TREATMENT OF

ADVANCED MELANOMA

This continuing pharmacy education discussion guide is part of an educational initiative designed to provide pharmacists with timely education and resources for treating patients with advanced melanoma.

For additional resources on this topic, visit www.cemidday.com

The estimated time to complete this activity is 60 minutes. This activity is provided free of charge and is available from March 15, 2015, to May 15, 2016.

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Target Audience

This continuing pharmacy education activity was planned to meet the needs of pharmacists in a variety of practice settings, including large and small health systems, ambulatory care clinics, managed care organizations, and academia. The activity is particularly beneficial for pharmacists, clinical specialists, managers, leaders, and educators who are interested in melanoma.

Learning Objectives

After participating in this knowledge-based educational activity, participants should be able to

- Review the economic impact, epidemiology, patient presentation, diagnosis, staging, and prognosis of melanoma.
- Describe the pathogenesis of melanoma, including the role of genetic mutations and the immune system.
- Compare and contrast the mechanisms of action, indications, dosing, efficacy, and safety of various new and emerging immunotherapies and targeted therapies for advanced melanoma, including combination therapy.
- Recommend drug therapy for a patient with advanced melanoma, taking into consideration the results of tests for genetic mutations and prior treatment, if any.

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TREATMENT OF ADVANCED MELANOMA

Executive Summary

Nearly 5 million Americans are treated for skin cancer at an estimated cost of $8.1 billion each year. Melanoma accounts for the majority of skin cancer deaths but less than 2% of skin cancer cases. The incidence of melanoma in the United States has increased over the past three decades. Melanoma has been attributed to a combination of environmental and genetic factors, including exposure to ultraviolet radiation and mutations in genes associated with cellular proliferation, differentiation, and apoptosis. Melanoma may be suspected based on the characteristic location and appearance of lesions but diagnosis involves biopsy of tissue samples from lesions and if regional or distant spread is suspected, sentinel lymph nodes. The prognosis depends on lymph node involvement, tumor thickness, and other factors used in staging the disease. Improvements in survival of patients with melanoma have been observed in recent years largely because of the development of new immunotherapies and targeted therapies. The adverse event profiles of these new therapies differ from those of conventional chemotherapy. Resistance often emerges to some of the new therapies for advanced melanoma, resulting in relapse. Combination therapy may prove useful for overcoming resistance and providing additive antitumor activity. The optimal therapeutic regimen for advanced melanoma remains to be determined as additional experience is gained. Pharmacists can play an important role in evaluating clinical research findings of the efficacy and safety of new and emerging drug therapies, making recommendations for formulary inclusion of new products, and advising other health care professionals and patients about the proper use of and management of toxicity from new drug therapies.

Introduction

Melanoma (also referred to as malignant melanoma and cutaneous melanoma) is a cancer of melanocytes, the cells that form the dark pigment in skin (melanin). In 2015, melanoma will be responsible for an estimated 9940 deaths in the United States.[1] Other types of skin cancer (e.g., basal cell and squamous cell cancers) are far more common than melanoma but they rarely are invasive and they are treated differently from melanoma.[2]

Melanoma has a substantial economic impact in the United States. Approximately $3.3 billion is spent annually to treat melanoma.[3] The estimated annual cost of lost workdays and days of restricted activity due to melanoma is $29.4 million.[3] An average of 20.4 years of life are lost due to premature death from melanoma.[3] The estimated cost of the lost productivity associated with these years amounts to $3.5 billion.[3]

Reflective Question

To what extent does melanoma impact the patient population served by your institution? How substantial is the economic impact?

Epidemiology

In 2015, approximately 73,870 new cases of melanoma will be diagnosed in the United States.[1] Melanoma is the fifth most common cause of new cases of cancer in American men and the seventh most common cause of new cases of cancer in American women.[1] Melanoma is the third most common type of cancer in adolescents and young adults 15-39 years of age, and it is particularly common among young white women.[3]

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The incidence of melanoma has increased progressively over the past 30 years in the United States, with an annual increase of 2.6% between 2007 and 2011 among persons 50 years of age or older.[1] The risk for melanoma increases with age. The median age at the time of diagnosis is 61.[2] Women are at greater risk for melanoma than men until the age of 50 but the risk in men is twofold higher than in women by the age of 65 and threefold higher than in women by the age of 80.[1] The lifetime risk for melanoma is 2% in whites, 0.5% in Hispanics, and 0.1% in blacks.[2]

Exposure to ultraviolet (UV) radiation from sunlight or artificial sources (e.g., tanning beds, sun lamps) is a major risk factor for melanoma (Table 1) because it causes damage to DNA in melanocytes. Up to 9 out of 10 cases of melanoma are attributed to UV radiation.[3] Intermittent extreme sun exposure increases the risk for melanoma to a greater extent than chronic low-level exposure.[7] Experiencing frequent or severe (especially blistering) sunburns increases the risk for melanoma as a result of unrepaired damage to DNA in melanocytes, especially when sunburns occur at a young age (childhood or adolescence). The risk due to sunburn is increased in children to a greater extent than in adolescents who are at greater risk than adults with sunburns.[3] Persons with fair skin that burns or freckles readily are at high risk for melanoma, especially if they have red or blond hair and blue or green eyes.[2]

Heredity plays a role in melanoma. A family history of melanoma is a major risk factor for the disease. Approximately 10% of patients with melanoma have a family history of the disease.[2] The presence of melanoma in a first-degree relative increases the risk for the disease by 50%.[5]

A personal history of melanoma is a risk factor for the disease. Approximately 5% of persons with a personal history of melanoma will develop a second melanoma unrelated to the first.[2]

Table 1
Melanoma Risk Factors[1-6]

- Exposure to ultraviolet radiation
- Personal or family history of melanoma
- Advanced age
- Male sex
- Xeroderma pigmentosum[a]
- Fair skin
- Presence of atypical, large (>6 mm diameter), or numerous (>50) moles
- Dysplastic nevi
- Immune suppression

[a]Xeroderma pigmentosum is a rare, inherited condition resulting from a defect in the gene encoding an enzyme that repairs damage to DNA.

The presence of atypical, large, or numerous (>50) moles increases the risk for melanoma.[4] Benign moles (also referred to as nevi) are evenly-colored brown, tan, or black blemishes often referred to as "beauty marks" that appear on the skin in the early decades of life.[2,5] They may be flat or raised and round or oval but they usually are less than 6 mm in diameter.[2] Dysplastic nevi are larger than other moles and have an atypical (i.e., irregular) shape or color. Dysplastic nevi are benign but they may be precursors to melanoma. The larger the number of dysplastic nevi, the greater the risk for melanoma.[8] The risk for melanoma is 12 times higher in patients with 10 or more dysplastic nevi than in the general population.[8] Dysplastic nevi are found in 2% to 8% of Caucasians.[8]

Persons with a weakened immune system due to certain diseases (e.g., HIV infection), conditions (e.g., organ transplantation), or medications (e.g., cancer chemotherapy) are at increased risk for melanoma.[1,4]

Natural History

Melanocytes are found in the epidermis, the outermost layer of the skin that protects the body from the environment.[9] The epidermis is separated from the deeper dermis by the basement membrane. The dermis regulates body temperature, supplies the epidermis with nutrients, and contains blood and lymphatic vessels. It comprises the upper papillary dermis and the deeper denser reticular dermis.

Melanoma is the result of rapid and excessive proliferation of abnormal melanocytes due to unrepaired DNA damage (often caused by exposure to UV radiation) or mutations affecting oncogenes, tumor suppressor genes, and signaling pathways that control cellular proliferation. The Clark model is used to describe the histologic changes involved in malignant transformation of healthy melanocytes.[7] The first step, benign nevus, involves the proliferation of structurally normal melanocytes leading to formation of a benign nevus in the epidermis, with limited growth. The second step, dysplastic nevus, may arise from a benign nevus or as a new lesion. It involves aberrant growth of dysplastic cells with random atypia (structural abnormality) resulting in a dysplastic nevus. These lesions are characterized by asymmetry, irregular borders, multiple colors, and an increased diameter. This step is considered premalignant.

The third step of the Clark model, the radial-growth phase, is characterized by unlimited hyperplasia and decreased differentiation.[10] Genetic mutations are detected in this phase. The fourth step, the vertical-growth phase, is characterized by invasiveness, with tumor formation and expansion through the basement membrane into the deeper dermis. In the fifth phase, metastatic melanoma, tumor migration and invasion of blood vessels and the lymphatic system result in spread to distant sites. The liver, lungs, and brain are common sites of metastasis.

Melanoma is probably the result of a combination of genetic and environmental factors. It has been attributed in part to multiple mutations in genes associated with cellular proliferation, differentiation, and apoptosis (Table 2). Genetic mutations (e.g., BRAF, NRAS, KIT) have been found in nearly 70% of patients with melanoma.[11] Mutations in BRAF and NRAS are found in approximately 50% and 20% of melanomas arising from skin without chronic sun damage, respectively.[11]

Table 2
Role of Genetic Mutations in Melanoma[11]

Site	Genetic Mutation Prevalence
Arising from skin without chronic sun damage	BRAF 50% NRAS 20% KIT 0%
Arising from skin with chronic sun damage	BRAF 10% NRAS 10% KIT 2%
Arising from mucosal surfaces	BRAF 5% NRAS 15% KIT 20%
Arising from acral surfaces	BRAF 15% NRAS 15% KIT 15%
Uveal melanoma	GNAQ 25% GNA11 55%

Whether genetic mutation leads to invasive malignancy depends in part on the ability of tumor cells to evade the endogenous immune response to cancer, which involves a complex array of cellular and humoral surveillance activities designed to detect antigens associated with tumor cells, differentiate these cells from healthy host cells, and eradicate tumor cells. Activation of T cells with antitumor activity plays an important role in preventing malignant transformation. The endogenous immune system

has escape mechanisms designed to avoid an autoimmune response, and these escape mechanisms may be hijacked by tumor cells to serve as inhibitory checkpoints, circumvent the immune response to tumor cells, and allow tumor cell proliferation.[12]

Cytotoxic T-lymphocyte antigen (CTLA)-4 is an important inhibitory checkpoint because it reduces T-cell activation and antitumor activity.[13] The major histocompatibility complex presents antigens on tumor cells to T cells.[12] Costimulatory B7 molecules on antigen-presenting cells (APCs) bind to either CD28 or CTLA-4 on T cells, causing T-cell activation or inhibition, respectively.[12] Drug therapies that inhibit CTLA-4 have been developed to hinder T-cell inhibition, thereby allowing T-cell activation and antitumor activity to predominate.

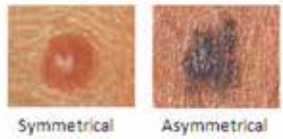
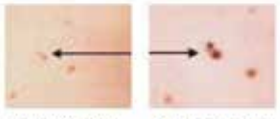
The programmed cell death protein-1 (PD-1) is an inhibitory T-cell receptor involved in another immunoregulatory pathway that affects tumor cell survival.[12,14] There are two known ligands for PD-1: PD-L1 and PD-L2.[12] These ligands are expressed on melanoma cells as well as APCs. Drug therapies that inhibit PD-1 or PD-L1 have been developed to reduce T-cell inhibition (i.e., activate T cells to serve as anticancer effector cells).

Patient Presentation

Melanoma lesions can appear anywhere but they typically appear on the torso in men and the legs in women.[3] The lesions usually are brown or black due to the presence of melanin, but they may be tan, pink, or white.[2] The neck and face are other common sites for melanoma lesions.[2] Melanoma lesions on the palms of the hands or soles of the feet (referred to as acral surfaces) are uncommon in whites (<10% of melanomas) but comprise more than half of the melanomas seen in African Americans.[2] Acral surface involvement suggests a role for factors other than exposure to UV radiation in the pathogenesis of melanoma.[3] Involvement of the mucosal surfaces of the mouth and genital and anal areas is less common than the skin.[2] Intraocular (i.e., uveal) melanoma is rare.[15]

The ABCDE rule (Table 3) can be used to evaluate a mole for possible melanoma. Other warning signs of melanoma include a sore that does not heal, the spread of pigment from the border of a mole to surrounding skin, erythema or new edema beyond the border, a change in sensation (e.g., pruritus, tenderness, pain), a change in the surface of a mole (e.g., scaliness, oozing, bleeding), and the appearance of a bump or nodule.[2]

Table 3
ABCDE Rule for Evaluating Moles[2,16]

Asymmetry One side does not match the other.	 Symmetrical Asymmetrical
Border The edges are irregular instead of even	 Borders are even Borders are uneven
Color The color is not uniform, and more than one color is present instead of just one color.	 One Color Multiple Colors
Diameter It is more than 6 mm (~¼ inch) in diameter or the size of a pencil eraser instead of smaller.	 Smaller than ¼ inch Larger than ¼ inch
Evolving It is changing in size, shape, or color.	 Ordinary Mole Changing in size, shape and color

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Diagnostic Work Up

In patients with suspected melanoma, biopsies are essential to obtain tissue samples for pathologic evaluation to confirm the diagnosis of melanoma and provide the information needed for staging and making therapeutic decisions, including the presence of genetic mutations in patients with metastatic disease.[17] An excisional biopsy with 1- to 3-mm margins is preferred, but it may not be feasible because of a large size or the location of the lesion (e.g., on the face, palms, or feet). Full thickness incisional or punch biopsy of the thickest part of the lesion is an acceptable alternative in these cases.

Lymph node involvement is an important prognostic factor in patients with melanoma.[18] In the past, complete lymph node dissection (CLND) was the only intervention available to detect metastasis in patients with suspected regional lymph node involvement, and it was used for patients with intermediate thickness tumors (i.e., 1 mm or greater).[19] However, CLND is labor intensive, and it may result in false-negative results because it involves staining only a portion of the tissue sample.[20] Moreover, only one in five patients with intermediate thickness tumors has lymph node involvement, and CLND is associated with acute and chronic morbidity (e.g., wound problems, nerve injury, lymphedema, complications from anesthesia) in four out of five patients.[20] Because dissemination of melanoma to the lymph nodes follows a predictable pattern, sentinel lymph node biopsy is now used as an alternative to CLND in patients with suspected lymph node involvement. If the sentinel lymph node biopsy results are positive, CLND is performed for lymph nodes in the region.[2]

Additional elements of the diagnostic work up include a history and physical examination, further dermatologic examination for other lesions, and for patients with tumors that are more than 1 mm deep, radiographic evaluation (e.g., chest, abdominal, or pelvic computed tomographic scans; brain magnetic resonance imaging; positron emission tomography scans) to establish a baseline and evaluate specific signs and symptoms.[17]

The pathology report for the tumor sample includes the Clark level of invasion, which reflects the extent to which the tumor has invaded through the layers of the skin (Table 4). The Clark level of invasion is a prognostic factor used only for melanomas that are less than 1 mm deep.[21]

Table 4
Clark Level of Invasion in Melanoma[21]

Level I:	Confined to the epidermis, above the basement membrane (in situ)
Level II:	Invades the papillary dermis, below the basement membrane
Level III:	Fills the papillary dermis and extends to the interface between the papillary and reticular dermis
Level IV:	Invades the reticular dermis
Level V:	Invades the subcutaneous tissue (i.e., has metastasized)

The tumor thickness as defined by the Breslow depth of invasion is the most important prognostic factor in patients with melanoma.[21] Increased tumor thickness correlates with metastasis and a poor prognosis (short survival) compared with thinner tumors.[18] The Breslow thickness is measured directly using a micrometer and classified in one of four levels that roughly correspond to the Clark level of invasion:[21]

- ≤0.75 mm (Clark level II)
- 0.76-1.5 mm (Clark level III)
- 1.51-4 mm (Clark level IV)
- ≥4 mm (Clark level V)

The pathology report also provides information about the presence of ulceration and the dermal mitotic rate.[17] The presence of ulceration is the second most important prognostic factor in patients with melanoma.[21] The prognosis is worse when ulceration is present than when no ulceration is present. A high mitotic rate is associated with tumor proliferation and poor survival.[17]

The serum concentration of lactate dehydrogenase (LDH) is measured in patients with metastatic disease because elevated levels are associated with a worse prognosis compared with normal LDH levels.[2] Testing for mutations in BRAF (at a minimum) is now a standard part of the diagnostic work up for patients with metastatic disease.

Staging

Melanoma is staged on the basis of the Breslow thickness; Clark level (if 1 mm or less in diameter and the mitotic rate is not available); the presence of ulceration, nodal involvement, and distant metastasis; and if metastases are present, the serum LDH concentration (Table 5).[17,22] Staging correlates with 5-year survival rates and is used to guide treatment.[19] Melanoma is highly curable if it is diagnosed at an early stage, with a 5-year survival rate of 92% to 97% in 2008 for patients with stage I disease.[2] The prognosis is worse for patients with regional involvement or metastatic disease, with 5-year survival rates of 53% to 81% for stage II disease, 40% to 78% for stage III disease, and 15% to 20% for stage IV disease in 2008. The overall 5-year survival rate of all patients with melanoma improved substantially between 1975-1977 (82%) and 2004-2010 (93%).[1]

Table 5
Melanoma Staging[17,22]

Stage 0:	confined to epidermis (in situ)
Stage I:	1 mm or less in diameter, without nodal involvement or metastases (stage IA without ulceration, stage IB with ulceration)
Stage II:	>1 mm diameter, without nodal involvement or metastases
Stage III:	any size tumor with nodal involvement but no metastases
Stage IV:	with metastases • Stage M1a for distal skin, subcutaneous, or nodal metastases and normal LDH level, • Stage M1b for lung metastases and normal LDH, • Stage M1c for all other visceral metastases with normal LDH or any distant metastases with elevated LDH

Prevention

Because exposure to UV radiation is a major risk factor for melanoma, strategies to reduce exposure (e.g., the use of sunscreen products and protective clothing and sunglasses, avoiding outdoor activities at times of day when UV radiation is strongest, seeking shade, avoiding tanning beds and sun lamps) play an important role in preventing melanoma.[3,23] The

advantages of minimizing UV radiation exposure must be weighed against the benefits of UV radiation for preventing vitamin D deficiency. The appendix to this discussion guide lists resources for use in educating patients about melanoma, its risk factors and symptoms (e.g., the ABCDEs), and ways to reduce UV radiation exposure. Increasing the proportion of adolescents in grades 9-12 and adults 18 years of age and older who participate in behaviors that reduce their exposure to harmful UV radiation and avoid sunburn and reducing the death rate from melanoma by 10% are among the Healthy People 2020 goals for improving the health of Americans.[24]

Reflective Question

Does your institution have a formal or informal outreach program to provide patient education about the need for skin cancer prevention and early detection?

Treatment

Surgical excision is the primary treatment for melanoma, and it may suffice alone for early-stage disease.[17] However, advanced disease often is unresectable. Surgery often serves only a palliative role in patients with metastatic melanoma.[2] Radiation therapy also may be used for palliation in patients with metastatic disease.[17]

Adjuvant high-dose interferon alfa for 1 year or peginterferon alfa-2b for up to 5 years is sometimes used for selected patients with stage II or III disease because it has been shown to improve disease-free survival, but its impact on overall survival is unclear.[17] Conventional chemotherapy (e.g., dacarbazine, which was the standard of care in the past; paclitaxel with or without carboplatin) has been used in patients with metastatic disease but response rates are less than 20%.[17] Adding immunotherapies (i.e., interferon alfa or interleukin-2 [IL-2]) to chemotherapy improves response rates in patients with metastatic melanoma, but the risk for toxicity is increased and survival rates remain low.[17] Nevertheless, a small subset of patients with metastatic melanoma (6%) experience a durable response to high-dose IL-2 and can be considered cured after 2.5 years.[25] However, high-dose IL-2 is impractical because it must be administered on an inpatient basis and it is associated with substantial toxicity. Identifying the subset of patients with metastatic melanoma who will respond to high-dose IL-2 remains a challenge.

The current approach to treating advanced melanoma depends largely on the presence of the BRAF mutation.[17] BRAF (and NRAS) are components of the RAS-RAF-mitogen-activated protein (MAP) kinase-extracellular signal regulated kinase (ERK) signaling pathway. This RAS-RAF-MEK-ERK pathway plays a vital role in cellular proliferation, differentiation, and survival, although pathway abnormalities contribute to malignancy in only a subset of patients with melanoma.[26] The most common BRAF mutation results in alteration of the amino acid valine at the 600 base pair location.[11] Up to 90% of these BRAF mutations involve replacement of the amino acid valine with glutamic acid (V600E) and 5% to 12% involve replacement of valine with lysine (V600K).[11,27] The BRAF and NRAS mutations up regulate the RAS-RAF-MEK-ERK pathway so that activation of downstream components and tumor cell proliferation can occur despite the absence of upstream signals (e.g., growth factors).[11] Targeted inhibitors of BRAF or MEK have been developed with antitumor activity.

If the patient is BRAF V600 mutation-positive, targeted therapy with the BRAF inhibitor vemurafenib, BRAF inhibitor dabrafenib, or a combination of

dabrafenib plus the MEK inhibitor trametinib may be used. Immunotherapy (e.g., high-dose IL-2, the CTLA-4 inhibitor ipilimumab, and in patients with disease progression following ipilimumab and a BRAF inhibitor, the PD-1 inhibitor pembrolizumab or nivolumab) or enrolling in a clinical trial is an alternative for these patients.

If the patient is BRAF V600 mutation-negative, ipilimumab or either of the two PD-1 inhibitors pembrolizumab or nivolumab should be considered, with high-dose IL-2 or participation in a clinical trial as alternatives. In guidelines released by the National Comprehensive Cancer Network, ipilimumab, pembrolizumab, and nivolumab are among the preferred options for treatment of advanced or metastatic melanoma, although these PD-1 inhibitors are approved by the Food and Drug Administration (FDA) for patients with disease progression after treatment with ipilumumab.[17] The tyrosine kinase inhibitor, imatinib, is used for the rare KIT-mutated tumors.[17,28]

Ipilimumab, a human CTLA-4-blocking antibody, was approved by FDA in 2011 for the treatment of patients with unresectable or metastatic melanoma.[29] Table 6 provides information about the FDA-approved indications, usual dosage, common adverse events, and cautions associated with ipilimumab and other new and emerging immune checkpoint inhibitors for advanced melanoma. Approval of ipilimumab was based in part on the results of a phase 3, randomized, double-blind, controlled study of 676 patients with unresectable or metastatic melanoma whose disease had progressed despite treatment.[35] Improved overall survival was demonstrated from the use of ipilimumab compared with use of a glycoprotein 100 (gp100) peptide cancer vaccine that induces immune responses but has limited antitumor activity. The median overall survival was 10.1 months with ipilimumab and 6.4 months with the gp100 vaccine (p=0.003). Improved overall survival also was demonstrated in another phase 3, randomized, double-blind, placebo-controlled study in which ipilimumab was used with dacarbazine in 502 previously untreated patients with metastatic melanoma.[36] Compared with placebo plus dacarbazine, the overall survival rate with ipilimumab plus dacarbazine was 47.3% (vs. 36.3%) after 1 year, 28.5% (vs. 17.9%) after 2 years, and 20.8% (vs. 12.2%) after 3 years (p<0.001).

The most common adverse events in patients receiving ipilimumab are immune-related due to T-cell activation, and these events involve the gastrointestinal (GI) tract (especially diarrhea), skin (e.g., pruritus, rash), liver (liver enzyme elevations), or endocrine system (e.g., hypophysitis, with headache, nausea, vertigo, behavior change, visual disturbances, and weakness).[35-37] These immune-mediated adverse events usually are delayed and follow a pattern, with dermatologic adverse events manifesting 2 to 3 weeks after initiating therapy, GI and hepatic adverse events after 6 to 7 weeks of therapy, and endocrinologic adverse events after 9 weeks of therapy.[37] Life-threatening immune-mediated enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy can occur.[29] An adverse reaction management guide for health care providers has been developed as part of an FDA-approved risk evaluation and mitigation strategy (REMS) program.[30] Patients should be educated to notify their health care provider at the first sign of side effects because the severity can escalate quickly if medical attention is not obtained promptly.

Pembrolizumab, a human PD-1 blocking antibody formerly known as lambrolizumab, was approved in 2014 by FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor.[34]

Approval by FDA was based in part on the results of a study of 135 patients with advanced melanoma, including patients with prior ipilimumab, BRAF inhibitor, or other treatment.[38] The response rate was 38%, and it was not affected by prior treatment. The response was durable after a median follow up time of 11 months in most (81%) patients experiencing a response. The overall median progression-free survival time was more than 7 months. Fatigue, rash, pruritus, and diarrhea were the most common adverse events. Other immune-mediated adverse events can occur (Table 6).

In late 2014, the PD-1 inhibitor nivolumab (formerly known as BMS-936558) was approved by FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor.[31] The efficacy and safety of nivolumab were evaluated in a phase 1 dose-escalation study of

Table 6
New and Emerging Drug Therapies for Advanced Melanoma–Immune Checkpoint Inhibitors[29-34,a]

Drug	FDA-Approved Indication	Usual Dosage	Common Adverse Events[b]	Cautions[b]
CTLA-4 Inhibitor				
Ipilimumab (fully human IgG1 monoclonal antibody)	Treatment of patients with unresectable or metastatic melanoma	3 mg/kg i.v. over 90 min every 3 weeks for 4 doses	Diarrhea, pruritus, rash, and liver enzyme elevations	Immune-mediated enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy[c]
PD-1 Inhibitors				
Nivolumab (fully human IgG4 monoclonal antibody)	Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor	3 mg/kg i.v. over 60 min every 2 weeks until disease progression or unacceptable toxicity	Fatigue, rash, pruritus, diarrhea, and nausea	Immune-mediated pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, and hyperthyroidism or hypothyroidism
Pembrolizumab (humanized IgG4 monoclonal antibody)	Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor	2 mg/kg i.v. over 30 min every 3 weeks until disease progression or unacceptable toxicity	Fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea	Immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism or hypothyroidism

CTLA = cytotoxic T-lymphocyte antigen; FDA = Food and Drug Administration; i.v. = intravenously; PD = programmed death

[a] The sequence of agents listed in this table does not reflect preferences for treating advanced melanoma.

[b] Please consult the full prescribing information for additional details about potential adverse events and warnings. All agents listed in this table can cause embryo-fetal toxicity.

[c] Ipilimumab is subject to FDA risk evaluation and mitigation strategy requirements.

patients with advanced malignancies, including 94 patients with advanced melanoma.[33] Prior systemic therapy was required but prior treatment with antibodies that modulate T-cell function (i.e., anti-CTLA-4, anti-PD-1, or anti-PD-L1 therapy) was an exclusion criterion. An objective response rate (i.e., rate of complete responses and partial responses) of 28% was observed in patients with advanced melanoma. No maximum tolerated dose was found. Thirteen (72%) of 18 patients with melanoma and an objective response who were treated for 1 year or longer had a durable response. Tumor samples were analyzed for PD-L1 expression on the cell surface using immunohistochemistry, and the results were predictive of a response in patients with various types of malignancy, including advanced melanoma. An objective response was observed in none of the 17 tumor samples that were negative for PD-L1 expression and 9 of 25 tumor samples that were positive for PD-L1 expression. In another analysis of 107 patients with treatment-refractory advanced melanoma who received nivolumab, the 1- and 2-year survival rates were 62% and 43%, respectively.[39] Common treatment-related adverse events included fatigue, rash, and diarrhea.[33,39] Other immune-mediated adverse events can occur (Table 6).

In a phase 3, randomized, double-blind study, nivolumab was compared with dacarbazine in 418 previously untreated patients with advanced melanoma without BRAF mutation.[32] Compared with dacarbazine, the 1-year overall survival rate and median progression-free survival time were significantly greater with nivolumab (72.9% and 5.1 months versus 42.1% and 2.2 months for dacarbazine, $p<0.001$ for both comparisons). The most common adverse events from nivolumab were similar to those in previous studies.

In 2011, the BRAF inhibitor vemurafenib, was approved by FDA for the treatment of patients with unresectable or metastatic melanoma and BRAF V600E mutation as detected by an FDA-approved test (Table 7).[40] Vemurafenib was compared with dacarbazine in a phase 3 study of 675 patients with previously untreated, unresectable or metastatic melanoma and the BRAF V600E mutation.[41] The overall survival rate after 6 months of treatment and the median progression-free survival time were greater with vemurafenib (84% and 5.3 months) than dacarbazine (64% and 1.6 months). Cutaneous events (e.g., rash, keratoacanthoma, squamous-cell carcinoma) were the most common adverse events from vemurafenib. Secondary squamous cell carcinoma and keratoacanthoma in patients receiving BRAF inhibitors have been attributed to paradoxical MAP kinase activation.[44] Patients receiving vemurafenib should be monitored for skin reactions by a dermatologist.[17]

Dabrafenib and trametinib are targeted therapies approved by FDA in 2013 for the treatment of patients with unresectable or metastatic melanoma and BRAF V600 mutation (Table 7). In contrast to dabrafenib, which targets BRAF, the target for trametinib is MEK, which is downstream in the RAS-RAF-MEK-ERK pathway. Resistance to BRAF inhibitors is common and often involves downstream activation of this pathway.[45] Relapse typically occurs 6-7 months after initiating BRAF inhibitor therapy.[46] Inhibition of MEK may help overcome this downstream mechanism for resistance to BRAF inhibitors, although resistance may be the result of a variety of mechanisms.[44]

Dabrafenib can be used alone (trametinib monotherapy should be reserved for patients unable to tolerate vemurafenib or dabrafenib), but

Table 7
New and Emerging Drug Therapies for Advanced Melanoma–Targeted Therapies [40-43,a]

Drug	FDA-Approved Indication	Usual Dosage	Common Adverse Events[b]	Cautions[b]
BRAF Inhibitors				
Dabrafenib	As a single agent for treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test or in combination with trametinib for treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test	150 mg orally twice daily as a single agent or in combination with trametinib at least 1 hr before or at least 2 hr after a meal until disease progression or unacceptable toxicity	Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and hand-foot syndrome	New primary malignancies, hemorrhage, venous thromboembolism, cardiomyopathy, ocular toxicity, serious febrile reactions, skin toxicity, hyperglycemia, and glucose-6-phosphate dehydrogenase deficiency
Vemurafenib	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test	960 mg orally twice daily taken approximately 12 hr apart with or without a meal until disease progression or unacceptable toxicity	Cutaneous events, arthralgia, and fatigue	Serious hypersensitivity, severe dermatologic reactions, QT prolongation, and hepatotoxicity
MEK Inhibitor				
Trametinib	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test and no prior BRAF inhibitor therapy	2 mg orally once daily taken at least 1 hr before or at least 2 hr after a meal until disease progression or unacceptable toxicity	Rash, diarrhea, and lymphedema	Cardiomyopathy, ocular toxicity, interstitial lung disease, and skin toxicity

FDA = Food and Drug Administration; MEK = mitogen-activated protein kinase-extracellular signal regulated kinase

[a] The sequence of agents listed in this table does not reflect preferences for treating advanced melanoma.

[b] Please consult the full prescribing information for additional details about potential adverse events and warnings. All agents listed in this table can cause embryo-fetal toxicity.

combination therapy with dabrafenib and trametinib was explored because of the potential for additive antitumor activity. In a randomized, double-blind, phase 3 study of 423 previously untreated patients with unresectable or metastatic melanoma and a BRAF V600E or V600K mutation, a significantly longer median progression-free survival time was observed with combination dabrafenib and trametinib therapy (9.3 months) than with dabrafenib alone (8.8 months, p=0.03).[47] The overall survival rate after 6 months of treatment was significantly longer with combination therapy than dabrafenib alone (93% vs. 85%, p=0.02). Patients with an elevated LDH concentration derived a greater survival benefit than did patients with a normal LDH level. Adverse events were similar in the two treatment groups, although pyrexia was more common in the combination therapy group and cutaneous squamous cell carcinoma was more common in the group receiving dabrafenib alone.

Patients receiving dabrafenib should be monitored for secondary skin lesions by a dermatologist.[17] If a febrile reaction occurs during treatment with dabrafenib with or without trametinib, the fever should be managed using antipyretic agents (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs).[17] Treatment with dabrafenib with or without trametinib should be interrupted and once the fever resolves, it may be resumed using reduced doses.[17] Low-dose oral corticosteroids may be required for recurrent fever.[45]

The combination of dabrafenib plus trametinib was compared with vemurafenib in a randomized, open-label, phase 3 study of 704 previously untreated patients with metastatic melanoma and a BRAF V600E or V600K mutation.[48] The overall survival rate after 12 months of treatment was significantly higher with combination therapy than vemurafenib (72% vs. 65%, p=0.005). The median progression-free survival time also was significantly longer with combination therapy than vemurafenib (11.4 months vs. 7.3 months, p<0.001). Pyrexia was more common in the combination-therapy group than in the vemurafenib group, and dermatologic toxicity was more common in the vemurafenib group than in the combination-therapy group.

Combining the CTLA-4 inhibitor ipilimumab with the PD-1 inhibitor nivolumab was explored in a phase 1 study of patients with advanced melanoma.[49] Fifty-three patients received concurrent therapy with nivolumab and ipilimumab every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses and then maintenance therapy with both drugs every 12 weeks for up to 8 doses. A dose-escalating regimen was used for both drugs in this concurrent regimen. Another 33 patients who previously had been treated with ipilimumab received nivolumab alone every 2 weeks for up to 48 doses as sequential therapy.

The objective response rate was 40% with the concurrent regimen, although it varied with the doses used and was as high as 53% in patients receiving the maximum doses associated with an acceptable level of adverse events (nivolumab 1 mg/kg and ipilimumab 3 mg/kg).[49] By contrast, the objective response rate was 20% with the sequential regimen. The rate of objective response to the concurrent regimen did not vary based on expression of PD-L1, possibly because of the assay used, variations in assay conditions or biopsy samples, or tumor heterogeneity. Rash and pruritus were the most common treatment-related adverse events from both regimens, and these events were manageable with the use of immunosuppressants.

The use of other combination therapies in patients with advanced melanoma (e.g., a BRAF inhibitor with or without a MEK inhibitor plus immunotherapy) to improve on the response rate and durability of response from monotherapy has been the subject of much interest. The efficacy and long-term safety of combination therapies are unknown in part because of a lack of experience and data.[44] Increases in autoimmune toxicities and paradoxical decreases in antitumor activity could occur as a result of complex unanticipated mechanisms when combination therapies are used.[44] A phase 1 study of a combination of the BRAF inhibitor vemurafenib and the CTLA-4 inhibitor ipilimumab was terminated early because the combination caused substantial hepatotoxicity.[50] The optimal combination of agents, sequence, and dosing for treating advanced melanoma remain to be determined.[51] Using

intermittent instead of continuous BRAF inhibitor therapy may delay the emergence of resistance.[44] Clinical trials are under way to clarify the impact of various therapeutic strategies on patient outcomes.

Role of the Pharmacist

Pharmacists can play an important role in evaluating new and emerging drug therapies for treating advanced melanoma for inclusion in the institutional formulary based on clinical trial results and other considerations. Educating other health care professionals and patients about the role and proper use of these drug therapies is another potential contribution of the pharmacist. Pharmacists can assume an important role in recommending supportive care for adverse effects from these therapies (especially ipilimumab, which has a medication guide as part of FDA REMS requirements). Remaining abreast of the latest information about the treatment of advanced melanoma may present a challenge because of the rapid pace of research and new product development, but it is essential because of the current uncertainty and need for clarity about the optimal therapeutic approach.

Reflective Question

What issues were taken into consideration and weighed most heavily on decisions by your pharmacy and therapeutics committee when evaluating and choosing among the new immunotherapies and targeted therapies recently introduced for the treatment of advanced melanoma for inclusion in the institutional formulary?

Conclusion

The clinical and economic burdens associated with advanced melanoma in the United States are substantial. The introduction of new immunotherapies and targeted therapies has led to improvement in survival rates in patients with advanced disease. Additional research is needed to identify the optimal therapeutic strategy for treating advanced melanoma. Pharmacists can play a vital role in educating other health care professionals and patients about the proper use of new drug therapies for the disease.

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Appendix. Melanoma Resources

American Academy of Dermatology

- Information for patients on skin cancer prevention, detection, risk factors (View Resource), diagnosis, and treatment (View Resource)
- Downloadable toolkits with presentations, handouts, posters, and flyers for use in community outreach (View Toolkit)

American Cancer Society

- Information about melanoma epidemiology, signs, symptoms, risk factors, diagnosis, staging, treatment, and research (View Resource)
- Skin cancer prevention (View Resource)

American Society of Clinical Oncology

- Clinical practice guidelines (e.g., 2012 sentinel lymph node biopsy for melanoma) (View Guidelines)

Centers for Disease Control and Prevention

- Answers to patients' frequently asked questions about skin cancer risk factors, symptoms, prevention, and screening (View FAQs)
- Links to July 2014 U.S. Surgeon General's call to action to prevent skin cancer (View Call to Action) and companion consumer booklet (View Booklet) (PDF)

National Cancer Institute

- Information for patients and healthcare professionals about melanoma epidemiology, causes, genetics, screening, detection, prevention, and treatment (View Resource)

The Skin Cancer Foundation

- Skin cancer information for patients (View Resource)

U.S. Department of Health and Human Services

- The Surgeon General's call to action to prevent skin cancer (View Call to Action) (PDF)

U.S. Food and Drug Administration

- List of cleared or approved companion diagnostic devices (in vitro and imaging tools), including tests required before use of dabrafenib, trametinib, and vermurafenib for patients with unresectable or metastatic melanoma. (View Resource)

U.S. Preventive Services Task Force

- Screening for skin cancer recommendation statement (*Ann Intern Med.* 2009; 150:188-93.) (View Article)

Continuing Education Credit Information

To Receive Continuing Pharmacy Education Credit

Once you have read the discussion guide (an assessment test is provided below as a study aid only), click on the link below to take the online assessment test (minimum score 70%) and complete your evaluation. Continuing pharmacy education (CPE) credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of a live activity or completion of a home study activity.

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1 hour (0.1 CEU, no partial credit) of continuing pharmacy education credit (ACPE activity # 0204-0000-15-417-H01-P).

Take Test and Process CPE

Assessment Test Study Aid

This assessment test is provided as a study aid only. Follow the instructions above to complete this assessment test and the evaluation online to obtain CE credit for this activity.

1. **Which of the following is a risk factor for melanoma?**
   - A Female sex.
   - B Blistering sunburns during childhood.
   - C Chronic low level exposure to UV radiation.
   - D African-American race.

2. **Which step in the Clark model for the histologic changes involved in the development of melanoma is genetic mutation usually first detected?**
   - A Benign nevus.
   - B Dysplastic nevus.
   - C Radial-growth phase.
   - D Metastatic melanoma.

3. **Which of the following is part of the ABCDE rule for evaluating moles for possible melanoma?**
   - A Asymmetry.
   - B Bleeding.
   - C Diameter >1 mm.
   - D Erythema.

4. **Which of the following is recommended for a patient with melanoma, an intermediate-thickness lesion, and suspected lymph node involvement?**
   - A Complete lymph node dissection.
   - B Sentinel lymph node dissection.
   - C Sentinel lymph node biopsy.
   - D Radiation therapy.

5. **Which of the following is the most important prognostic factor in patients with melanoma?**
   - A Breslow depth of invasion.
   - B Clark level of invasion.
   - C Dermal mitotic rate.
   - D Presence of ulceration.

6. **Which of the following currently is considered first-line therapy for BRAF mutation-negative metastatic melanoma?**
   - (A) Dacarbazine.
   - (B) Ipilimumab.
   - (C) Vemurafenib.
   - (D) Dabrafenib with or without trametinib.

7. **In theory, which of the following agents is most likely to be effective in treating a patient with advanced melanoma and a tumor that expresses PD-L1?**
   - (A) Dabrafenib.
   - (B) Trametinib.
   - (C) Vemurafenib.
   - (D) Nivolumab.

8. **Which of the following new drug therapies for advanced melanoma acts downstream in the RAS-RAF-MEK-ERK pathway and might stem resistance associated with drugs that act upstream?**
   - (A) Dabrafenib.
   - (B) Ipilimumab.
   - (C) Trametinib.
   - (D) Vemurafenib.

9. **Which of the following new drug therapies for treating advanced melanoma has the Food and Drug Administration established risk evaluation and mitigation strategy requirements because of safety concerns?**
   - (A) Dabrafenib.
   - (B) Ipilimumab.
   - (C) Trametinib.
   - (D) Vemurafenib.

10. **Which of the following adverse events has been attributed to paradoxical MAP kinase activation in patients receiving BRAF inhibitors?**
    - (A) Diarrhea.
    - (B) Febrile reactions.
    - (C) QT prolongation.
    - (D) Squamous cell carcinoma.

11. **Which of the following drug combinations is most appropriate for treating BRAF mutation-positive metastatic melanoma?**
    - (A) Nivolumab + ipilimumab.
    - (B) Vemurafenib + ipilimumab.
    - (C) Dabrafenib + trametinib.
    - (D) Dabrafenib + vemurafenib.