New treatments are improving outcomes in melanoma

Targeted therapy, combination therapies, vaccines, and new treatment modalities demonstrate promising prognoses for melanoma patients.

BY JOHN SCHIESZER

Although the incidence of many common cancers is declining, the incidence of melanoma continues to increase at a rate faster than any of the seven most common cancers. An estimated 70,230 new cases of melanoma will be diagnosed in the United States in 2011, resulting in nearly 8,790 deaths according to the National Cancer Institute (NCI).¹ However, significant advances in the laboratory are translating into new treatments for melanoma and hope that new approaches may soon reduce its morbidity and mortality.

Immunotherapy agents and therapeutic vaccines are changing the way patients with malignant melanoma are counseled and treated. Currently, the American Cancer Society (ACS) estimates the 5-year survival rate for persons with stage IV disease at 15% to 20%.² However, new therapies are demonstrating an ability to improve overall survival for persons with melanoma. This article reviews some of the new developments in melanoma treatment.

TARGETED THERAPY

“Until recently, we’ve had limited options for our patients, and little hope for long-term survival. In the past 2 years, we’ve seen remarkable progress with immunotherapy, and now, a promising targeted therapy,” said Lynn Schuchter, MD, professor of hematology-oncology and division chief at the Abramson Cancer Center at the University of Pennsylvania, Philadelphia.

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A randomized, international phase III trial found that vemurafenib (Zelboraf), which targets the V600E mutation in the BRAF gene, is the first drug to improve overall survival (OS) compared with standard chemotherapy in patients with advanced melanoma. Approximately 50% of all melanomas harbor a V600E mutation in the BRAF gene. Researchers compared the effectiveness of vemurafenib with dacarbazine (DTIC-Dome, generics) in terms of progression-free survival (PFS) and overall survival in 675 patients with previously untreated, inoperable stage IIIC and stage IV metastatic melanoma and a V600E mutation in the BRAF gene.

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In the planned interim analysis at a median of 3 months, the risk of death was reduced by 63% in patients receiving vemurafenib compared with those receiving dacarbazine. The risk of disease progression was reduced by 74% in the vemurafenib group compared with the dacarbazine group. The response rate was robust. The patients in the vemurafenib group had a 48.4% response rate, whereas the response rate was 5.5% in the dacarbazine group. At the first trial interim analysis, investigators recommended that those patients receiving dacarbazine switch to vemurafenib.

“This is really a huge step toward personalized care in melanoma,” said lead study author Paul Chapman, MD, who is an attending physician at Memorial Sloan-Kettering Cancer Center, New York, New York. “This is the first successful melanoma treatment tailored to patients who carry a specific gene mutation in their tumor.”

Chapman said vemurafenib is the first drug to show improved PFS and overall survival rates in this patient population. If approved by the FDA, vemurafenib could become a new standard treatment for patients with melanoma who have this gene mutation.

Fewer than 10% of patients who received vemurafenib experienced problems with high levels of toxicity (grade 3 or higher). The most common adverse effects in the vemurafenib group were diarrhea, rash, alopecia, photosensitivity, fatigue, arthralgia, and keratoacanthoma/skin squamous cell carcinoma. The researchers currently are planning to test vemurafenib in combination with other agents in patients with advanced melanoma. A phase I trial has already begun with vemurafenib and ipilimumab (Yervoy), an immunotherapy that received approval earlier this year.

IMMUNOTHERAPY PLUS CHEMOTHERAPY

Immunotherapy for melanoma patients is becoming an option. First-line treatment with a combination of the immunotherapy drug ipilimumab and dacarbazine has been found to improve OS in patients with previously untreated metastatic melanoma, according to a new phase III randomized study of 502 patients. It is the first to show that combining chemotherapy with immunotherapy is safe and effective in this patient population.

“This trial’s 3-year end point is significant. No randomized trial for metastatic melanoma has followed patients for this long, and it demonstrates the durability of this survival benefit, now out to 3 years in this population, and even 4 years in some cases,” said lead study investigator Jedd Wolchok, MD, who is director of immunotherapy clinical trials and an associate attending physician at Memorial Sloan-Kettering Cancer Center, New York, New York. “It is one of the advantages of immunotherapy. The immune system is a living drug able to adapt itself to changes in the tumor that might otherwise lead to resistance when treated with chemotherapy or a pathway inhibitor.”

Wolchok said these findings are important because melanoma incidence has climbed faster than any other cancer type in the past 30 years in the United States. The researchers randomized patients with metastatic melanoma to ipilimumab plus dacarbazine (n = 250) or dacarbazine and a placebo (n = 252). The overall survival rate for the ipilimumab group was 47.3% at 1 year compared to 36.3% in the dacarbazine alone group. After 2 years, the OS rate was 28.5% for the ipilimumab group compared to 17.9% for the dacarbazine alone group. At 3 years, the OS rate was 20.8% compared to 12.2% for the dacarbazine alone group.

The median OS rate was 11.2 months for patients who received ipilimumab compared to 9.1 months for those in the dacarbazine only group. The median progression-free survival times, however, were very similar (2.8 months versus 2.6 months for the dacarbazine only group). Wolchok attributed this finding to the way ipilimumab may work. The effects of immunotherapy treatment can take much longer to be seen than those from traditional chemotherapy or targeted therapies. He noted that patients may sometimes even get worse before they improve.

Wolchok said the combination of ipilimumab and dacarbazine had a good safety profile. No gastrointestinal perforations were noted and the rate of colitis was lower than expected based on prior studies with ipilimumab alone.
However, approximately 56% of the patients in the ipilimumab group and 27% in the dacarbazine only group had significant grade 3/4 adverse events from their therapy, including elevated liver enzymes.4

**THERAPEUTIC CANCER VACCINE**

Results from a large clinical trial have found that a vaccine combined with interleukin-2 can improve response rate and progression-free survival in patients with metastatic melanoma.5 This marks the first vaccine study in the disease and one of the first in all cancers to show clinical benefit in a randomized phase III clinical trial.

Therapeutic cancer vaccines, unlike typical vaccines that prevent infections, are meant to jump-start the immune system to help it battle existing tumors. In a study involving 21 centers in the United States, researchers randomly assigned 185 patients with metastatic melanoma to either a combination of the peptide vaccine and interleukin-2 (n = 91) or a high dose of interleukin-2 alone (n = 94).5 Currently, the peptide vaccine is only known as gp 100:209–217 (210M). It works through injections that prime the immune system to recognize a protein present on the surface of the melanoma cancer cells. The vaccine activates the body’s cytotoxic T cells to recognize the antigens and seek out and destroy the tumor cells.

The researchers found that 16% of study participants given the vaccine and interleukin-2 saw tumors shrink by 50% or more compared with shrinkage of 6% in the interleukin-2 only group.5 Those in the vaccine group also had slightly longer PFS rates of 2.2 months versus 1.6 months in the interleukin-2 only group.5 Overall, patients given the vaccine lived an average of nearly 7 months longer than those given only interleukin-2 (17.8 months versus 11.1 months).5

“If we can use the body’s own defense system to attack tumor cells, we provide a mechanism for ridding the body of cancer without destroying healthy tissue,” said Howard Kaufman, MD, who is director of the Cancer Center at Rush University, Chicago, Illinois.

In order for this vaccine to work, patients must have a particular tissue type, HLA-A2, which is present in about 50% of all whites. The vaccine, if eventually approved by the FDA, would be relatively inexpensive because it is based on a protein present in most melanoma tumors. Other approved cancer vaccines, such as sipuleucel-T (Provenge) for prostate cancer, have to be created for each individual patient.

“This is one of the first positive, randomized vaccine trials in cancer and the findings represent a significant step forward for treatment of advanced melanoma,” said Kaufman.

Oncology nurses will be playing a much more important role in the treatment and management of patients with metastatic melanoma. It is now possible to identify patients with tumor markers that will predict immune responses. “I think there is no question about it. The targeted therapy and the immunotherapy are now changing the treatment paradigm. We are now in an area of personalized medicine,” Kaufman told Oncology Nurse Advisor. “I see an expanding role for the nurses. In both managing the treatments and side effects, and administering these therapies. The nurses are going to be playing a very important role. They are front and center with a lot of these vaccine approaches.”

Kaufman said oncology nurses can also play a key role in educating patients about these new therapies and what side effects to expect during the course of their treatment.

**COMBINATION THERAPY FOR LATE-STAGE MELANOMA**

Melanoma cells often produce a protein called Grm1, which aids in the growth of the disease. Riluzole (Rilutek, generic), which is FDA approved for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease, has been shown to block Grm1’s action. Recent studies at the Cancer Institute of New Jersey (CINJ) in New Brunswick demonstrated evidence of tumor shrinkage with riluzole in patients with melanoma. This work is based on studies conducted by Suzie Chen, PhD, a research member at CINJ and a professor of chemical biology at Rutgers, The State University of New Jersey.

Sorafenib (Nexavar), already FDA approved for renal cell carcinoma and one form of liver cancer, is considered a targeted therapy shown to slow the spread of cancer cells. Recent laboratory studies at CINJ have shown a more positive effect in the treatment of melanoma with riluzole and sorafenib together than with either drug alone. Currently, a clinical trial is underway to determine safe dosing levels when the drugs are used in combination to treat stage III or IV melanoma.

“By combining riluzole and sorafenib, we have the ability to block different signaling pathways that promote tumor growth. We are investigating whether the combination of
The researchers found the experimental regimen was safe and well tolerated, with minimal systemic toxicity. Biopsy of local treated lesions demonstrated at least 20% clearance of the tumor in 76% of patients, with 100% clearance of the tumor in 34% of patients. The researchers also found at least stable disease or objective (partial or complete) regression in 10 (53%) of 19 patients with distant untreated lesions. In addition, 15% of these patients demonstrated 100% clearance of distant untreated metastatic melanoma tumors.

“This first-in-man study demonstrated that local intratumoral electroporation of DNA IL-12 in melanoma induces systemic immune responses that can stabilize or cause regression of not only local treated but also distant untreated metastatic melanoma tumors,” said principal study investigator Adil Daud, MD, clinical professor of medicine at the University of San Francisco, California.

The researchers conducted additional analysis following their phase I study and found blood markers may predict patients’ response to electroporation of DNA IL-12. Three phase III clinical trials are planned to further assess the efficacy of electroimmunotherapy technology in patients with melanoma.

Blocking the receptor found on the surface of melanoma cells can cause many tumors to shrink and often completely disappear.

The treatment paradigm for melanoma is certainly changing. We are now focusing on improved immunotherapies and therapies that target mutations found only in cancer cells. Melanoma treatments are leading the way in a profound paradigm shift in the treatment of all cancers,” Goydos told Oncology Nurse Advisor. “Nurses play a huge role in the treatment of all cancer patients, but the new immunotherapies and targeted treatments present new challenges to oncology nurses who must contend with a whole new set of toxicities and long-term problems that will face our patients. Nurses are adapting to these changes with their usual efficiency and professional competence.”

ELECTROIMMUNOTHERAPY

Researchers in California are achieving promising results with electroimmunotherapy. In a phase I study, a DNA plasmid encoded to express IL-12 resulted in regression of locally treated lesions as well as distant untreated lesions. Electroimmunotherapy uses a DNA plasmid encoded for IL-12 delivered via electroporation, which enables cellular uptake of the DNA IL-12. Essentially, a jolt of electricity is delivered directly into a melanoma tumor via an applicator the size of an ink pen. Electroimmunotherapy makes the cell wall membrane more porous. IL-12 stimulates the release of T cells and IFN-gamma, and initiates a cascade of events that lead to cancer cell death.

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REFERENCES

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