nucleotide; and the requirement of a relatively small sample (only 80 ng of DNA are required). Older techniques such as FISH can demonstrate heterogeneity for monosomy 3 within a lesion, which will confound test results. Intratumoural heterogeneity has been noted as a potential problem for newer techniques such as MLPA by some groups. However, GEP is less susceptible to heterogeneity than cytogenetic studies because a complex molecular genetic signature captures a better snapshot of the tumour microenvironment than does a sampling of individual tumour cells. Furthermore, a fine-needle biopsy has greater accuracy than step sections with slides because more of the tumour is being scanned by the multiple passes made when using the needle.

Implications for clinical practice

Molecular genetic testing of uveal melanoma has implications for clinical practice. It has resulted in an evolved understanding of tumourigenesis. We can better explain why some tumours behave aggressively while others are relatively quiescent, irrespective of size and other features. Identifying high-risk patients based on molecular class will provide useful information to both patient and practitioner regarding the risk for disease-related metastasis and mortality. Issues regarding the availability, cost, and ethics of molecular genetic testing will have to be considered. In our practice, all patients with uveal melanoma exhibiting high-risk clinical features undergo trans-scleral fine-needle aspiration biopsy (FNAB) for intraoperative histologic confirmation of the diagnosis and subsequent molecular genetic testing.

Although an enucleation specimen provides an adequate sample for histologic and molecular genetic analyses, there is a trend to treat lesions with globe-preserving therapies and these tumours can be sampled by FNAB. Despite reports of poor sampling in as much as 19% of cases, we have found that adequate samples are attained in more than 98% of lesions when FNAB is performed intraoperatively and a skilled cytopathologist is present.

Fine-needle aspiration biopsy Concerns about potential systemic seeding of malignant cells during FNAB are unfounded; this technique has been used safely for more than 30 years in cancers throughout the body. We have routinely used FNAB for uveal melanoma and found no adverse effects on melanoma-related mortality rates or ocular sequelae. Many other groups have also found FNAB to be safe for uveal melanomas. We use a 25-gauge needle passed directly into the tumour by the trans-scleral route, although the biopsy may also be performed transvitreally. The aspirate is smeared onto a glass slide in the operating room and immediately fixed in 95% ethanol, stained with H&E, and then evaluated by the cytopathologist for histologic confirmation of melanoma. The aspirate can undergo testing to determine cell type, DNA content, flow cytometry, presence of specific cell cycling proteins, and molecular genetic analyses.

Surveillance for metastasis Patients may travel long distances to be evaluated at specialized ophthalmic oncology centers by follow-up examinations, and they usually undergo routine blood work and imaging for metastatic screening. The most common site of involvement is the liver (up to 90%), so patients may have blood work for hepatic enzymes and chest or abdominal imaging using ultrasonography, radiography, computed tomography, or positive-emission tomography scans. Abdominal magnetic resonance imaging has proven to have greater sensitivity than the other techniques for detecting liver metastasis from malignant cutaneous melanoma. Eskelin et al. showed that liver ultrasonography and serum liver function tests identified metastatic disease in asymptomatic patients 59% of the time when done annually, 95% of the time when done twice yearly, and 97% of the time when done quarterly. Lactate dehydrogenase (LDH), γ glutamyl transpeptidase (GGT), and alkaline phosphatase are more sensitive than aspartate aminotransferase (AST), alanine aminotransferase, and bilirubin. There is, however, a lack...
of consensus regarding the desired frequency and choice of testing for metastatic screening. In fact, it may be futile to discriminate among various metastatic screening protocols because none have proven useful in improving disease-related survival rates. Augsburger et al. reviewed the literature and found no evidence that routine surveillance for metastasis confers any survival benefit on patients with primary uveal melanoma. However, an important limitation of their paper was that the studies reviewed did not employ molecular genetic prognostication or modern targeted therapies for metastasis. Rather than indiscriminately following all patients in a similar fashion, those with high-risk molecular features may be targeted for closer follow-up and or systemic evaluation by a medical oncologist.

Summary and future directions

Uveal melanoma arises from an abnormal proliferation of neural crest–derived melanocytes within the iris, ciliary body, or choroid. Chromosomal and molecular testing has elucidated several key genetic alterations that occur during the transition of a normal melanocyte to a malignant melanoma cell. The genetic profile for a given uveal melanoma lesion will impact its clinical behavior. Early disruption of cell cycling seems to occur as the result of a GNAQ gene mutation, which leads to activation of downstream signaling pathways (i.e., MAPK, receptor tyrosine kinase) and subsequent inhibition of tumour suppression mechanisms (i.e., Bcl-2). Ultimately, malignant proliferation ensues and a clinically evident lesion develops. At this stage, cytogenetic gene hybridization studies show minimum aneuploidy, and GEP shows a class 1 signature (class 1A melanoma). The lesion may then take one of two paths. It may become more differentiated, less aggressive, and unlikely to undergo metastasis (class 2B melanoma, associated with 6p gain). However, a mutation of BAP1 or similar genes makes the lesion less differentiated, more aggressive, and likely to metastasize (class 2A genetic signature, associated with monosomy 3). About 25% of these latter tumours will become even more aggressive and genetically unstable (class 2B genetic signature, associated with 8p gain).

This evolved understanding of the molecular pathobiology of uveal melanoma has resulted in the development of several systemic therapeutic agents that target candidate genes or their products implicated in the tumourigenesis pathway. A number of clinical trials based on demonstrable molecular changes are currently under way. Harbour and colleagues are planning to treat class 2 melanomas, which frequently exhibit a mutation in the BAP1 metastasis suppressor gene, with valproic acid, a histone deacetylase inhibitor that may prove effective. See Table 4 for other clinical trials currently investigating molecular-targeted agents for advanced uveal melanoma. Although gene-based systemic therapy shows promise, our knowledge of deregulated pathways is still emerging. This contrasts somewhat with cutaneous melanomas, for which several predisposing genes have been identified. Advanced cutaneous melanomas (BRAF V600E mutation) treated by inhibitors of the BRAF/MAPK pathway initially demonstrated response rates above 70% but many eventually recurred due to drug resistance.

Studying the molecular changes within a melanoma that allow it to adapt and resist targeted therapy will further elucidate underlying mechanisms of tumour progression.

CONCLUSIONS

Gene expression profiling separates uveal melanoma patients into two groups—those who are likely to undergo metastasis (class 2) versus those who are unlikely to undergo metastasis (class 1). The predictive value of molecular class supersedes clinical, histologic, and cytogenetic prognosticators. Local tumour control remains important, but we may find that early systemic intervention using targeted gene-based therapies proves to be most effective for prolonging life.

REFERENCES

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