Researchers Offer Insights on Immunotherapy for Melanoma

New strategies are being evaluated for people with nonresponsive or relapsing disease.

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Immunotherapy for melanoma was one of the key themes of the 2018 Clinical Immuno-Oncology Symposium held last month in San Francisco. ImmunoOnc18, cosponsored by the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer, focuses on treatments that help the immune system recognize and fight cancer.

Melanoma typically starts as a skin cancer, but it can spread to other parts of the body, a process known as metastasis. If it is not caught early, it often invades the lungs, liver, bones and brain.

Katy K. Tsai, MD, of the University of California, San Francisco, gave an overview of the integration of immune checkpoint inhibitors in melanoma treatment.

Most approved checkpoint inhibitors are monoclonal antibodies that block the PD-1 receptor on T cells or PD-L1, its binding partner on cancer cells. PD-1 is an immune checkpoint that plays a role in regulating immune function, acting as a brake on T-cell activity. Some tumors can hijack PD-1 to turn off immune responses against them; PD-1 inhibitors release the brake and restore T-cell function. Two PD-1 blockers, Keytruda (pembrolizumab) and Opdivo (nivolumab), are approved for advanced melanoma.

CTLA-4 is another type of immune checkpoint that turns off immune responses by suppressing T-cell multiplication. The CTLA-4 inhibitor Yervoy (ipilimumab) is approved for treatment of metastatic melanoma. Opdivo and Yervoy, both made by Bristol-Myers Squibb, are often used together.

Checkpoint inhibitors work best against so-called hot cancers like melanoma that have many mutations and attract T cells. But not everyone responds to these drugs, and some people who initially do respond eventually develop resistance, Tsai explained. In addition, checkpoint inhibitors—especially in combination—can lead to an overactive immune response that harms healthy tissue and organs.

Looking toward the future, studies are evaluating other types of immune-based therapy for

melanoma. One promising candidate is the IDO (indoleamine 2,3-dioxygenase) inhibitor epacadostat, used alone or in combination with PD-1 inhibitors. Merck recently announced that epacadostat plus Keytruda produced an overall response rate of 56 percent with a median progression-free survival of 12.4 months in the ECHO-202 trial.

Another potential target is LAG-3, a protein that appears to play a role in T-cell exhaustion. One study found that an experimental LAG-3 inhibitor plus Opdivo showed a 20 percent overall response rate in selected patients with "impressive" safety, Tsai said.

"These are very exciting days for immunotherapy in melanoma," she concluded.

Much work is being done on immunotherapy in the adjuvant setting, meaning preventive therapy after surgery to stop melanoma from relapsing or spreading. It may also be possible to use some of these drugs as neoadjuvant therapy, to shrink tumors before surgery. But session chair Ann Silk, MD, of Rutgers Cancer Institute in New Jersey, cautioned that this type of therapy must be highly effective; if not, it could prove harmful to treat patients before potentially curative surgery.

Antoni Ribas, MD, PhD, of the University of California Los Angeles Medical Center, reviewed how melanoma resists the immune system's attack and how to overcome it. Various strategies are being explored to attract T cells into tumors, including Imlygic or T-VEC, an oncolytic virus made from a genetically modified herpesvirus that is injected into tumors. Other promising drugs target melanoma with BRAF gene mutations. Ribas suggested that the best results may come from a combination approach using three or more therapies that work in different ways.

Sunandana Chandra, MD, MS, of Northwestern University in Chicago, discussed immunotherapy for the treatment of melanoma brain metastasis. About half of advanced melanoma patients develop brain metastases and their prognosis is very poor, with survival of around four months, she said. They are often treated with radiation, but this can cause cognitive problems—especially concerning for people who are still asymptomatic and have an otherwise good quality of life.

Many clinical trials for melanoma exclude people with brain metastases, and expanding access to trials for more advanced patients is a key goal of advocates. The studies that have been done have shown relatively good outcomes with targeted therapies and checkpoint inhibitors compared with standard therapy. They don't work for everyone, but "when they work, they can have quite a durable response," Chandra said.

Research Review

A number of research teams presented posters at the ImmunoOnc18 describing melanoma treatment studies:

- Krishna Prasad Joshi, MD, of the University of Arkansas for Medical Sciences, and colleagues reported that melanoma patients over age 65 treated with checkpoint inhibitors had overall survival, time to disease progression and adverse events similar to those of younger people,

challenging the belief that older people are unable to mount a potent immune response with this type of treatment.

- Sameer Ghate, PhD, of Novartis, and colleagues compared people with BRAF-positive metastatic melanoma who were treated with either the targeted therapies Tafinalr (dabrafenib) plus Mekinist (trametinib) or the immunotherapies Opdivo plus Yervoy. They found that patients taking the targeted therapy combination were more likely to stop treatment because of disease progression, while those taking the immunotherapy combination were more likely to stop due to side effects.

- Igor Samoylenko, of the Russian Cancer Research Center in Moscow, and colleagues treated patients with cutaneous melanoma using Keytruda or Opdivo injected directly into skin lesions. Patients who responded had more active tumor-infiltrating lymphocytes compared with nonresponders. The treatment was well tolerated, with the most common side effect being injection site pain. The researchers concluded that intralesional immunotherapy is a feasible approach, and response to local treatment might help predict which patients will respond to systemic therapy.

Finally, in related news, a study just published in JAMA Oncology showed that a blood biomarker test may help evaluate response in melanoma patients treated with PD-1 inhibitors.

One of the challenges with immunotherapy is that some people appear to have progressive disease after starting treatment as T cells start to attack the tumor. Because disease progression is often used as a stopping rule, patients may be prematurely taken off treatment that is actually working.

Jenny Lee, MBBS, of Macquarie University in Sydney, and colleagues measured circulating tumor DNA (ctDNA), a biomarker known to predict response and survival in patients with metastatic melanoma treated with PD-1 inhibitors, focusing on BRAF and NRAS mutations.

Out of 125 patients, 29 had apparently progressive disease. Of these, nine were determined to have pseudoprogression and 20 had true progression. Everyone with pseudoprogression had favorable ctDNA profiles, while almost all true progressors had unfavorable profiles. One-year survival rates were 82 percent for patients with favorable ctDNA profiles compared with 39 percent for those with unfavorable profiles.

“The results demonstrate that ctDNA profiles can accurately differentiate pseudoprogression from true progression of disease in patients with melanoma treated with PD-1 antibodies,” the study authors concluded. “Results of this blood test performed at regular intervals during systemic treatment reflect tumor biology and have potential as a powerful biomarker to predict long-term response and survival.”

Click here to read the JAMA Oncology abstract.
