Stony Brook Medicine

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Transformative Treatments for Metastatic Melanoma *(continued from cover)*

A fourth new drug, **Imlygic™** (T-VEC), isn't a checkpoint inhibitor but rather the first oncolytic viral therapy in the U.S. It is injected directly into subcutaneous metastasis to shrink the tumor (approved October 2015).

In 2015, the FDA approved using ipilimumab and nivolumab concurrently for patients with unresectable or metastatic melanoma who also have the BRAF mutation. This combination has shown a response in the range of 40 to 50 percent with significantly prolonged progression-free survival.

Genetic mutations in melanoma

The majority of melanoma malignancies have mutations in their genome. Several known pathways such as BRAF and MEK have mutated genes that help melanoma grow and spread. In fact, about 50 percent of cutaneous melanomas have a mutation in the BRAF oncogene.

Drugs targeted to specific mutations include two BRAF inhibitors and one MEK inhibitor:

- **Vemurafenib** (Zelboraf®) and **Dabrafenib** (Tafinlar®) are small molecules that bind the ATP-binding site of the tyrosine kinase BRAF. Tumors in roughly 40 percent of patients shrank by half in just a few weeks (approved August 2011 and August 2013 respectively).
- **Trametinib** (Mekinist®) targets the MEK protein, which is downstream from BRAF and encourages cancer growth and survival. Tumor shrinkage was seen in 10 percent of patients (approved 2013).

To more effectively target both the BRAF and MEK pathways, FDA approval was given in May 2014 for the use in two combination therapies — dabrafenib with trametinib and vemurafenib with cobimetnib. Response rates and overall survival increased slightly versus giving the drugs individually.

Although the initial response to these targeted therapies is greater than that from immunotherapy, eventually the response is lost and the cancer begins to grow again. Research teams continue to search for effective solutions with the goal of eventually providing a cure.

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Transformative Treatments for Metastatic Melanoma

Advances in Immunotherapy and Targeted Treatments

The rates of melanoma, the most fatal form of skin cancer, have been steadily rising over the past 30 years. The American Cancer Society predicts there will be more than 76,000 new melanoma diagnoses, and more than 10,000 deaths, in 2016.

When caught early, cutaneous melanoma, the most common form, has a very high cure rate. However, melanoma metastasizes very aggressively, and up to 10 percent of cases aren't caught until lymph nodes or distant organs are involved. Until recently, the prognosis for patients with advanced or metastatic Stage IV melanoma was poor.

A rapid pace in medical oncology breakthroughs

Historically, the normal course of medical oncology treatment for metastatic cutaneous melanoma was chemotherapy with dacarbazine (DTIC), which had a low response and overall survival rate.

Since 2011, the U.S. Food and Drug Administration (FDA) has approved seven new molecular treatments that have shown success against metastatic melanoma. The treatments include targeted therapies that use drugs to destroy or incapacitate molecules that encourage the growth of cancer, and immunotherapy treatments that activate the patient's own immune system to work against melanoma.

Immunotherapeutic checkpoint inhibitor agents

Melanoma has complex pathobiology, and is highly immunogenic, which makes the disease particularly receptive to immunotherapies. Instead of targeting cancer cells directly, immunotherapy activates T cells to recognize and destroy cancer, or enhances the immune system's response to antigens produced by melanoma cells.

In the immune system, there are "checkpoint" proteins in T cells that stop those cells from attacking healthy cells. Melanoma can sometimes use immune checkpoint molecules to trick the immune system into identifying cancer cells as normal cells. Drugs called "checkpoint inhibitors" reactivate T cells to attack cancer.

Three monoclonal antibodies that function as checkpoint inhibitors have been approved by the FDA and are used at Stony Brook for metastatic melanoma.

"Thanks to the ongoing development of scientific breakthroughs and new treatment modalities, patients now have many, many options which were not present in the past,"

– **Andrzej Kudelka, MD**
Medical Oncologist, Stony Brook University Cancer Center

- **Ipilimumab** (Yervoy®) binds to and deactivates the CTLA-4 molecule that stops T cells from attacking melanoma cells. It shrinks metastatic melanoma tumors in approximately 10 to 15 percent of patients and may increase long-term survival by as much as 20 percent (approved March 2011).
- **Pembrolizumab** (Keytruda®) blocks the checkpoint action of PD-1 and activates the immune system to attack tumors. Approximately 20 to 40 percent of patients experience a shrinkage of their melanoma (approved September 2014).
- **Nivolumab** (Opdivo®) is the second anti-PD-1 antibody approved by the FDA for advanced melanoma. Approximately 20 to 40 percent of patients receiving nivolumab experience tumor shrinkage (approved December 2014).

(continued on back cover)

IN THIS ISSUE

Case Study for Melanoma

Evaluation and Diagnosis. In 2015, a 62-year-old female presented with an enlarging and then painful mass on the right lateral chest wall. Pathology revealed malignant melanoma.

Treatment. Pembrolizumab infusions every three weeks.

Prognosis. She had a rapid response as evidenced initially by the reduction of the subcutaneous nodules and reduction in the chest wall pain and size of the chest wall tumor. Imaging studies confirm the initial and continued response (Image 2).

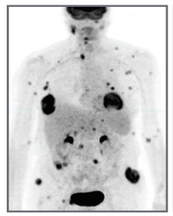


Image 1: *PET maximum projection image (MIP) for staging showed multiple subcutaneous nodules.*

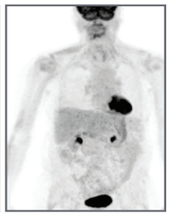


Image 2: *Follow-up PET MIP image obtained five months after the treatment. The larger right chest wall and inguinal lesions disappeared as well as the subcutaneous nodules.*

Message From the Deputy Director

Samuel Ryu, MD
Deputy Director, Clinical Affairs
Stony Brook University Cancer Center

Every day we look for hopeful signs that innovative cancer treatments may someday lead to a cure. Relentless efforts by investigators of immuno-oncology have now resulted in transformative progress in the field.

That's what is happening currently in cancer treatment, metastatic melanoma in particular. Breakthroughs in advanced checkpoint blockade immunotherapy are leading to previously unseen results even in advanced cases. We've had patients with extensive melanoma metastases whose tumors start disappearing after just a short period of treatment with longer survival rates.

Close inter-disciplinary collaboration between basic scientists and clinicians is key to these breakthroughs. The researchers at Stony Brook work to identify treatable targets and translate these into innovative clinical trials. Clinical results then inform further refinement of agents to achieve better, longer-lasting clinical outcomes with fewer side effects.

The biggest advances, as discussed in this issue, are the targeted immuno-therapeutic agents, as well as drugs that target specific genetic mutations in melanoma malignancies, used in combination with other advanced oncological methods. With research and translational clinical trials, our goal of eradicating cancer seems more in reach than ever.

As always, I invite you to call me to discuss any aspect of the Cancer Center. You can contact me at (631) 444-2200.

Did You Know?

After age 50, melanoma is more common in men. Before age 50 it is seen more in women, and melanoma is one of the most common cancers in women under 30. Melanoma can also occur in young children with a family history of melanoma, according to cancer.org.

Advanced Treatments for Skin Cancers Delivered in a Multispecialty Setting

For patients with all types of skin cancers, Stony Brook University Cancer Center offers a comprehensive range of diagnostic, treatment and follow-up services, including expedited diagnosis and technologically advanced radiation, surgical and systemic (chemotherapy, hormonal therapy, targeted drugs and immunotherapy) therapies. Exceptional clinical support services contribute to the coordinated care.

Each year, more than five million cases of skin cancer are diagnosed in the U.S. About 80 percent are basal cell carcinoma, 16 percent are squamous cell carcinoma, and 4 percent are melanoma. Other rarer types of skin cancer account for less than one percent of diagnoses.

Skin cancer is among the top five malignancies treated at Stony Brook University Cancer Center, and it is the major referral center for patients with melanoma in Suffolk County. Patients with skin cancer are treated by a multidisciplinary team of oncology surgeons, dermatologists, pathologists, radiation oncologists, medical oncologists, plastic surgeons and a nurse navigator. Tara L. Huston, MD, FACS, is Team Leader of the Melanoma Management Team.

Diagnosis and Treatment Modalities

Although melanoma accounts for 75 percent of skin cancer deaths, the five-year survival rate is 98 percent when it's diagnosed and treated before it metastasizes.

Lesions that meet even one of the ABCDE criteria (**A**symmetry; irregular **B**orders; **C**olor variation; a **D**iameter greater than 6 mm; and **E**volution, or any change in a mole, including itching or bleeding) warrant evaluation by a board-certified dermatologist. Dermatologists are not only trained to perform thorough total body skin exams, they regularly utilize advanced diagnostic methods, including dermoscopy to determine what should be biopsied. Dermoscopy is the use of a skin surface microscope to better characterize pigmented lesions. It cannot only better identify lesions, which should be biopsied, but it can also help to decrease unnecessary biopsies that result in increased cost and possible scarring.

For diagnosis, dermatologists can choose from multiple biopsy techniques depending on the characteristics of the tumor. Excisional biopsy, if feasible, is generally preferred and may sometimes remove the entire tumor. If metastasis is suspected, other types of biopsies, possibly of multiple sites, may be required.

Surgical and adjuvant treatments

For locally advanced disease or metastatic disease, most patients need surgery along with adjuvant radiation or chemoradiation.

Wide excision of the primary tumor along with a margin of normal skin is the standard of care for early melanoma. At Stony Brook, surgeons use minimally invasive surgical techniques when possible and perform procedures on an outpatient basis for the patient's convenience.

If pathology identifies malignant cells in the margins, additional surgery may be necessary and, depending on the size, location and thickness of the cancer, a sentinel node biopsy may also be recommended.

- If malignancy is found in a sentinel lymph node, a completion lymph node dissection, which surgically removes all lymph nodes near the cancer, may be offered.
- Adjuvant high-dose interferon treatment may be recommended to help lower the risk of recurrence.
- A current National Cancer Institute (NCI) study is comparing the disease-free survival rates of high-dose interferon versus high-dose ipilimumab. Final results have not been published yet.

Postoperatively, patients with stage III or IV melanoma may also receive one or more additional treatments including radiation, vaccine injection, chemotherapy, targeted therapy, immunotherapy and often combinations of modalities. Several of these are described in the cover article on metastatic melanoma.

Five-year follow up

At Stony Brook, patients who have been treated for early stage melanoma are carefully surveilled for many years to help ensure that recurring or new disease is spotted early. For the first two years, when recurrence risk is highest, patients return every three months for total body scans. For the next three years, they return every six months. At year five, the follow-up visits become annual if no new lesions have been found. ■

Treatments for Basal Cell and Squamous Cell Carcinomas

Basal cell and squamous cell cancers are caused by exposure to ultraviolet rays from the sun and tanning booths. The cancers develop primarily, but not exclusively, on areas of the body that are exposed to the sun, and even dark-skinned individuals can get them.

Basal cell cancers tend to grow slowly and rarely metastasize, though if untreated, the cancer can spread to nearby areas, including bone and other tissues. Squamous cell carcinomas are somewhat more likely than basal cell to affect deeper layers of the skin and to spread to other parts of the body, though it doesn't happen often. Both types can be caught early and generally respond well to treatment.

Basal and squamous cell cancers

Diagnosis is done by skin biopsy, or by incisional or excisional biopsies. Depending on the size and location of the tumor, a wide local excision may be the only treatment needed. Non-melanoma skin cancers may occasionally spread into nearby lymph nodes. Lymph node biopsies can be done surgically or via fine needle aspiration (FNA).

Treatment modalities

Many basal and squamous cell skin cancers are treated in dermatologists' offices, though advanced or recurrent carcinomas may require additional treatments.

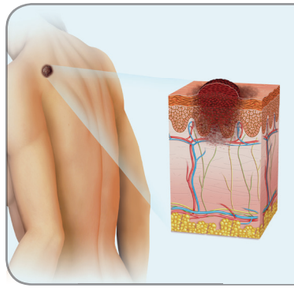
- Surgical excision of the tumor and surrounding skin may be needed.
- Cancers confined to the top layer of skin may be treated by curettage — scraping the lesion with a curette — followed by electrodessication, which destroys remaining malignant cells with an electrode.
- Radiation therapy may be used after surgery or as the only treatment for large tumors that aren't resectable, or for patients who are not good surgical candidates.

Mohs surgery

Mohs micrographic surgery (MMS) is highly complex microscopically controlled surgery done by a specially trained surgeon. It is considered to have a very high cure rate for basal cell and squamous cell skin cancers.

With this procedure, the surgeon removes thin slices of tissue from the tumor and the tumor margins. The tissue is immediately frozen, then stained and examined under a microscope. If cancer cells are visible, another thin slice is removed, frozen, stained and examined. The process is repeated until no cancer is seen.

This technique combines complete removal of the skin cancer with excellent preservation of normal skin. However, the surgery can take many hours and is very expensive, so guidelines have been developed outlining the type and size of skin cancers best suited to this procedure. ■



Risk Factors for Melanoma

According to the National Cancer Institute, the risk factors for melanoma include the following:

- Fair skin that burns easily
- High lifetime exposure to natural or artificial sunlight
- History of blistering sunburns (particularly at a young age)
- Many common moles
- Personal or family history of dysplastic nevi or melanoma
- Being white

PHYSICIANS:
To discuss your patient's case, refer a patient or to learn more, call the Melanoma Management Team at (631) 444-1244.

Focus On Clinical Trials and Research

Current Clinical Trials for Melanoma

Opportunities for patients to participate in clinical trials are an important part of the skin cancer program. Two current trials are described here:

MSLT-II — A Phase III Multicenter Randomized Trial of Sentinel Lymphadenectomy and Complete Lymph Node Dissection Versus Sentinel Lymphadenectomy Alone in Cutaneous Melanoma Patients with Molecular or Histopathological Evidence of Metastases in the Sentinel Node

Stony Brook and National PI: Tara L. Huston, MD
In collaboration with: National Institutes of Health (NIH) and National Cancer Institute (NCI)

This ongoing interventional study is evaluating the role of lymph node surgery in patients with melanoma to determine the optimum protocol. It is investigating if completion lymph node dissection (CLND) is necessary when the sentinel node is positive. After receiving sentinel lymphadectomy, participants are randomized to receive either CLND or to not receive CLND and be monitored with nodal ultrasound. Subjects are followed for 10 years to compare overall survival, disease-free survival and recurrence rates. Recruitment is complete and awaiting results.

Clinical Trial ECOG 1609: A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High-Dose Interferon a-2b for Resected High-Risk Melanoma

Stony Brook PI: Andrzej Kudelka, MD
Sponsor: National Cancer Institute

This randomized phase III trial studies the efficacy of ipilimumab versus high-dose interferon alfa-2b in treating patients with high-risk stage III-IV melanoma that has been resected. Monoclonal antibodies, such as ipilimumab, may interfere with the ability of tumor cells to grow and spread. Interferon alfa-2b may interfere with the growth of tumor cells and slow cancer growth. Primary outcome measures are overall survival and recurrence-free survival over 20 years. Results are not yet known.

Upcoming Trial

A randomized study sponsored by the National Cancer Institute aims to determine if a patient with metastatic melanoma should be treated with molecular agents followed by immune checkpoint inhibitors, or if the reverse sequence is more effective.

To contact the Office of Clinical Trials, call (631) 638-0846.