MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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The Newest Treatments for Uveal Melanoma

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H&O What are the most important differences between uveal melanoma and cutaneous melanoma?

JL Uveal melanoma and cutaneous melanoma are very different diseases. The most obvious difference is that cutaneous melanoma occurs in the melanocytes of the skin, whereas uveal melanoma occurs in the melanocytes of the uveal tract of the eye. Uveal melanoma is also far less common than cutaneous melanoma. In the United States, approximately 85,000 people develop cutaneous melanoma annually, whereas approximately 2000 people develop uveal melanoma.

In addition, the molecular biology of uveal melanoma is quite different from that of cutaneous melanoma, as we described in a 2015 article in *Pigment Cell & Melanoma Research*. The sun, or ionizing radiation, is what most commonly drives cutaneous melanoma, which is not the case in uveal melanoma. In this context, we find somewhere between 10 and 100 times fewer mutations in uveal melanoma than in cutaneous melanoma.

Unfortunately, we do not truly understand why people develop uveal melanoma. Although it is not a very complex disease genomically in terms of nonsynonymous mutations, it appears that the epigenome of uveal melanoma is more complicated than is generally appreciated. In cutaneous melanoma we tend to see mutations in *BRAF* or *NRAS* that never occur in uveal melanoma. Instead, we see mutations in pathways associated with G-coupled proteins—usually GNAQ or GNA11—in nearly all uveal melanomas. These genetic differences translate into immunologic differences. For example, cutaneous melanoma tends to be highly immune infiltrated and immunotherapy-sensitive, whereas the reverse is seen with uveal melanoma. Patients with metastatic disease show very little immune response against the tumor.

H&O Is there a difference in prognosis between the 2 forms?

JL Uveal melanoma may be more aggressive upon metastasis than cutaneous melanoma, although direct comparison is difficult. The more important distinction is that we have seen the development of greatly improved treatments for cutaneous melanoma over the past 10 to 15 years, whereas no standard systemic treatment exists for uveal melanoma. Nearly all of the new treatments for cutaneous melanoma have very modest activity in uveal melanoma.

H&O Are patients with uveal melanoma more likely to develop metastasis?

JL Whereas the risk of metastasis can be clearly stratified by stage in cutaneous melanoma, uveal melanoma demonstrates an overall chance of metastasis of approximately 50%. Patients with metastatic uveal melanoma have a poor prognosis, as we do not have any approved treatments that make a significant difference in overall survival. Cutaneous melanoma can metastasize anywhere in the body, including the lung, liver, and brain. Uveal melanoma, for reasons that are not entirely clear, tends

to metastasize to the liver. This tendency is so strong—more than 80% of patients with metastatic disease have liver metastases—that if someone is diagnosed with uveal melanoma and then develops metastasis without liver involvement, many doctors will question the initial diagnosis. Something about the biology of the liver makes uveal melanoma tumors want to move there; we think this may have something to do with growth factors and growth factor receptors, such as hepatic growth factor, insulin-like growth factor, and epidermal growth factor receptor.

H&O What is the standard approach to treatment of patients with uveal melanoma?

JL Historically, enucleation of the eye was the treatment in the setting of primary disease. Fortunately, this is far less common now and the field has moved to radiation approaches using proton therapy or brachytherapy. Sometimes enucleation is required in cases of primary disease progression or recurrence, but not all the time. A great deal of research has been pursued in an effort to predict which patients are most likely to develop recurrent disease. Some gene-expression signatures are commercially available for testing, but these are not used as widely as they might be. Given the lack of therapeutic options in the metastatic setting, some ophthalmologists believe that testing to predict metastasis adds cost without improving outcomes. In medical oncology, we would prioritize clinical trials for high-risk patients—as well as early detection and intervention in the metastatic setting—and therefore believe that prognostic testing can be helpful. Unfortunately, the standard of care for metastatic disease continues to be hepatic tumor embolization, in which a catheter is placed in the liver and delivers either chemotherapy or radiotherapy directly to the liver tumors. This is the same approach used to treat hepatocellular carcinoma. Some patients receive multiple rounds of hepatic embolization.

If the patient is not a good candidate for hepatic embolization, such as in cases of multifocal disease, most doctors will try one of the immunotherapy agents that are approved to treat cutaneous melanoma. The efficacy of these in uveal melanoma is questionable at best, however. Multiple retrospective series have looked at the use of checkpoint inhibitors such as ipilimumab (Yervoy, Bristol-Myers Squibb), nivolumab (Opdivo, Bristol-Myers Squibb), and pembrolizumab (Keytruda, Merck) for uveal melanoma and found response rates of 5% or less as single agents. The real response rate may be even lower; it is possible that the patients who responded in these case cohorts had been misdiagnosed and actually had cutaneous melanoma.

Recently, 2 research groups from Europe (Piulats Rodriguez and colleagues) and the United States (Pelster and colleagues) described treating a series of patients with dual combination checkpoint inhibition—ipilimumab and nivolumab at the same time. These groups saw a response rate of approximately 10% to 17% with dual checkpoint blockade. Because patients with uveal melanoma do not have *BRAF* mutations, the use of BRAF inhibitors is not an option. Chemotherapy is also not an option for uveal melanoma, given its lack of efficacy in this disease. The best option is always enrollment in a clinical trial, which is our only hope of improving outcomes in this difficult disease.

H&O What is the appropriate follow-up for patients diagnosed with primary uveal melanoma?

JL No consensus has emerged on appropriate follow-up. Most patients with uveal melanoma are diagnosed by ophthalmologists, and many in that community do not believe that substantial follow-up is necessary. Medical oncologists, by contrast, generally advocate regular follow-up visits. In my own practice, I conduct follow-up visits every 3 to 6 months that include imaging of the liver using magnetic resonance imaging as well as intermittent imaging of the chest with a computed tomography scan or an x-ray.

H&O What are the most promising clinical trials that are being conducted?

JL Several years ago, researchers learned that most uveal melanomas signal through the mitogen-activated protein kinase (MAPK) cascade downstream of the G-coupled protein receptors GNAQ and GNA11, as mentioned. This led to hopes that MEK inhibitors, which block that signaling cascade, could be beneficial. These agents did not turn out to be widely active in uveal melanoma, as shown in the SUMIT trial (Selumetinib in Metastatic Uveal Melanoma) by Carvajal and colleagues. However, researchers are continuing to explore agents that target different signaling pathways, such as the phosphoinositide 3-kinase (PI3K) signaling pathway (NCT02273219). There is also the potential to target the Yes-associated protein (YAP) signaling pathway.

The most promising area of investigation currently is an alternative kind of immune-system treatment. The lead molecule in this approach is called IMCgp100. This is a bispecific molecule, in which one side of the drug grabs the gp100 protein in melanoma, and the other side of the drug grabs the immune cells by linking to a molecule called CD3 that is on the surface of T cells. This agent is being studied for uveal melanoma in a registration-intent

randomized phase 2 trial (NCT03070392). We are all looking forward to seeing the results of this trial, given that results from a previous study were encouraging.

The study proved another important point, which is that national clinical trials in uveal melanoma are possible to pursue.

One caveat is that the agent is restricted to patients with HLA-A*02 blood type, who make up only approximately half of the population. Other bispecific molecules are also being developed to target antigens such as the melanoma antigen (MAGE) and preferentially expressed antigen in melanoma (PRAME), although clinical trials of these agents have not yet started in uveal melanoma.

Another approach, which is being used in a phase 2 trial here at the University of Pittsburgh Medical Center (NCT03467516), involves harvesting tumor-infiltrating lymphocytes for adoptive cell therapy. My colleague leading this program is Dr Udai Kammula, who previously demonstrated early success with this approach at the National Cancer Institute. The procedure is for patients with uveal melanoma who have surgery to remove a tumor from somewhere in the body, usually the liver. Immune cells are then isolated from the tumor, expanded in the laboratory, and returned to the patient after they have grown to a certain volume. In results that were published in 2017 in *Lancet Oncology* with Chandran as the first author, 7 of 20 evaluable patients had objective tumor regression. This is a complicated approach that is not widely available, but we know from studies in other diseases that it can work very well, with some patients going into long-term remission.

H&O Do you know why certain patients responded to adoptive cell transfer but not others?

JL I think that a combination of factors are responsible. An important aspect of this process regards the immune cells that are removed from the patient's tumor after surgery. These are heterogeneous, and may or may not grow in the laboratory. Beyond that, if they grow we do not yet know how to select the correct population of cells, and it is possible that they are not the cancer-specific cells. We try to start with as many immune cells as possible, but we still may not have the ones we really need to attack the tumor. Another reason why certain patients may not respond is that their tumors develop mutations to become more aggressive and block the immune system. A final reason why some patients may not respond to treatment is that they are too sick from the cancer, and their bodies are no longer able to mount the kind of systemic immune response that is needed in order to actually generate an anti-tumor response.

H&O Can you talk about your study of cabozantinib in metastatic uveal melanoma?

JL That study grew out of the observation that uveal melanoma tends to metastasize to the liver. One of the proteins in the liver that seems to attract uveal melanoma is c-MET, which led to the idea that cabozantinib (Cabometyx, Exelixis)—which blocks c-MET—might lead to shrinkage of the liver tumors. A previous clinical trial supported that idea, so we embarked on a phase 2 multisite clinical trial in which patients were randomly assigned to either cabozantinib or chemotherapy. Unfortunately, our trial—which Dr Daniel Olson presented at the 2019 American Society of Clinical Oncology annual meeting—did not show a benefit from cabozantinib. This was an important finding because some physicians were already using the drug off-label in metastatic uveal melanoma.

The study proved another important point, which is that national clinical trials in uveal melanoma are possible to pursue. One of the big problems with doing research on a rare tumor is that funding agencies will deny support based on the idea that researchers will be unable to find enough patients for clinical trials. This trial countered that argument—it took a while, but we were able to get the trial done thanks to the Alliance for Clinical Trials in Oncology.

The study actually had a third benefit, which is that we learned a lot from the genomic analyses we pursued based on the tumor specimens obtained from patients before treatment. These analyses taught us more about the many differences between uveal melanoma and cutaneous melanoma, giving us some new molecular targets to explore. We can use this information to encourage pharmaceutical companies to include uveal melanoma when they are developing certain drugs.

H&O What sort of future studies would you like to see?

JL I would like to see more studies in both the genomic category and the immune category. On the genomic side, which we understand so much better thanks to efforts

such as The Cancer Genome Atlas, I am seeing the most potential with agents that target PI3K, YAP, and protein kinase C (PKC), and with combination targeted therapy. On the immune side, the early data on IMCgp100 support the idea that immunotherapy may be beneficial in uveal melanoma, so we are trying to build on that—perhaps by adding additional immune therapies, such as checkpoint inhibitors.

If the research on tumor-infiltrating lymphocytes continues to go well, we might be able to determine precisely which T-cell receptor actually mediated the phenomenon of killing the cancer. If we could figure that out, we could clone that T-cell receptor and turn it into a drug. All of these approaches are potentially very exciting for patients facing metastatic uveal melanoma.

Disclosure

Dr Luke has served on the data and safety monitoring board of TTC Oncology and the scientific advisory board of 7 Hills, Actym, Alphamab Oncology, Mavupharma, Pyxis, Spring Bank, and Tempest. He has consulted for AbbVie, Akrevia, Array, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Compugen, EMD Serono, IDEAYA, Immunocore, Incyte, Janssen, Jounce, Leap, Merck, Mersana, Novartis, RefleXion, Spring Bank, Tempest, and Vividion. He has received research support from AbbVie, Array, Boston Biomedical, Bristol-Myers Squibb, Celldex, Checkmate, Compugen, Corvus, EMD Serono, Evelo, Delcath, Five Prime, RAPT Therapeutics, Genentech, Immunocore, Incyte, Leap, MedImmune, Macrogenics, Novartis, Pharmacyclics, Palleon, Merck, Tesaro, and Xencor. He has received travel reimbursement from Akrevia, Array, AstraZeneca, Bayer, Bristol-Myers Squibb, Castle, Checkmate, EMD Serono, IDEAYA, Immunocore, Incyte, Janssen, Jounce, Merck, Mersana, Novartis, and RefleXion. He has the following provisional patents: serial #15/612,657 (cancer immunotherapy) and PCT/US18/36052 (microbiome biomarkers for anti-PD-1/PD-L1 responsiveness: diagnostic, prognostic and therapeutic uses thereof).

Suggested Readings

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