67.1. Uvea: Iris Melanomas

Authors

Emerging Prognostic Factors for Clinical Care

Mutational Analysis
Preliminary results suggest that identification of mutations in BAP1, EIF1AX, and SF3B1 may further enhance prognostication in uveal melanoma, especially if the BAP1 gene is not mutated and the tumor has disomy 3 (AJCC Level of Evidence: III).1-5 Mutations in these genes may be assessed from either a biopsy sample of the tumor or a resection specimen using sequencing (e.g., Sanger sequencing). Expression of BAP1 protein also may be assessed immunohistochemically.6-8 Mutation leads to the absence of normally occurring nuclear immunoreaction. Currently, it is estimated that BAP1 is mutated in 45–55%, EIF1AX in 10–20%, and SF3B1 in 10–20% of all primary uveal melanomas, the first predominantly in those with monosomy 3 and the second two in those with disomy 3. EIF1AX is mutated in about 6% and 48% of monosomy 3 and disomy 3 primary uveal melanomas, and SF3B1 (usually in codon 625) in 3–7% and 27–29% of tumors, respectively. Mutations in BAP1 have been found in 80–85% and those in SF3B1 in about 5% of metastatic uveal melanomas, according to preliminary studies.9 BAP1 mutations also may occur in the germline, and these inherited mutations predispose to familial uveal melanoma and other cancers, especially cutaneous melanoma, mesothelioma, and renal cell cancer.10 If EIF1AX is mutated in a disomy 3 melanoma (typically with wild-type BAP1), the risk of metastasis is preliminarily estimated to be 6 to 10 times lower than if EIF1AX is wild type.4 When it rarely is mutated in a monosomy 3 melanoma (typically with mutated BAP1), the risk of metastasis is estimated to be three or four times lower than if EIF1AX is wild type. Patients with SF3B1 mutations also carry a lower risk of metastasis than those with wild-type SF3B1 in their tumor.2,3

Mutations in GNAQ are found in 40–45% and those in QNA11 in 30–35% of primary uveal melanomas, usually in codon 626, and are considered early or initiating events.11-13 These mutations may be assessed from a biopsy sample, from a resection specimen, or potentially, from circulating DNA by using sequencing (e.g., Sanger sequencing) or related techniques. GNA11 mutations are more frequent than GNAQ mutations in uveal melanomas with BAP1 mutations, and the former may mark a higher risk of metastasis and, in metastatic uveal melanoma, shorter survival (AJCC Level of Evidence: III).9,14

Tumor-infiltrating Lymphocytes
The number of tumor-infiltrating lymphocytes is associated with metastatic risk and may be relevant with regard to immunotherapy (AJCC Level of Evidence: III).15-18 The presence of lymphocytes may be
assessed semiquantitatively or quantitatively—for example, by confocal imaging of cells stained by immunohistochemistry or immunofluorescence. Higher numbers are associated with shorter survival.

**Human Leucocyte Antigen Expression**

The level of expression of human leukocyte antigen (HLA) molecules is associated with metastatic risk and may be relevant with regard to immunotherapy (AJCC Level of Evidence: III).\(^ {19,20} \) The level of expression is determined by assessing the percentage of immunopositive tumor cells. Higher expression is related to shorter survival.

**Risk Assessment Models**

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.\(^ {21} \) Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

**Recommendations for Clinical Trial Stratification**

Clinical trials addressing treatments for metastatic uveal melanoma are recommended to stratify patients on the basis of the M categories (M1a-c).

**Bibliography**

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